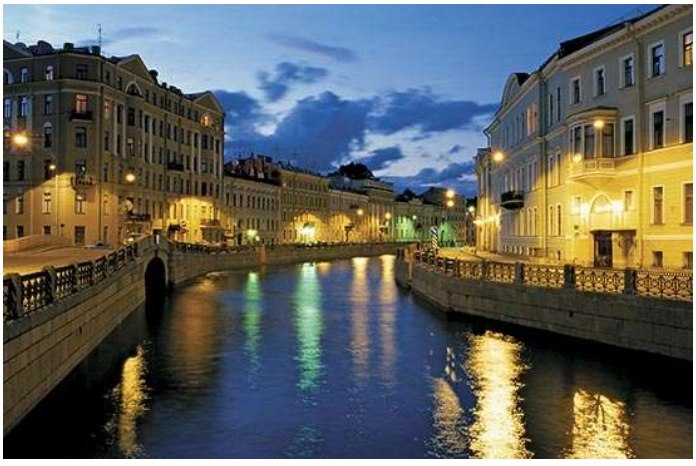
The International Stress and Behavior Society (ISBS)
Institute of Experimental Medicine
Institute of Translational Biomedicine, St. Petersburg State University

Program and Proceedings

28th Multidisciplinary International Neuroscience and Biological Psychiatry Conference

"Stress and Behavior"

Dedicated to the Year of Science and Technologies (2021) in Russia



St. Petersburg, Russia
May 16-18, 2021

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ZEBRAFISH NEUROSCIENCE RESEARCH CONSORTIUM

WITH PLATFORM SUPPORT FROM:

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1906

CONFERENCE PROGRAM

Day 1. Sun, May 16, 2021

Fireplace Hall (Kaminnyy Hall), Oktiabrskaya Hotel, 10 Ligovsky Prospect, St. Petersburg

09.00-17.00 **REGISTRATION DESK OPEN**

09.30-10.00 **OPENING AND WELCOMING ADDRESSESS**
Prof. AV Kalueff, ISBS President and Conference Chair
Prof. VM Klimenko, Program Committee Chair
Prof. OV Shamova, Deputy Director, Institute of Experimental Medicine

10.00-10.40 **OPENING PLENARY LECTURE:** BEHAVIORAL AND NEUROBIOLOGICAL CONSEQUENCES OF EXCESSIVE CONSUMPTION OF WESTERN DIET: A STUDY ON MICE. T Strekalova, Department of Psychiatry and Neuropsychology, University of Maastricht, Netherland, Sechenov 1st Moscow State Medical University, Moscow, Russia

10.40-15.55 **SYMPOSIUM 1: LAPIN SYMPOSIUM ON PRECLINICAL NEUROSCIENCE**
Chairs: AV Kalueff (China, Russia, USA) and VM Klimenko (Russia)

10.40-10.45 INTRODUCTION: PROFESSOR IZYASLAV LAPIN

10.45-11.05 TRANSGENIC ANIMAL MODELS IN NEUROPHARMACOLOGY. RR Gainetdinov, Institute of Translational Biomedicine, St. Petersburg State University, St. Petersburg, Russia

11.05-11.25 TONIC LOCUS COERULEUS ACTIVITY PLAYS A CAUSAL ROLE IN STRESS-ASSOCIATED INCREASES IN ALCOHOL DRINKING. EA Budygin, Wake Forest School of Medicine, Winston Salem, NC, USA

11.25-11.40 APPROACHES TO PARALLEL MODELING NEUROBIOLOGICAL CONDITIONS IN COMPLEX CELLULAR AND ANIMAL MODELS. EV Petersen, Moscow Institute of Physics and Technology, Moscow, Russia

11.40-11.50 EFFECT OF MELANOCORTIN RECEPTOR AGONISTS ON SEXUAL MOTIVATION IN RATS AFTER CHRONIC SOCIAL ISOLATION, IY Tissen, LA Magarramova, MD Ayzup, AA Lebedev, PD Shabanov, Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia

11.50-12.00 MOLECULAR MECHANISMS OF SUPPRESSION OF THE PROGRESSION OF FUS PROTEINOPATHY IN THE NERVOUS SYSTEM OF TRANSGENIC MICE EXPRESSING C-TERMINALLY TRUNCATED HUMAN FUS, EA Lysikova, S Funikov, AP Rezvykh, KD Chaprov, Institute of Physiologically Active Substances RAS, Chernogolovka, Engelhardt Institute of Molecular Biology RAS, Moscow, Russia

12.00-12.15 ***TECHNICAL BREAK***

12.15-12.30 SEROTONIN METABOLISM IN GENETICALLY DETERMINED DOPAMINE METABOLISM DISORDERS, DS Traktirov, NS Pestereva, ZS Fesenko, IS Ivleva, MN Karpenko, VM Klimenko, Institute of Experimental Medicine, Peter the Great St. Petersburg Polytechnic University, St. Petersburg State University, Institute of Translational Biomedicine, St. Petersburg, Russia

12.30-12.45 ARE PAIN AND ANXIETY INTERCONNECTED SIGNALS OF HUMAN DISEASE? AS Tadevosyan, A Avetisyan, Heratsi Yerevan State Medical University, Yerevan, Armenia

12.45-13.00 ISBS AND BIOLOGICAL PSYCHIATRY OF STRESS TODAY, IN THE YEAR OF SCIENCE. AV Kalueff, Southwest University, Chongqing, China

13.00-13.15 UNDERSTANDING TRANSLATIONAL AND EVOLUTIONALLY CONSERVATIVE MOLECULAR BIOMARKERS OF AFFECTIVE DISORDERS IN THE ZEBRAFISH, RAT AND HUMAN, KA Demin, AV Kalueff, Institute of Translational Biomedicine, St. Petersburg State University, Institute of Experimental Medicine, Almazov National

Medical Research Centre, Ministry of Healthcare of Russian Federation, St. Petersburg, Neuroscience Program, Sirius University, Sochi, Russia; Southwest University, Chongqing, China

13.15-13.30 THE ROLE OF SYNUCLEINS IN BEHAVIORAL IMPAIRMENT MEDIATED BY COMPROMISED DOPAMINE TRANSMISSION, KD Chaprov, IuS Sukhanova, Institute of Physiologically Active Compounds RAS, Chernogolovka, Russia

13.30-13.40 MATERNAL HYPERHOMOCYSTEINEMIA LEADS TO NEUROINFLAMATORY PROCESSES IN RAT HIPPOCAMPUS DURING THE FIRST MONTH AFTER BIRTH, INDUCING MEMORY DEFICIT IN ADULTS, DS Vasilev, NL Tumanova, AD Shcherbitskaia, DS Kalinina, NM Dubrovskaya, Sechenov Institute of Evolutionary Physiology and Biochemistry RAS, St. Petersburg, Russia

13.40-13.50 REFERENCE GENE VALIDATION WITHIN THE RAT BRAIN UNDER MILD KETOSIS, AP Schwarz, AS Shcherbakova, VA Nikitina, DU Krytskaya, AN Trofimov, VM Klimenko Institute of Experimental Medicine, Sechenov Institute of Evolutionary Physiology and Biochemistry RAS, St. Petersburg, Russia

13.50-14.05 DELAYED EFFECTS OF CHRONIC SLEEP RESTRICTION ON MEMORY AND EMOTIONALITY IN RATS, MV Chernyshev, MA Guzeev, VD Borschenko, IV Ekimova, Sechenov Institute of Evolutionary Physiology and Biochemistry RAS, St. Petersburg, Russia

14.05-14.20 TEMPORAL ANALYSES OF DRUG-INDUCED LOCOMOTOR ACTIVITY IN ZEBRAFISH BASED ON NEURAL NETWORK PREDICTIONS, DV Bozhko, GK Galumov, AI Polovjan, SM Kolchanova, VO Myrov, AV Kalueff, ZebraML, St. Petersburg, Russia; Neuroscience Center, Helsinki Institute of Life Science, University of Helsinki, Helsinki, Department of Neuroscience and Biomedical Engineering, Aalto University, Helsinki, Finland; School of Pharmacy, Southwest University, Chongqing, China

14.20-15.30 ***TECHNICAL BREAK***

15.30-15.50 **CONFERENCE PRESENTATION:** SOCIABILITY TEST IN MICE USING LABORAS AND SONOTRACK SYSTEM, L Bachdasarian, R Bulthuis, Metris BV, Hoofddorp, Netherlands

15.50-17.10 **ISBS SYMPOSIUM 2: ZUKOWSKA STRESS NEUROSCIENCE SYMPOSIUM**
Chairs: VM Klimenko (Russia)

15.50-16.00 INTRODUCTION: PROFESSOR ZOFIA ZUKOWSKA

16.00-16.10 MOTOR ACTIVITY DURING SWIMMING AND WALKING IN THE TAAR5 KNOCKOUT MICE, AV Goriainova, DS Kalinina, RR Gainetdinov, PE Musienko, Institute of Translational Biomedicine, St. Petersburg State University, Sechenov Institute of Evolutionary Physiology and Biochemistry RAS, Pavlov Institute of Physiology RAS, St. Petersburg, Sirius National Technical University, Neuroscience Program, Sochi, Russia

16.10-16.20 EXPLORING THE CONSEQUENCES OF A SINGLE SOCIAL DEFEAT STRESS ON ACCUMBAL DOPAMINE IN MALE AND FEMALE RATS, VV Nemets, VA Zavyalov, PA Chepik, RR Gainetdinov, EA Budygin, St. Petersburg State University, Institute of Translational Biomedicine, St. Petersburg, Russia; Wake Forest School of Medicine, Department of Neurobiology and Anatomy, Winston-Salem, NC, USA

16.20-16.30 FEATURES OF AUTONOMOUS REGULATION OF THE CARDIOVASCULAR SYSTEM IN ELDERLY UNDER STRESS, VP Nesterov, AI Burdygin, KB Ivanov, SV Nesterov, Sechenov Institute of Evolutionary Physiology and Biochemistry RAS, St. Petersburg, Russia

16.30-16.40 EFFECTS OF GLIBENCLAMIDE ADMINISTRATION ON COGNITIVE FUNCTIONS OF RATS IN NORMOGLYCEMIA, AS Zubov, TV Tiutiunnik, MN Karpenko, VM Klimenko, Institute of Experimental Medicine, St. Petersburg State University, St. Petersburg, Russia

16.40-16.55 THERAPEUTIC EFFECT OF HESPERIDIN ON THE INFLAMMATORY RESPONSE AND OXIDATIVE STRESS INDUCED BY A TRAUMATIC BRAIN INJURY IN RATS, YL Yang, MA Tikhonova, TG Amstislavskaya, KT Lu, Novosibirsk State University, Novosibirsk, Russia, National Chia-Yi University, Chia-Yi, National Taiwan Normal University, Taipei, Taiwan

16.55-17.10 THE EFFECTS OF MAFEDINE ADMINISTRATION ON BRAIN ELECTRICAL ACTIVITY AFTER BRAIN TRAUMA IN RATS, YuI Sysoev, VA Prikhodko, RT Chernyakov, RD Idiyatullin, PE Musienko, SV Okovityi, St. Petersburg State Chemical and Pharmaceutical University, Laboratory of Neuroprosthetics, Institute of Translational Biomedicine, St. Petersburg State University, Pavlov Institute of Physiology RAS, St. Petersburg State Research Institute of Phthisiopulmonology, Ministry of Healthcare of Russian Federation, St. Petersburg, Russia

Day 2. Mon, May 17, 2021

Small Hall, Oktiabrskaya Hotel, 10 Ligovsky Prospect, St. Petersburg

09.30-17.00 **REGISTRATION DESK OPEN**

10.00-14.00 **SYMPOSIUM 3: CLINICAL STRESS NEUROSCIENCE AND NEUROLOGY**
Chairs: VA Rozanov (Russia) and D Kozic (Serbia)

10.00-10.20 MULTIPARAMETRIC NEUROIMAGING MODALITIES IN DETECTION OF SUBTLE BRAIN CHANGES IN AGING, D Kozic, University of Novi Sad Faculty of Medicine, Novi Sad, Serbia

10.20-10.40 THE USEFULNESS OF STRESSING PEOPLE IN VOCATIONAL TRAINING, Ph Fauquet-Alekhine, J Bleuze, H Mouret, Ch. Lenoir, Ph Kessler, SEBE-Lab, Department of Psychological and Behavioural Sciences, LSE, London, UK; Laboratory for Research in Science of Energy, INTRA Robotics, West Catholic University, Angers, France

10.40-10.55 THE PATIENT'S OWN BONE MARROW-DERIVED STROMAL CELLS: DISEASE MODIFIERS IN (NEURO)DEGENERATIVE DISORDERS, J de Munter, Maastricht University, Maastricht, Netherlands

10.55-11.10 A COMMUNICATIVE EDUCATION SUPPORT BY ICT FOR SOCIAL DEVELOPMENT IN CHILDREN PLAYING AT DIFFERENT REAL SPACES ONE ANOTHER, M Ohta, F Tomoto, M Koshiba, Graduate School of Science and Technology for Innovation, Yamaguchi University, Yamaguchi, Department of Pediatrics, Saitama Medical University, Saitama, Graduate School of Information Sciences, Tohoku University, Tohoku, Japan

11.10-11.30 **CONFERENCE PRESENTATION:** AUTOMATED COGNITIVE AND BEHAVIORAL SCREENING OF INDIVIDUAL MICE LIVING IN SOCIAL GROUPS, REDUCING STRESS COMPONENT. D Verma TSE Systems GmbH, Bad Homburg, Germany

11.30-11.50 ***TECHNICAL BREAK***

11.50-14.45 **SYMPOSIUM 4: ZNRC ZEBRAFISH NEUROSCIENCE SYMPOSIUM**
Chair: AV Kalueff (Russia, USA, China)

11.50-12.00 INTRODUCTION

12.00-12.15 LASER IRRADIATION FOR MODELING TRAUMATIC BRAIN INJURY IN ADULT ZEBRAFISH, NA Maslov, EO Tsibulskaya, MA Tikhonova, AV Kalueff, YL Yang, TG Amstislavskaya, Novosibirsk State University, Novosibirsk, Russia; National Chia-Yi University, Chia-Yi, Taiwan; Khristianovich Institute of Theoretical and Applied Mechanics SO RAS, Novosibirsk, Russia

12.15-12.25 EFFECTS OF LASER-INDUCED TRAUMATIC BRAIN INJURY ON BEHAVIORAL AND MORPHOLOGICAL CHARACTERISTICS IN ZEBRAFISH, AA Bashirzade, AS Belova, AA Akopyan, VY Babchenko, MA Tikhonova, AV Kalueff, TG Amstislavskaya,

Novosibirsk State University, Khristianovich Institute of Theoretical and Applied Mechanics SO RAS, Novosibirsk, Russia

12.25-12.40 PERSPECTIVES OF STUDYING PSYCHEDELIC SUBSTANCES ON ZEBRAFISH (*Danio rerio*), NA Krotova, KA Demin, KA Derzhavina, TO Kolesnikova, AV Kaluleff, Institute of Translational Biomedicine, St. Petersburg State University, Institute of Experimental Medicine Almazov National Medical Research Centre, Ministry of Healthcare of Russian Federation, St. Petersburg, Russia, School of Pharmacy, Southwest University, Chongqing, China; Neuroscience Program, Sirius University, Sochi, Granov Russian Research Center of Radiology and Surgical Technologies, Ministry of Healthcare of Russian Federation, Pesochny, Russia

12.45-13.00 MODELING MEMORY IMPAIRMENT EVOKED BY ACUTE PREDATOR ODOR STRESS IN ADULT ZEBRAFISH, VV Kurashenko, TO Kolesnikova, DS Galstyan, AV Kalueff, Institute of Translational Biomedicine, St. Petersburg State University, Institute of Experimental Medicine, Almazov National Medical Research Centre, Ministry of Healthcare of Russian Federation, St. Petersburg, Russia; School of Pharmacy, Southwest University, Chongqing, China; Neuroscience Program, Sirius University, Sochi, Granov Russian Research Center of Radiology and Surgical Technologies, Ministry of Healthcare of Russian Federation, Pesochny, Russia

13.00-13.10 CHRONIC BEHAVIORAL EFFECTS OF ACETYLSALICYLIC ACID IN ADULT ZEBRAFISH, VV Zakharova, DS Galstyan, TO Kolesnikova, KA Demin, AV Kalueff, Institute of Translational Biomedicine, St. Petersburg State University, Institute of Experimental Medicine, Almazov National Medical Research Centre, Ministry of Healthcare of Russian Federation, St. Petersburg, Russia; School of Pharmacy, Southwest University, Chongqing, China; Ural Federal University, Ekaterinburg, Neuroscience Program, Sirius University, Sochi, Russia Granov Russian Research Center of Radiology and Surgical Technologies, Ministry of Healthcare of Russian Federation, Pesochny, Russia

13.10-13.20 PROLONGED CHRONIC UNPREDICTABLE STRESS IN THE ZEBRAFISH: EFFECTS ON BEHAVIORAL AND NEUROCHEMICAL ALTERATIONS PRODUCED BY FLUOXETINE, EPA AND LPS, MV Seredinskaya, TO Kolesnikova, DS Galstyan, KA Demin, NA Krotova, NP Ilyin, KA Derzhavina, DV Sorokin, AV Kalueff, Institute of Translational Biomedicine, St. Petersburg State University, Institute of Experimental Medicine, Almazov National Medical Research Centre, Ministry of Healthcare of Russian Federation, St. Petersburg, Russia; School of Pharmacy, Southwest University, Chongqing, China; Granov Russian Research Center of Radiology and Surgical Technologies, Ministry of Healthcare of Russian Federation, Pesochny, Neuroscience Program, Sirius University, Sochi, Russia

13.20-13.30 BEHAVIORAL EFFECTS OF FLY AGARIC (*AMANITA MUSCARIA*) EXTRACT IN ADULT ZEBRAFISH, YuM Kositsyn, KA Derzhavina, AASh Khaibaev, KI Nechesanova, AV Kalueff, Institute of Translational Biomedicine, St. Petersburg State University Institute of Experimental Medicine, Almazov National Medical Research Centre, Ministry of Healthcare of Russian Federation, St. Petersburg, Russia; School of Pharmacy, Southwest University, Chongqing, China

13.30-13.40 CHRONIC EFFECTS OF ESTRADIOL VALERATE IN ADULT ZEBRAFISH: A PILOT STUDY, AASh Khaibaev, KA Derzhavina, DV Sorokin, TO Kolesnikova, KA Demin, AV Kalueff, Institute of Translational Biomedicine, St. Petersburg State University, Institute of Experimental Medicine, Almazov National Medical Research Centre, Ministry of Healthcare of Russian Federation, St. Petersburg, Neuroscience Program, Sirius University, Sochi, Russia; School of Pharmacy, Southwest University, Chongqing, China

13.40-13.50 ACUTE AND CHRONIC EFFECTS OF DESOGESTREL, ORAL CONTRACEPTIVE, IN ADULT ZEBRAFISH IN NOVEL TANK TEST: A PILOT STUDY. DV Sorokin, AASh Khaibaev, KA Derzhavina, TO Kolesnikova, KA Demin, AV Kalueff, Institute of Translational Biomedicine, St. Petersburg State University, Institute of Experimental Medicine, Almazov National Medical Research Centre, Ministry of Healthcare of Russian Federation, St. Petersburg, Neuroscience Program, Sirius University, Sochi, Russia; School of Pharmacy, Southwest University, Chongqing, China

13.50-14.00 THE ROLE OF COMBINED ORAL CONTRACEPTIVES (COC) IN THE DEVELOPMENT OF DEPRESSIVE- LIKE BEHAVIOR IN ADULT ZEBRAFISH: A

PILOT STUDY, KA Derzhavina, AASh Khaibaev, DV Sorokin, TO Kolesnikova, KA Demin, AV Kalueff, Institute of Translational Biomedicine, St. Petersburg State University, Institute of Experimental Medicine, Almazov National Medical Research Centre, Ministry of Healthcare of Russian Federation, St. Petersburg, Neuroscience Program, Sirius University, Sochi, Russia; School of Pharmacy, Southwest University, Chongqing, China

14.00-14.10 ACUTE BEHAVIORAL EFFECTS OF CELEBREX, A SELECTIVE INHIBITOR OF COX-2, IN ADULT ZEBRAFISH, M Nerush, DS Galstyan, KA Demin, TO Kolesnikova, AV Kalueff, Institute of Translational Biomedicine, St. Petersburg State University, Institute of Experimental Medicine, Almazov National Medical Research Centre, Ministry of Healthcare of Russian Federation, Granov Russian Scientific Center for Radiology and Surgical Technologies, St. Petersburg, Russia; School of Pharmacy, Southwest University, Chongqing, China; Ural Federal University, Ekaterinburg, Neuroscience Program, Sirius University, Sochi, Russia

14.10-14.20 ACUTE BEHAVIORAL EFFECTS OF MV-007, BETA-ALANINE DERIVATE, ON ZEBRAFISH BEHAVIOR IN CONDITIONED PLACE AVERSION TEST AND NOVEL TANK TEST, UV Menshikova, TO Kolesnikova, DS Galstyan, AV Kalueff, Institute of Translational Biomedicine, St. Petersburg State University, Institute of Experimental Medicine, Almazov National Medical Research Centre, Granov Russian Scientific Center for Radiology and Surgical Technologies, St. Petersburg, Russia; School of Pharmacy, Southwest University, Chongqing, China; Ural Federal University, Ekaterinburg, Neuroscience Program, Sirius University, Sochi, Russia

14.20-14.30 NEUROPEPTIDE SYSTEMS MODULATE POST-STRESSOR RESPONSE IN ZEBRAFISH (*DANIO RERIO*), PP Khokhlov, AA Blazhenko, AD Devyashin, LK Khnychenko, ER Bychkov, SV Kazakov, AA Lebedev, PD Shabanov, Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia

14.30-14.40 CORTISOL CONCENTRATION IN ZEBRAFISH (*DANIO RERIO*) AFTER STRESS EXPOSURE AND PHARMACOLOGICAL SUBSTANCIES ADMINISTRATION, AA Blazhenko, PP Khokhlov, IYu Tissen, ER Bychkov, AS Devyashin, SV Kazakov, VA Lebedev, AA Lebedev, SN Proshin, PD Shabanov, Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia

14.40-14.50 ZEBRAFISH EEG UNDER VARIOUS TYPES OF ANESTHESIA: A PILOT STUDY. MA Gubaydullina, SL Khatsko, AV Kalueff, Ural Federal University, Yekaterinburg, Russia; Southwest University, Chongqing, China

14.50-15.00 ANHEDONIA MODELS IN ZEBRAFISH: ARE WE THERE YET? MS de Abreu, F Costa, ACVV Giacomini, KA Demin, EV Petersen, DB Rosemberg, AV Kalueff, Laboratory of Cell and Molecular Biology and Neurobiology, Moscow Institute of Physics and Technology, Moscow, Neuroscience Program, Sirius University, Sochi, Russia; Bioscience Institute, University of Passo Fundo, Passo Fundo, RS, Graduate Program in Biological Sciences, Federal University of Santa Maria, Santa Maria; Brazil; School of Pharmacy, Southwest University, Chongqing, China

15.00-15.20 **ISBS SPECIAL TALK:** NEUROPROSTHETICS OF MOTOR AND VISCERAL FUNCTIONS, PE Musienko, Institute of Translational Biomedicine, St. Petersburg State University, Pavlov Institute of Physiology RAS, St. Petersburg, Sirius National Technical University, Neuroscience Program, Sochi, Russia

15.20-15.35 ***TECHNICAL BREAK***

15.35-18.00 **SYMPOSIUM 5: CONSOLIDATED POSTER SESSION PART 1**
Chairs: AV Kalueff (China, Russia, USA) and VM Klimenko (Russia)

EFFECTIVENESS EVALUATION OF GROOMING MICROSTRUCTURE INDICATORS TO IDENTIFY DEPRESSIVE BEHAVIORAL FEATURES OF TAAR1-KO AND TAAR5-KO MICE, AL Manasyan, SA Apryatin, EM Turkeeva, VM Klimenko, Institute of Experimental Medicine, St. Petersburg, Russia

THE RESEARCH FOR DIAGNOSIS OF STRESS USING TGI TECHNIQUE, K Oda, M Koshiba, Graduate School of Science and Technology for Innovation, Yamaguchi University, Yamaguchi,

Department of Pediatrics, Saitama Medical University, Saitama, Graduate School of Information Sciences, Tohoku University, Tohoku, Japan

INTER-AND TRANSGENERATION INHERITANSE OF CHEMICAL AND PSYCHOLOGICAL STRESS IMPACTS. EPIGENETIC MECHANISMS, EL Patkin, SG Tsikunov, Institute of Experimental Medicine, St. Petersburg, Russia

INFLAMMATION AND OXIDATIVE STRESS PERIPHERAL INDICATORS AS BIOMARKERS OF EARLY DIAGNOSIS OF CHRONIC CEREBROVASCULAR INSUFFICIENCY, OS Tumashova, ZM Muruzheva, IS Ivleva, MN Karpenko, VM Klimenko, Institute of Experimental Medicine, St. Petersburg State Chemical Pharmaceutical University, St. Petersburg, Russia

DEXAMETHASONE INCREASES ACTIVITY OF CALPAIN- 2 IN THE HIPPOCAMPUS AND CORTEX, TV Tyutyunnik, AS Zubov, MN Karpenko, VM Klimenko, St. Petersburg State University, Pavlov Department of Physiology, Institute of Experimental Medicine, St. Petersburg, Russia

AGE-DOSE-DEPENDENT ANALGETIC EFFECT OF A TYPE 2 VASOPRESSIN RECEPTOR AGONIST, 1-DESAMINO-8-D-ARGININE-VASOPRESSIN, IN A MODEL OF ACUTE THERMAL RAT PAIN, AA Nikitina, VA Maistrenko, SG Belokoskova, SG Tsikunov, Institute of Experimental Medicine, St. Petersburg University of the Ministry of the Interior of Russian Federation, St. Petersburg, Russia

DEVELOPMENT OF ANHEDONIA IN ADULTS AND YOUNG FEMALE RATS AFTER VITAL STRESS, NK Apraksina, TV Avaliani, SG Tsikunov, Institute of Experimental Medicine, St. Petersburg University of the Ministry of the Interior of Russian Federation, St. Petersburg, Russia

BLOOD PLASMA BUTYRYLCHOLINESTERASE ISOFORMS ACTIVITY IN MILD COGNITIVE IMPAIRMENT, VV Khizha, DE Zaitsev, MF Balluzek, AB Shishkin, SV Symina, DS Vasilyev, DI Kozlova, Sechenov Institute of Evolutionary Physiology and Biochemistry RAS, St. Petersburg Clinical Hospital RAS, St. Petersburg, Russia

CHANGES IN THE BRAIN EXPRESSION OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR GENES IN THE RAT MODEL OF TEMPORAL LOBE EPILEPSY, AA Kovalenko, MV Zakharova, AP Schwarz, AV Dyomina, TB Melik-Kasumov, OE Zubareva, Sechenov Institute of Evolutionary Physiology and Biochemistry RAS, St. Petersburg, Russia; Institute of Physiology NASB, Minsk, Belarus

PLASMA BDNF CONTENT IN CHILDREN WITH VARIOUS FORMS OF AUTISM SPECTRUM DISORDERS, EM Malsagova, ZM Muruzheva, SG Belokoskova, MN Karpenko, SG Tsikunov, Institute of Experimental Medicine, St. Petersburg University of the Ministry of the Interior of Russian Federation, St. Petersburg, Russia

NEUROBEHAVIORAL EFFECT OF THE NEWLY FORMULATED DRUG AS AN AGONIST OF SEROTONIN RECEPTORS [2,5-DIMETHOXY-N-[(2-METHOXYPHENYL)METHYL]ANILINE], TZ Mbutho, AV Zhdanov, VA Shevyrin, OV Kuprianeova, SL Khatsko, AV Kalueff, Ural Federal University, Yekaterinburg, Russia; Southwest University, Chongqing, China

BEHAVIORAL ASSESSMENT OF DIFFERENT GLOFISH® ZEBRAFISH STRAINS IN THE NOVEL TANK TEST (NTT): A PILOT STUDY. AS Starodvorskaya, GO Maslov, CR Shakirova, KN Zabegalov, AV Kalueff, Ural Federal University, Ekaterinburg, Institute of Translational Biomedicine, St. Petersburg State University, Russia; Southwest University, Chongqing, China

EFFECTS OF EXTRACTS OF INONOTUS OBLIQUUS FUNALLIA TROGII AND GANODERMA APPLANATUM ON ZEBRAFISH BEHAVIOR IN THE NOVEL TANK TEST: A PILOT STUDY. MS Chernykh, AA Ermoshin, SL Khatsko, AV Zhdanov, AV Kalueff, Ural Federal University, Yekaterinburg, Russia; Southwest University, Chongqing, China

INVESTIGATION OF THE LINKAGE OF FIN LENGTH AND SKIN COLOR WITH NEUROBEHAVIORAL PHENOTYPES IN ZEBRAFISH. PART I: THE NOVEL TANK TEST. KN Zabegalov, AA Bashirzade, YY Babchenko, TG Amstislavskaya, AV Kalueff, Ural Federal University, Yekaterinburg, Scientific Research Institute of Physiology and Basic Medicine, Novosibirsk, Russia; Southwest University, Chongqing, China

CHANGES IN EXPRESSION OF SUBUNITS OF NMDA RECEPTORS IN THE STRIATUM IN A RAT MODEL OF PARKINSON'S DISEASE, KK Sitdikova, VD Dergachev, EE Yakovleva, ER Bychkov, PD Shabanov, Institute of Experimental Medicine, St. Petersburg, Russia

STRESS AS A MOTIVATOR OF COGNITIVE DISSONANCE AFFECTING BEHAVIOR IN THE SYSTEM OF DISTANT EDUCATION, LV Shabanov, SV Marihin, AA Lebedev, St. Petersburg Military Institute of National Guard of Russia, Pushkin Leningrad State University, Institute of Experimental Medicine, St. Petersburg, Russia

SEARCH FOR ANTIHYPOXIC DRUGS AMONG NEW COUMARIN DERIVATIVES, AF Safonova, OM Rodionova, AO Kashirin, ER Bychkov, AA Lebedev, PD Shabanov, Institute of Experimental Medicine, St. Petersburg, Russia

STUDY OF EMOTIONAL BEHAVIOR AND DESACYL-GRELIN CONTENT IN RAT BRAIN AFTER PSYCHOEMOTIONAL STRESS, VA Raptanova, AA Lebedev, SG Tsikunov, PP Khokhlov, AG Pshenichnaya, IYu Thyssen, ER Bychkov, VA Lebedev, NS Efimov, KE Gramota, PD Shabanov, Institute of Experimental Medicine, St. Petersburg Medico-Social Institute, St. Petersburg, Russia

DEVELOPMENT OF EROSIVE INFLAMMATION IN THE STOMACH MUCOSA AFTER EXPERIMENTAL EMOTIONAL STRESS, VA Raptanova, PS Bobkov, SG Tsikunov, AV Droblenkov, Institute of Experimental Medicine, St. Petersburg Medico-Social Institute, St. Petersburg, Russia

EXPERIMENTAL STUDY OF THE EMOTIONOGENIC EFFECTS OF PEPTIDES OF THE KISSPEPTIN GROUP, LA Magarramova, AA Lebedev, AG Pshenichnaya, VA Lebedev, PD Shabanov, Institute of Experimental Medicine, St. Petersburg, Russia

ANTIHYPOXIC EFFECT OF NEW COUMARIN DERIVATIVES IN THE MODEL OF ACUTE HYPOBARIC HYPOXIA IN RATS, AO Kashirin, EN Selina, IB Krylova, NR Evdokimova, ER Bychkov, VA Polukeev, PD Shabanov, Institute of Experimental Medicine, St. Petersburg, Russia

THE EFFECT OF ACUTE MENTAL STRESS ON THE EXCHANGE OF MONOAMINES IN THE MESOCORTICAL AND NIGROSTRIATAL SYSTEMS OF THE RAT BRAIN, IV Karpova, SG Tsikunov, DV Kritskaya, LK Khnychenko, AA Lebedev, ER Bychkov, IYu Thyssen, SS Pyurveev, PD Shabanov, Institute of Experimental Medicine, St. Petersburg, Russia

PHARMACOLOGICAL ANALYSIS OF THE IMPACT OF GHRELIN AND OREXIN ON GAMBLING BEHAVIOR, KE Gramota, AA Lebedev, ER Bychkov, VA Lebedev, IYu Thyssen, ND Yakushina, SS Pyurveev, PD Shabanov, Institute of Experimental Medicine, St. Petersburg, Russia

OREXIN BRAIN OX1R mRNA INCREASES IN RISK-PRONE RATS IN A MODEL OF GAMBLING, KE Gramota, EA Sexte, AA Lebedev, ER Bychkov, MI Airapetov, IYu Thyssen, VA Lebedev, SS Pyurveev, PD Shabanov, Institute of Experimental Medicine, St. Petersburg, Russia

A GHRELIN RECEPTOR ANTAGONIST, [D-LYS3]-GHRP-6, REDUCES THE RISK BEHAVIOR IN THE RAT GAMBLING MODEL BY ALTERING THE TURNOVER OF DOPAMINE AND SEROTONIN, KE Gramota, AA Lebedev, IV Karpova, ER Bychkov, ND Yakushina, IYu Thyssen, NS Efimov, VA Lebedev, SS Pyurveev, PD Shabanov, Institute of Experimental Medicine, St. Petersburg, Russia

ANTICONVULSANT PROPERTIES OF THE 1,2-SUBSTITUTED DERIVATIVES OF IMIDAZOLE-4,5-DICARBOXYLIC ACID, SP Foksha, EE Yakovleva, MA Brusina, ER Bychkov, LV Myznikov, LB Piotrovskij, PD Shabanov, Institute of Experimental Medicine, St. Petersburg, Russia

BEHAVIORAL EFFECTS OF ANTIDEPRESSANTS ON THE NOVEL TANK STRESS IN ZEBRAFISH, DANIO RERIO, AS Devyashin, AA Blazhenko, VA Lebedev, AA Lebedev, SV Kazakov, PD Shabanov, Institute of Experimental Medicine, St. Petersburg, Russia

INTRANASAL ADMINISTRATION OF TYRAMINE LEADS TO REDUCED ANXIETY IN RATS, SA Apryatin, RR Gainetdinov, VM Klimenko, Institute of Experimental Medicine, Institute of Translational Biomedicine, St. Petersburg State University, St. Petersburg, Russia

EFFECT OF HINDLIMB UNLOADING ON HAMSTRING MUSCLE DURING TREADMILL LOCOMOTION IN RATS, A Popov, V Lyakhovetskii, O Gorskii, D Kalinina, PE Musienko, Institute of Translational Biomedicine, St. Petersburg State University, Pavlov Institute of Physiology RAS, St. Petersburg, Russia

EVALUATION OF SEXUAL MOTIVATION IN TAAR1 KNOCKOUT MICE, IS Zhukov, MA Ptukha, IY Tissen, IV Karpova, AB Volnova, RR Gainetdinov, Institute of Translational Biomedicine, St. Petersburg State University, Institute of Experimental Medicine, St. Petersburg University Hospital, St. Petersburg State University, St. Petersburg, Russia

Day 3. Tue, May 18, 2021

Small Hall, Oktiabrskaya Hotel, 10 Ligovsky Prospect, St. Petersburg

09.30-14.00 **REGISTRATION DESK OPEN**

09.30-10.00 **ISBS SPECIAL LECTURE:** SUICIDES IN THE PANDEMIC – WHAT KIND OF STRESS ACTUALLY PROVOKES SUICIDAL BEHAVIOR? VA Rozanov, St. Petersburg State University, Bekheterev National Research Center for Psychiatry and Neurology, St. Petersburg, Russia

10.00-12.00 **SYMPOSIUM 6: PSYCHIATRIC GENETICS: STRESS-RELATED ASPECTS**
Chairs: VE Golimbet and AO Kibitov (Russia)

10.00-10.20 GENE-ENVIRONMENT INTERACTIONS AND THEIR INFLUNCE ON THE RISK AND SEVERITY OF PSYCHIATRIC DISEASES, VE Golimbet, Mental Health Research Center, Moscow, Russia

10.20-10.40 GENETIC MARKERS OF THE STRESS-REACTIVITY SYSTEMS IN SUICIDAL BEHAVIOR, VA Rozanov, St. Petersburg State University, Bekheterev National Research Center for Psychiatry and Neurology, St. Petersburg, Russia

10.40-11.00 DNA METHYLATION AS A POTENTIAL MEDIATOR OF EARLY LIFE STRESS EFFECTS ON COGNITIVE PERFORMANCE IN SCHIZOPHRENIA, M Alfimova, Department of Clinical Genetics, Mental Health Research Center, Moscow, Russia

11.00-11.20 GENETIC STUDIES OF MOOD DISORDERS WITH FAMILY DESIGN: NEW PERSPECTIVES, E Kasyanov, E Kasyanov, Bekheterev National Research Center for Psychiatry and Neurology, St. Petersburg, Russia

11.20-11.40 THE ASSOCIATION BETWEEN INTERNET ADDICTION AND STRESS IN SOCIAL COMMUNICATION: PSYCHOLOGICAL AND GENETIC FACTORS, AV Trusova, St. Petersburg State University, Bekhterev National Research Center for Psychiatry and Neurology, St. Petersburg, Russia

11.40-12.00 GENETIC MARKERS OF THE INTERNET ADDICTION RISK: POSSIBLE LINKS WITH CHILDHOOD TRAUMA AND PERSONALITY TRAITS, AO Kibitov, Serbsky National Medical Research Centre on Psychiatry and Addictions, Moscow, Russia

12.00-12.20 ***TECHNICAL BREAK***

12.20-15.00 **SYMPOSIUM 7: CONSOLIDATED POSTER SESSION PART 2**
Chairs: AV Kalueff (China, Russia, USA) and VM Klimenko (Russia)

INVESTIGATION OF THE LINKAGE OF FIN LENGTH AND SKIN COLOR WITH NEUROBEHAVIORAL PHENOTYPES IN ZEBRAFISH. PART II: THE SOCIAL PREFERENCE TEST. KN Zabegalov, AA Bashirzade, TG Amstislavskaya, AV Kalueff, Ural Federal University, Yekaterinburg, Scientific Research Institute of Physiology and Basic Medicine, Novosibirsk, Russia; Southwest University, Chongqing, China

INVESTIGATION THE LINKAGE OF FIN LENGTH AND SKIN COLOR WITH NEUROBEHAVIORAL PHENOTYPES IN ZEBRAFISH. PART III: MIRROR-INDUCED AGGRESSION TEST. KN Zabegalov, AA Bashirzade, TG Amstislavskaya, AV Kalueff, Ural Federal University, Yekaterinburg, Scientific Research Institute of Physiology and Basic Medicine, Novosibirsk, Russia; Southwest University, Chongqing, China

REGENERATIVE MEDICINE CELL QUALITY CONTROL SYSTEM "AICELEX", K Ito, M Koshiba, Graduate School of Science and Technology for Innovation, Yamaguchi University, Yamaguchi, Department of Pediatrics, Saitama Medical University, Saitama, Graduate School of Information Sciences, Tohoku University, Tohoku, Japan

SOCIAL BEHAVOIR COMPARISON OF DIFFERENT GLOFISH® ZEBRAFISH STRAINS: A PILOT STUDY. GO Maslov, CR Shakirova, AS Starodvorskaya, KN Zabegalov, AV Kalueff, Ural Federal University, Ekaterinburg, Institute of Translational Biomedicine, St. Petersburg State University, Russia; Southwest University, Chongqing, China

BIOCHEMICAL ASSESSMENT OF STRESS RESPONSES IN DIFFERENT GLOFISH® ZEBRAFISH STRAINS: A PILOT STUDY, KN Zabegalov, CR Shakirova, GO Maslov, T Mbutho, AS Starodvorskaya, AV Zhdanov, SL Khatsko, AV Kalueff, Ural Federal University, Ekaterinburg, Institute of Translational Biomedicine, St. Petersburg State University, Russia; Southwest University, Chongqing, China

AGGRESSIVE BEHAVIOR ASSAY OF DIFFERENT GLOFISH® ZEBRFISH STRAINS: A PILOT STUDY. CR Shakirova, AS Starodvorskaya, GO Maslov, KN Zabegalov, AV Kalueff, Ural Federal University, Ekaterinburg, Institute of Translational Biomedicine, St. Petersburg State University, Russia; Southwest University, Chongqing, China

HYPOLIPIDEMIC EFFECTS OF KRAMIZOLE ON THE EXPRESSION PDIA2 GENE IN THE RAT'S HYPERCHOLESTEROL DYSLIPIDEMIA MODEL, AV Lizunov, IV Okunevich, GP Kosyakova, LB Piotrovskiy, PD Shabanov, Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia

THE ROLE OF THE GRELIN SYSTEM IN REDUCING ANXIETY AND STABILITY OF THE PERIPHERAL BLOOD GENOME AFTER VITAL STRESS IMPACT, GP Kosyakova, AG Pshenichnaya, AV Lizunov, VE Mikhailova, IV Kazurov, PV Shalyapin, VA Lebedev, Institute of Experimental Medicine, St. Petersburg State University of Chemistry and Pharmacy, St. Petersburg, Russia

ANTIPARKINSONIAN ACTIVITY OF NEW N-METHYL-D-ASPARTATE RECEPTOR LIGANDS IN THE ARECOLINE HYPERKINESIS TEST, VD Dergachev, EE Yakovleva, MA Brusina, EV Litasova, ER Bychkov, LB, PD Shabanov, Institute of Experimental Medicine, St. Petersburg State Pediatric Medical University, Kirov Military Medical Academy, St. Petersburg, Russia

NEW SYNTHETIC COUMARINS DECREASE COMPULSIVE BEHAVIOR IN THE RAT MARBLE TEST, BB Daliev, M Kvasov, AA Lebedev, ER Bychkov, LV Myznikov, LB Piotrovsky, PD Shabanov, Institute of Experimental Medicine, St. Petersburg, Russia

NEUROPROTECTIVE EFFECT OF GALANTAMINE IN MALE RAT REPRODUCTIVE FUNCTION UNDER IMMOBILIZATION STRESS, EV Stashina, MA Ganzenko, AO Zelener, RN Magradze, AD Lisovsky, AA Bairamov, PD Shabanov, Institute of Experimental Medicine, St. Petersburg, Russia

EFFECTS OF IMMOBILIZATION STRESS ON SEXUAL BEHAVIOR OF MALE RATS EXPOSED PRENATALLY TO CHOLINOLYTICS, MA Ganzenko, EV Stashina, AO Zelener, AD Lisovsky, NSh Mamina, AA Bairamov, PD Shabanov, Institute of Experimental Medicine, St. Petersburg, Russia

INFLUENCE OF PRENATAL STRESS ON THE CONTENTS OF DOPAMINE AND SEROTONIN IN THE BRAIN OF RAT FETUS, MA Ganzenko, EV Stashina, RN Magradze, DE Fisenko, AA Bairamov, PD Shabanov, Institute of Experimental Medicine, St. Petersburg, Russia

CHOLINERGIC MODULATION OF SEXUAL BEHAVIOR AFTER STRESS: NEUROCHEMICAL CORRELATIONS, EV Stashina, MA Ganzenko, AO Zelener, AD Lisovsky, YaV Kozak, AA Bairamov, PD Shabanov, Institute of Experimental Medicine, St. Petersburg, Russia

GINSENOSIDES INFLUENCE THE EXPRESSION OF INNATE IMMUNITY GENES IN THE NUCLEUS ACCUMBENS OF BRAIN OF RATS AFTER PROLONGED ALCOHOL INTOXICATION, MI Airapetov, SO Eresko, ER Bychkov, AA Lebedev, PD Shabanov, St. Petersburg State Pediatric Medical University, St. Petersburg State University, St. Petersburg State Chemical and Pharmaceutical University, Institute for Experimental Medicine, Kirov Military Medical Academy, St. Petersburg, Russia

EFFECT OF OREXIGENIC PEPTIDES ON OVEREATING AND EMOTIONAL RESPONSES INDUCED BY SOCIAL ISOLATION IN RATS, ME Abrosimov, EA Vetlugin, AR Moskalev, AG Pshenichnaya, NR Evdokimova, VA Lebedev, ER Bychkov, AA Lebedev, SS Pyurveev, PD Shabanov, Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia

POST-CONFERENCE DAY
Wed, May 19, 2021

VISIT TO PAVLOV LABORATORY AND MUSEUM, INSTITUTE OF EXPERIMENTAL MEDICINE

ABSTRACTS

Day 1. Sun, May 16, 2021

Fireplace Hall (Kaminnyy Hall), Oktiabrskaya Hotel, 10 Ligovsky Prospect, St. Petersburg

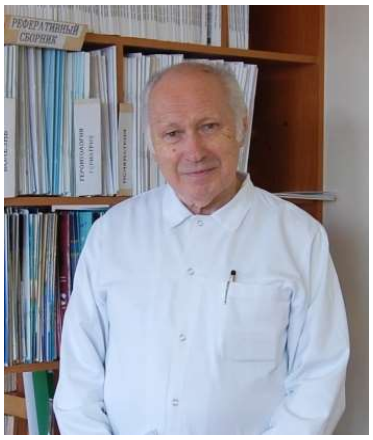
OPENING AND WELCOMING ADDRESSESS

Prof. AV Kalueff, ISBS President and Conference Chair
Prof. VM Klimenko, Program Committee Chair
Prof. OV Shamova, Deputy Director, Institute of Experimental Medicine

OPENING PLENARY LECTURE: BEHAVIORAL AND NEUROBIOLOGICAL CONSEQUENCES OF EXCESSIVE CONSUMPTION OF WESTERN DIET: A STUDY ON MICE. T Strekalova, Department of Psychiatry and Neuropsychology, University of Maastricht, Netherland, Sechenov 1st Moscow State Medical University, Moscow, Russia

SYMPOSIUM 1: LAPIN SYMPOSIUM ON PRECLINICAL NEUROSCIENCE

Chairs: AV Kalueff (China, Russia, USA) and VM Klimenko (Russia)



INTRODUCTION: PROFESSOR IZYASLAV LAPIN. This regular ISBS symposium is dedicated to Professor Izyaslav 'Slava' P. Lapin (1930-2012), a true pioneer of experimental neuro-psychopharmacology and biological psychiatry. Slava Lapin graduated from Pavlov Medical School in St. Petersburg, and shortly after receiving PhD, was invited in 1960 to establish the first psychopharmacology laboratory at the Bekhterev Psychoneurological Institute. The most important scientific contribution of Prof. Lapin was establishing the link between serotonin levels and mood-elevating (thymoleptic) action of antidepressants. He suggested that enhanced central serotonergic tone is essential for the mood-elevating effects of antidepressants. This serotonin hypothesis of antidepressant action, published (together with G Oxenkrug) in Lancet in 1969, became one the most cited papers published in this journal in the last 50 years. Lapin's studies have contributed greatly to the development of newest serotonergic antidepressants, such as SSRIs, currently representing the most prescribed group of psychotropic drugs in the world. Prof. Lapin was also the first to report the neuroactive effects of kynurenine and its derivatives – a discovery that opened another rapidly expanding area of glutamatergic psychopharmacology. A talented professional musician, prolific writer, painter, and an enthusiastic athlete, Prof. Lapin was a strong supporter of ISBS, and generously shared his knowledge with colleagues and students at our "Stress and Behavior" conferences and ISBS summer schools. His enthusiasm, friendship, generous support of junior colleagues, and the deep knowledge as both a clinical and experimental neuropharmacologist ('humanists' and 'animalists', as he called them), made a long-lasting impact on his colleagues and students. This ISBS symposium will continue Lapin's scientific legacy in the field of biological psychiatry and translational neuroscience.

TRANSGENIC ANIMAL MODELS IN NEUROPHARMACOLOGY. RR Gainetdinov, Institute of Translational Biomedicine, St. Petersburg State University, St. Petersburg, Russia

TONIC LOCUS COERULEUS ACTIVITY PLAYS A CAUSAL ROLE IN STRESS-ASSOCIATED INCREASES IN ALCOHOL DRINKING. EA Budygin, Wake Forest School of Medicine, Winston Salem, NC, USA

INTRODUCTION: The activation of brain stress systems is hypothesized to be a key component of the destructive emotional state produced by alcohol use disorders (AUD) that initiates alcohol seeking and intake through negative reinforcement mechanisms. It has been speculated for some time that norepinephrine (NE) release, which is enhanced by stress, might have a significant impact on alcohol-drinking behaviors. Indisputably, multiple studies have identified numerous neurochemical alterations in different brain circuits following stress and alcohol drinking. However, a major challenge has been to establish whether these changes play a contributory role in the triggering of alcohol-seeking and –taking behaviors. Previously, we used optogenetic methods to make a number of advances demonstrating how specific manipulations of the temporal characteristics of neurotransmitter release influence addictive behaviors. One important conclusion from these studies is that research should focus not only on the strength of neuronal signaling within distinct circuitry but also on the patterns of released neurotransmitter. Here, we used optogenetics to activate the locus coeruleus (LC)-NE circuitry in rats

during an operant alcohol self-administration test in order to reveal the role of distinct NE patterns in alcohol-drinking behavior. METHODS: In this work, we applied a viral technology to restrict the expression of Channelrhodopsin-2 (ChR2) to NE cells in the LC of Long Evans rats. Fast-scan cyclic voltammetry was used to confirm that the level of the expression was sufficient to mimic tonic (stress-associated) and phasic patterns of NE release in the brain. Optogenetically-evoked NE was identified by the background-subtracted cyclic voltammograms and pharmacologically confirmed. Alcohol-seeking (or motivational) and –taking behavior was evaluated using an operant drinking paradigm that procedurally separates appetitive and consummatory components of alcohol drinking. RESULTS AND DISCUSSION: The data clearly indicate that viral-mediated gene delivery can be successfully used to express ChR2 on NE cell bodies in Long-Evans rats. The expression level allowed us to manipulate real time NE release in terminal fields, including the prefrontal cortex and basolateral amygdala through the LC optostimulation. Combining this approach with an operant alcohol-drinking paradigm, we revealed that optostimulating the LC NE circuit with tonic pattern significantly increased alcohol intake, while phasic activation resulted in a decrease of this measure. Furthermore, stimulation during extinction trials, when the lever press response was not reinforced, did not alter alcohol-seeking behavior if a tonic pattern was applied. However, phasic stimulation significantly suppressed the number of lever presses, indicating decreased alcohol seeking under the same experimental condition. These findings may guide future studies looking to pharmacologically or nonpharmacologically (transcranial magnetic stimulation, deep brain stimulation) manipulate NE release dynamics in order to treat AUD, especially in the common condition where there is also a comorbid anxiety/stress disorder. RESEARCH SUPPORT: This Research was supported by NIAAA grant AA022449.

APPROACHES TO PARALLEL MODELING NEUROBIOLOGICAL CONDITIONS IN COMPLEX CELLULAR AND ANIMAL MODELS. EV Petersen, Moscow Institute of Physics and Technology, Moscow, Russia

EFFECT OF MELANOCORTIN RECEPTOR AGONISTS ON SEXUAL MOTIVATION IN RATS AFTER CHRONIC SOCIAL ISOLATION, IY Tissen, LA Magarramova, MD Ayzup, AA Lebedev, PD Shabanov, Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia

INTRODUCTION: Social isolation in early life deregulates reproductive function by disruptig homonal and neuronal mechanisms. Melanocortins are a group of small protein molecules that share the same precursor molecule, POMC (proopiomelanocortin) including ACTH, the melanocyte-stimulating hormones (α-MSH, β-MSH and γ-MSH), β- and γ-lipotropin, and β-endorphin. Five melanocortin receptors have been identified that are associated with such diverse biological functions as skin pigmentation, food intake, the sleep–wake cycle and sexual response. Investigations into the role of the melanocortin system on sexual response has focused on the melanocortin 3 (MC3R) and melanocortin 4 (MC4R) receptors in the CNS. There is abundant expression of both MC3R and MC4R in the brain and in peripheral genital sensory outputs. The aim of this study was to examine the effects MC3R and MC4R agonists on sexual motivation in male rats after chronical social isolation. MATERIALS AND METHODS: Wistar males (n=40) were used, into 4 groups. Animals in the first group were intact. In the other groups, the rats were housed in full social isolation since the 17th up to 100 days. Control animals were administrated with saline while the remaining groups were administrated with MC3R, MC4R agonist PT-141 0.3μg intraperitoneally and selective MC4R agonist THIQ 0.1μg intranasally. Open-field reward-proximity chamber was used for assessment of sexual motivation. The chamber construction allowed the subjects to investigate estrous female but prevented copulation. Behaviour was registered in the dark room with red light for 10 minutes. RESULTS: Social isolation did not significantly act on latent time before trying to reach the female (11.2±9.6 sec. vs 8.0±4.5 sec. in control) but decrease number of trying to reach female (8.7±3.5 vs 13.8±3.1 in control) and time spent near the female cage (62.8±18.3 sec. vs 142.2±43.2 sec. in control). Isolated animals didn't shown any genital area grooming acts. Both PT-141 and THIQ reduced latent time (3.2±1.7 and 4.1±0.9 sec). Both PT-141 and THIQ induced genital area grooming (7.5±3.5 PT-141, 9.1±3.9 THIQ vs 2.2±0.3 in control). Only PT-141 induced trying to reach the female (16.7±3.5). Only PT-141 increased time spent near female chamber (137.2±58 sec.) CONCLUSION: These data show that the effect of social isolation affects sexual motivation. Effects of non-selective MC3R and MC4R agonist PT-141 and selective MC4R agonist THIQ show that melanocortin receptors are involved differently in motivation and executive components of sexual behavior. This provides the preconditions for finding new mechanisms underlying the regulation of reproductive behavior and the effect of stress factors on its realization. KEY WORDS: social isolation stress, melanocortins, sexual behavior

MOLECULAR MECHANISMS OF SUPPRESSION OF THE PROGRESSION OF FUS PROTEINOPATHY IN THE NERVOUS SYSTEM OF TRANSGENIC MICE EXPRESSING C-TERMINALLY TRUNCATED HUMAN FUS, EA Lysikova, S Funikov, AP Rezvykh, KD Chaprov, Institute

of Physiologically Active Substances RAS, Chernogolovka, Engelhardt Institute of Molecular Biology RAS, Moscow, Russia

Malfunction of DNA/RNA-binding protein FUS causes certain forms of amyotrophic lateral sclerosis. A transgenic mouse line, tg_hFUS[1-359], with the expression of a highly aggregation-prone C-terminally truncated form of human FUS (FUS 1-359) reproduce ALS phenotype with the early lethality. After four generations of backcrossing with CD1 mice a new L-FUS[1-359] line with an increased lifespan and the absence of the ALS phenotype was produced. RT-PCR analysis revealed a similar number of tandemly arranged copies of the same transgenic cassette in both lines. However, in L-FUS [1-359] mice the level of human FUS expression and the content of the pathogenic form of the FUS protein in neurons was significantly reduced. The low level of aberrant FUS is not sufficient for triggering ALS phenotype and can be successfully compensated by certain intrinsic defense mechanisms of motor neurons. The genome-wide RNA sequencing of the spinal cord transcriptomes of L-FUS [1-359] mice and a bioinformatic analysis revealed set of differentially expressed genes encoding proteins involved in important biological processes: cell adhesion, organisation of extracellular matrix, protein folding, regulation of neuronal differentiation. This suggests that motor neurons successfully employ certain intracellular defence systems that prevent damaging effects of the pathogenic protein when its level is still low. The original tg_hFUS line [1-359] is actively used as a test model for the new compounds that might be potential therapeutics for ALS. We performed analysis of the spinal cord transcriptomes of tg_hFUS [1-359] mice after 5 week administration of the DF402 compound, a bioisoster of the drug Dimebon (Latrepiridine). DF402 was diluted to a final concentration of 70 μg/ml in drinking water and the approximate dose for the experimental animals were 15 mg/kg/d. Groups of genes were revealed, expression of which under the action of the DF402 treatment tended to the normal level of wild-type animals. In particular, these genes encoding proteins involved in the regulation of transcription. All RNA sequencing data from the spinal cord tissues of mice were confirmed by real-time PCR. Transgenic animals were provided and supported by Bioresource Collection of IPAC RAS and Centre for Collective Use IPAC RAS facilities and equipment was used to maintain animals in the framework of the State Assignment of IPAC RAS (No. 0090-2019-0005).

SEROTONIN METABOLISM IN GENETICALLY DETERMINED DOPAMINE METABOLISM DISORDERS, DS Traktirov, NS Pestereva, ZS Fesenko, IS Ivleva, MN Karpenko, VM Klimenko, Institute of Experimental Medicine, Peter the Great St. Petersburg Polytechnic University, St. Petersburg State University, Institute of Translational Biomedicine, St. Petersburg, Russia

INTRODUCTION: Dopamine and serotonin (5-HT) are two important neurotransmitters that play a crucial role in the regulation of the central nervous system. There are few reports on the interaction of these neurotransmitter systems at the neurochemical level in literature. The aim of this work was to study changes in the serotonin system, such as increased brain area-dependent changes in 5-HT and 5-HT turnover rates, and changes in the mRNA content of enzymes involved in 5-HT metabolism in rats with genetically determined dopamine metabolism disorders – DAT -/- rats (dopamine transporter (dat) gene knockout). METHODS: Adult male rats, 220–250 g, were used in this study. The experimental group consisted of 5 male DAT -/- rats. The control group consisted of Wistar rats (n = 5). HPLC-ED measured the level of 5-HT and 5-HIAA (its metabolite) in the different structures in CNS. The mRNA levels of MAO-A (enzyme, which metabolizes serotonin to 5-Hydroxyindoleacetic acid – 5-HIAA) were measured by RT-PCR. The presented data as experiment/control (relative units) ± SD, statistical analysis was applied with T-test, the differences were considered significant when p is less than 0.05. RESULTS AND DISCUSSION: There were found 30% decreasing of 5-HT level with a simultaneous increasing 5-HIAA level by 3.8 times (0.8±0.2 vs 3.2±0.5, p=0.002) in striatal cells of DAT-/- rats, also, we detected a 6-fold decrease mRNA of MAO-A. In the hippocampus was shown a 1.8-fold increase of 5-HIAA. The most pronounced changes were observed in the cerebellum: DAT-/- rat's level of 5-HT decrease by 12 times in comparison with DAT+/+ rat's level (0.07±0.01 vs 0.92±0.03, p=0.007) with unchanged 5-HIAA level. In the medulla oblongata the amount of 5-HT was lower than the level of detection, while in the control it is 0.6 ± 0.3. The most pronounced changes of MAO-A mRNA were observed in the cervical spinal: DAT-/- rat's level increase more than 6 times in comparison with control's level; was shown a 2-fold decrease of 5-HIAA. There was 5-fold decrease of MAO-A in the mesencephalon. CONCLUSION: a genetically determined disorder of dopamine metabolism leads a violation of serotonin metabolism. RESEARCH SUPPORT: The reported study was funded by RFBR, project number 19-34-90030.

ARE PAIN AND ANXIETY INTERCONNECTED SIGNALS OF HUMAN DISEASE? AS Tadevosyan, A Avetisyan, Heratsi Yerevan State Medical University, Yerevan, Armenia

INTRODUCTION: Pain and anxiety are two phenomena that for centuries have been viewed as separate signals of a health disorders. Pain specialists, studying pain, and psychiatrists studying anxiety disorders reviewed them separately. Recently, the slogan has become - "life - without pain." Our approach is

different - these phenomena are interconnected and interdependent, with an interchanging causes and effects. Pain and anxiety, depending on factor analysis, can be [1]indicators of health and illness. METHODS: Three groups of patients were analyzed: Group 1- patients with chronic back pain pain, Group 2 patients with paroxysmal acute short acting pain of different localization with a duration of symptoms more than 3 years; and Group 3 consisted of patients with phantom type of pain. We performed comparative analysis of the frequency of stressors and the qualitative characteristics of pain. RESULTS AND DISCUSSION: In the first group, there was a correlation between dull, aching pain and stressful life, especially in the last 5 years. This was more prevalent in women. In Group 2 no relationship was found between acute pain and the number of stressful life events, found. Patients in this group described pain as "acute, strong, like the first time" despite the fact that they have been suffering from this disease for more than one year. The pain had a real cause, but it happened in the past, once, and in a specific place.

ISBS AND BIOLOGICAL PSYCHIATRY OF STRESS TODAY, IN THE YEAR OF SCIENCE. AV Kalueff, Southwest University, Chongqing, China

UNDERSTANDING TRANSLATIONAL AND EVOLUTIONALLY CONSERVATIVE MOLECULAR BIOMARKERS OF AFFECTIVE DISORDERS IN THE ZEBRAFISH, RAT AND HUMAN. KA Demin, AV Kalueff, Institute of Translational Biomedicine, St. Petersburg State University, Institute of Experimental Medicine, Almazov National Medical Research Centre, Ministry of Healthcare of Russian Federation, St. Petersburg, Neuroscience Program, Sirius University, Sochi, Russia; Southwest University, Chongqing, China

INTRODUCTION: Affective disorders are widespread, debilitating and often treatment-resistant illnesses that represent an urgent, but unmet biomedical problem. Animal models of these disorders are widely used to study affective pathogenesis, often utilizing chronic stress protocols, such as chronic unpredictable stress (CUS) model. CUS typically exposes an animal to varying stressors for several weeks and evoke anxiety- and/or depression-like behavior in many vertebrates, including rats (Rattus Norvegicus) and zebrafish (Danio rerio). At the same time, the findings observed in animal models of psychiatric disorders often badly recapitulate the molecular and physiological nature of disorder observed in human and lack good translational and pharmacological reproducibility. Here we argue, that while severe differences exist between fish, rodents and human in terms of affective pathology, the evolutionally conservative pathological cascade remains between the species. Such cascade may allow us to target the “core” pathogenesis of affective pathology in vertebrates and more effective use of animal models if being properly targeted. We test our hypotheses comparing gene expression, gene set expression, and transcription factor analysis in human subiculum of hippocampus, rats hippocampus and zebrafish whole-brain. METHODS: Wild-type adult zebrafish (n=6, 1:1 sex ratio) and Wistar male rats (n=3) were subjected to CUS protocols reported elsewhere. Behavioral validation proven existence of anxiogenic- and depression-like phenotypes in both species. Brains were dissected on ice following standard procedures, and hippocampus was dissected from the whole brain of rats. isolation was made with TRI-reagent according to manufacturer instructions. Quality was checked with Quantus, electrophoresis, and QIAxel. Sequencing was performed on Illumina HiSeq2500 with 140 bp paired-read (zebrafish) and HiSeq4000 with 151 bp paired-read (rat), with at least 20 million reads generated for each sample. Human RNA-seq postmortem subiculum samples were taken from PRJNA398031 NCBI BioProject. Only male samples of control and MDD patients that did not receive any treatment and died from natural and accident causes were considered in the study, resulted in n=3. Samples were sequenced at 50 bp paired-read on Illumina HiSeq2500. Reads were mapped to zebrafish GRCz11, rat Rnor_6.0 and human GRCh38 using RNA STAR and further processed in featureCounts (usegalaxy.org). Counts were analyzed using the R software. Deseq2 package was used for differential gene expression (DE) analyses and generally applicable gene set enrichment (GAGE) package was used for gene sets analyses. Finally, CiiiDER software was used for transcription factors (TF) site analyses. We used 3 different approaches to compare RNA seq data between species. (1) qualitative comparison of DE and enriched sets between different analysis for each species analyzed separately; (2) Intraspecies comparison of stress/mdd vs. control effects using counts mapped 1 to 1 to 1 to human orthologues in unified form; (3) Intraspecies comparison of stress/mdd vs. control effects using counts map to human orthologues in 3 different studies for each species, compared using Meta-Analysis approach. All statistical analyses were implemented in a similar manner for every species. The results were further compared using Homologene and String data for qualitative comparison and hub genes determination in Cytospace. RESULTS AND DISCUSSION: Overall, we identified multiple genes and gene sets corresponding to a pathological condition in zebrafish, rats and human simultaneously. Technics were substantially different in terms of sensitivity to gene or sets comparison and led to partially different results. The study was severely complicated due to high heterogeneity of intraspecies expression data, accounting for 96% of variance using Principle Component Analyses in study 2. At the same time, all approaches identified some evolutionally conservative characteristics. Among DE genes

and differentially represented factors we identified two upregulated (FEZF2 and IKZF1) and 5 downregulated (FLI1, ARNT, ERG, USH2A and LDLR) “hub” proteins in the PPI network constructed from DE found using Meta-analysis approach and altered TF. Importantly, most altered DE and TF are highly expressed in microglial cells. Furthermore, most DE and TF that are highly specific for neurons were connected only though FEZF2-NEUROG6 link, supporting strong astrocytic effects on neuronal nodes. The use of zebrafish whole-brain and both sexes data may mask some differences correspond to region dependent changes. At the same time, note that human vs. rat comparison does not reveal substantially more similarities, thus not supporting this limitation. Finally, our findings implicate existence of complex interaction between different cell types in affective pathology development among different vertebrates and especially the role of FEZF2, IKZF1 and NEUROG6 in the disorders. RESEARCH SUPPORT: The research was supported by the Russian Science Foundation (RSF) grant 19-15-00053. The laboratory is supported by SPSU state budgetary funds ID 73026081, Almazov National Medical Research Centre, and Russian Scientific Center of Roentgenoradiology.

THE ROLE OF SYNUCLEINS IN BEHAVIORAL IMPAIRMENT MEDIATED BY COMPROMISED DOPAMINE TRANSMISSION. KD Chaprov, IuS Sukhanova, Institute of Physiologically Active Compounds RAS, Chernogolovka, Russia

INTRODUCTION: Synaptic transmission of nerve impulses by dopamine (DA) is utilised by many neural networks, influence the establishment and reinforcement of pathological dependencies and cognitive disorders, and its disruption leads to the development of severe mental and neurological disorders. Synuclein protein dysfunction associated with Parkinson's disease (PD), dementia with Lewy body (DLB), multiple system atrophy (MSA) and certain types of addiction, including alcohol addiction. Compromised DA neurotransmission in the dorsal striatum is the main cause of clinical symptoms typical for Parkinson's disease. Synucleins are implicated in the optimization of DA neurotransmission and inactivation of all three synucleins decrease the level of DA uptake by synaptic vesicles and also affects both vesicular endocytosis and exocytosis. It is widely accepted that the remaining member(s) of the synuclein family can compensate for the loss of function of one or even two family members, because of high structural similarity within the family. To further our understanding of the role of synucleins in synaptic transmission in the intact nervous system, a novel synuclein-free mouse line (triple knockout – abg-KO) that we produced on the background of a new alpha-synuclein (SNCA) knockout (a-KO) mouse line was studied in a set of behavioral tests. In contrast to all previously produced SNCA knockout mouse strains this new mouse a-KO line has no foreign sequences apart of a single loxP site in the modified genomic locus. METHODS: We compared behavioral characteristics of new synuclein-free mice (abg-KO) line compare with wild type (WT) mice. Changes in motor function of young (6-month old) and ageing (13 months) animals were analyzed using basic motor tests: «Grip strength», «Inverted grid» and «Accelerating rotarod» tests. Cognitive analysis in «Open field», «Novel object recognition», «Y-maze», «Morris water maze» tests was performed on 13-month old mice. RESULTS AND DISCUSSION: In motor performance tests 6m and 13m abg-KO mice displayed increased endurance but the strength of their grip was weaker than that of WT mice. New abg-KO animals showed same hyperactive phenotype in multiple cognitive and activity tests, which is consistent with our previous results on synuclein-free mice (triple knockout) produced on the background of widely used SNCA knockout strain Ab-KO. Cognitive tests in 13m age shows that the absence of all synuclein family proteins does not affect short-term memory formation and learning ability in general but has an effect on memorization rate and motor activity. RESEARCH SUPPORT: Behavioural studies were supported by RFBR (Grant 19-315-90049). Phenotype characteristic was supported by RSF (Grant 19-14-00064).

MATERNAL HYPERHOMOCYSTEINEMIA LEADS TO NEUROINFLAMATORY PROCESSES IN RAT HIPPOCAMPUS DURING THE FIRST MONTH AFTER BIRTH, INDUCING MEMORY DEFICIT IN ADULTS. DS Vasilev, NL Tumanova, AD Shcherbitskaia, DS Kalinina, NM Dubrovskaya, Sechenov Institute of Evolutionary Physiology and Biochemistry RAS, St. Petersburg, Russia

INTRODUCTION: The action of different stressors during pregnancy leads to various complications both in the maternal organism and developing fetus increasing risk of abnormal brain development and functioning via disturbance of the essential trophic factors balance. In this study we examined the effects of maternal hyperhomocysteinemia (HHC) on glial cells in dorsal hippocampus as well as on behavior of rat offspring. We investigated the distribution of neuron- and glia-specific marker proteins, ultrastructure of neuronal cells during the first month after birth. METHODS: HHC was induced in female rats by per os administration of 0.15% aqueous methionine solution (0.10-0.15 g per animal) in the period of days 4-21 of pregnancy. The hippocampus structure was investigated in rat pups. The distribution of neuronal (Fox3), astrocyte (GFAP) and microglia (Iba1) marker proteins in CA1 zone of hippocampus were analyzed by immunohistochemistry. The ultrastructure of cells was studied using FEI Tecnai V2 (FEI, USA) transmission electron microscope. We tested spatial memory of adult male offsprings using the Morris water maze test. RESULTS AND DISCUSSION: Adult rat offspring from HHC group were

characterized by worst performance in Morris water maze test, compared naive control, suggesting some memory impairment. In CA1 area of hippocampus of HHC pups the number of pyramidal neurons was decreased; the number of astrocytes and microglia cells was increased both on P5 and P20. The electronic microscopy of the CA1 hippocampus tissue of HHC pups on P5-P20 showed increased number of neuronal cells with lysis of the cell organelle, clustered lysosomes and autophagosoms in cell body and processes. In glial cells the increased number of phagosome and lysosomes suggested their activation. The proinflamatory cytokines content was increased indicating the possibility of the neuroinflamation. The data obtained suggest that maternal HHC affects hippocampus structure in early postnatal ontogenesis leading to memory deficit in adulthood. RESEARCH SUPPORT: RFBR 20-015-00388 and Russian state budget assignment AAAA-A18-118012290373-7.

REFERENCE GENE VALIDATION WITHIN THE RAT BRAIN UNDER MILD KETOSIS. AP Schwarz, AS Shcherbakova, VA Nikitina, DU Krytskaya, AN Trofimov, VM Klimenko Institute of Experimental Medicine, Sechenov Institute of Evolutionary Physiology and Biochemistry RAS, St. Petersburg, Russia

INTRODUCTION: RT-qPCR have become the gold standard in gene expression analysis. However, it requires an accurate choice of reference genes for adequate normalization. This work aims to validate the reference genes for qPCR experiments in the brain of rats in the model of mild ketosis established through supplementation with medium-chain triglycerides (MCT) and intermittent fasting. METHODS: The standard chow of adult Wistar rats was supplemented with MCT oil (2 ml/kg, i.g. after 6 hr fasting) or water (equivolume) for 1 month. The mRNA expression of 9 housekeeping genes (Actb, B2m, Gapdh, Hprt1, Pgk1, Ppia, Rpl13a, Sdha, Ywhaz) in the medial prefrontal cortex (mPFC), dorsal (DH) and ventral (VH) hippocampus were measured by RT-qPCR. The expression stabilities of the reference genes were analyzed using the RefFinder® online tool. RESULTS AND DISCUSSION: The reference gene stability ranking strongly depended on the analyzed brain region. The most stably expressed reference genes were found to be: Ppia, Actb, and Rpl13a in mPFC; Rpl13a, Ywhaz, and Pgk1 in DH; Ywhaz, Sdha, and Ppia in VH. The B2m was identified as an invalid reference gene in VH, while Sdha, Actb, and Gapdh were unstable in DH. The stabilities of the examined housekeeping genes were lower in DH compared to VH and mPFC. Thus, the expression stability of reference genes strongly depends on the examined brain regions. The dorsal and ventral hippocampal areas differ in reference genes stability rankings, which should be taken into account in the RT-qPCR experimental design. RESEARCH SUPPORT: This work is supported by the Russian Science Foundation, grant no. 19-75-10076.

DELAYED EFFECTS OF CHRONIC SLEEP RESTRICTION ON MEMORY AND EMOTIONALITY IN RATS. MV Chernyshev, MA Guzeev, VD Borschenko, IV Ekimova, Sechenov Institute of Evolutionary Physiology and Biochemistry RAS, St. Petersburg, Russia

INTRODUCTION: It is well known that lack of sleep exerts a negative effect on many important processes in CNS, resulting in cognitive deficit and emotional disorders. However, postponed consequences of the sleep deficit have not been well monitored yet and remain unclear in both humans and animal models. This research aims to reveal delayed effects of chronic sleep restriction (SR) on cognitive functions and emotional behavior in rats. METHODS: Experiments were carried out in male Wistar rats. Sleep restriction was performed using an orbital shaker by a cyclic protocol during a day (sleep deprivation (3 h) / opportunity (1 h)) for 5 consecutive days. A battery of tests for emotionality was used since 10-th day to 12-th day after the end of SR: elevated plus maze (anxiety-like behavior), open field (locomotion), forced swim (depressive-like behavior). A battery of tests for memory was used since 7 to 17 day after the end of SR: Y-maze (spatial working memory), Morris water maze (spatial working and reference memory), novel object recognition (non-spatial long-term memory). RESULTS AND DISCUSSION: The used battery of tests for emotionality revealed no effect of chronic SR. No effect of SR was found in the water maze test when examined reference memory. However, SR group exhibited impaired learning in detection time of reaching the platform during training days compared to control group. Surprisingly, using the paradigm of working memory assessment in this test elicited an increase in the number and time of entries into the platform zone in rats of SR group that indicates an enhancement in the memory. This result is consistent with the data obtained in the Y-maze test displayed an increase in spontaneous alternations that also demonstrate an enhancement in working memory. In contrast, novel object recognition test detected negative effect of SR on non-spatial long-term memory – rats of SR group exhibited a decrease in time of exploration of a novel object. The results of the experiment showed that chronic SR procedure followed by the delay does not alter emotional behavior related to locomotion, anxiety an depression. However, this SR procedure is capable to disrupt memory processes resulting in the opposite effects. Elicited an enhancement in spatial working memory may be considered as a compensatory response to an emerged attenuation non-spatial long-term memory. Therefore, this phenomenon should not be evaluated as a positive fact of delayed consequence of sleep deficit, since the whole process of learning was impaired. RESEARCH SUPPORT: This work was supported by the Ministry of Science and Higher Education of the Russian Federation grant (No. 075-

15-2020-916 dated November 13, 2020) for the establishment and development of the Pavlovsky Center “Integrative Physiology for Medicine, High-Tech Healthcare and Stress Resilience Technologies”.

TEMPORAL ANALYSES OF DRUG-INDUCED LOCOMOTOR ACTIVITY IN ZEBRAFISH BASED ON NEURAL NETWORK PREDICTIONS. DV Bozhko, GK Galumov, AI Polovjan, SM Kolchanova, VO Myrov, AV Kalueff, ZebraML, St. Petersburg, Russia; Neuroscience Center, Helsinki Institute of Life Science, University of Helsinki, Helsinki, Department of Neuroscience and Biomedical Engineering, Aalto University, Helsinki, Finland; School of Pharmacy, Southwest University, Chongqing, China

INTRODUCTION: Aquatic models, such as zebrafish (Danio rerio) represent a valuable tool to analyse neural, pharmacological and genetic underpinnings of behavior. Zebrafish models are rapidly emerging as a critical tool in translational CNS disease modeling and drug discovery, with high potential for high-throughput drug screening. There are multiple applications of neural networks in translational neuroscience. For example, they can help identify novel “biomarker” motor phenotypes that cannot be visually identified by experimenters, or those that have not yet been reported. Temporal characteristics of effects of CNS drugs represent a critical aspect of their biological activity. In this project, we took advantage of convolutional neural network-based algorithms and a convenient model organism to study temporal predictions for various psychotropic substances in order to detect similarities in movement patterns in a precise time scale manner. METHODS: In the present study we applied a convolutional neural network (CNN) approach to an extensive dataset of adult zebrafish locomotor tracks. Locomotor tracks of adult zebrafish were obtained by video recording fish exposed to different concentrations of various CNS-affecting psychotropic drugs with well-established pronounced in vivo CNS and behavioral effects and distinctive drug-specific features (e.g. MDMA, nicotine, LSD). Raw data were collected in Prof. Kalueff’s laboratory using Noldus Ethovision software recorded in the novel tank apparatus. First, we trained the CNN for track classification in multi-class and two-class experiments. To achieve better generalization we cut the tracks into short frames of 30s and augmented them with random rotations and shifting. Based on the results of neural network testing procedure, we calculated the most probable class label for each frame. Each prediction was then compared with the actual class label (drug or dose). Afterwards, we determined the most probable drug prediction (a class with the maximum number of predicted samples) for each timeframe. RESULTS AND DISCUSSION: The developed algorithm has the ability to distinguish behavioral patterns between different CNS drugs and different concentrations of the same drug in an exact exposure time frame. Our method correctly classified locomotor tracks of fish treated with MDMA, nicotine, arecoline and PCP (prediction accuracy >80%). Temporal predictions for nicotine as ‘arecoline’ were uniformly matched: there were no delayed effects or early “sober-ups”. Temporal predictions for MDMA as ‘arecoline’ showed an increase of 120 mg/L dosage predictions closer to the 5 min time frame. Use of the temporal predictions approach in novel drug screenings will help identify similarities between action profiles of tested drugs not only in the experiment as a whole, but also for every point in time. Using longer (20 min plus) experiments we can identify dose-dependent biphasic switches in the locomotor activity. Temporal analyses combined with neural networks approach will help accelerate preclinical research, mitigate human errors in interpretation of drug screening experiments on zebrafish, reveal shortcomings of experimental settings and methodology.

CONFERENCE PRESENTATION: SOCIABILITY TEST IN MICE USING LABORAS AND SONOTRACK SYSTEM. L Bachdasarian, R Bulthuis, Metris BV, Hoofddorp, Netherlands

INTRODUCTION: Several neuropsychiatric disorders are characterized by disruptions in social behavior and social recognition or social memory including depression, stress, PTSD, anxiety, autism spectrum disorders, bipolar disorders, obsessive-compulsive disorders, psychoses and schizophrenia. In laboratory tests Sociability in mice is often investigated by comparing different mouse strains such as C57BL/6J, DBA/2J and FVB/NJ and CD-1, having different genetic backgrounds and social behavior. Various pharmacological studies have also investigated the effect of dissociative drugs (such as PCP) to deteriorate social behavior and psychostimulant drugs (amongst others MDMA) to ameliorate decreased social behavior by diminishing responses to threatening stimuli and enhancing responses to rewarding social signals. Integrative research using appropriate animal models and tests for social behavior may lead to the development of improved treatments for social psychopathologies.
The Sociability Test provides a method to evaluate two important but distinguishable aspects of social behavior of the subject mouse: social affiliation/motivation, as well as social memory and novelty. METHOD: The LABORAS Sociability Cage consists of a standard Type-3 home cage which is divided in 3 chambers using two walls with sliding doors that control access to the left and right chamber. The left and right chamber each contains a cylinder in which another (familiar or unfamiliar) mouse can be introduced. Usually the Sociability Test consists of one of the following protocols: 1) The cylinder in one chamber contains an unfamiliar conspecific (stranger 1) and the cylinder in the other chamber is empty (Sociability preference) 2) In the second phase, the now familiar conspecific (stranger 1) is introduced in the cylinder of one chamber and a second unfamiliar conspecific (stranger 2) is introduced in the

(initially empty) cylinder in the other chamber (Preference for Social novelty) 3) As a variation on protocol 1 and 2, two unfamiliar conspecifics (strangers) can be introduced from the start in each of the cylinders in the left and right chamber. The unfamiliar conspecifics (strangers) in the Sociability test can be a different strain of mice and also variations in genetics, age, gender or mice with special disorders can be used as part of the social behavior test protocols. The test subject is introduced in the center chamber which serves as a neutral starting point of the test. RESULTS: In LABORAS the mouse cannot leave the center chamber before the doors are opened. This allows the researcher to precisely choose the start moment of the Sociability Test. After opening the doors LABORAS determines the following parameters: the number of each chamber and each contact zone, the time spent in each chamber and each contact zone, the latency time to left and right chamber and left and right contact zone. The size of the contact zone can be adjusted in the LABORAS software.
LABORAS makes it possible to collect data of up to 8 Sociability Cages at the same time. To enable this kind of higher throughput testing, the LABORAS system allows individual start of each LABORAS platform which gives the animal technician ample time to prepare and start each Sociability Cage. LABORAS provides also additional information including position tracking and behavioral data and can be easily combined with our Sonotrack Ultrasonic Vocalization measurement equipment, which can strengthen the application of the Sociability Test. Metris developed the first software that enables fully automatic classification of Ultrasonic Vocalizations of mice in 15 distinct categories based on spectral properties of the sound. In addition, the software calculates a large number of bio acoustic parameters that can be used to further profile each call and its syllables. Automatic call classification enables detailed analysis of very long recordings. Automatic analysis of Ultrasonic Vocalizations (USV) of mice is also expected to lead to more standardized and better definitions of the vocalizations. Based on this, larger databases can be built up which are crucial in developing new animal models for investigating complex social behavior and emotional parameters. CONCLUSION: Current trends in the Pharmaceutical industry requires new translational approaches for pre-clinical test. Those aspects can be achieved by animal experiments in which not only one variable (e.g. one behavior) at the time is analyzed but rather a multidimensional approach (physiology +several behaviors + Ultra Sounds Vocalization + different parameters from study) is applied. Therefore, automation and integration of different measuring technologies become the crucial aspects in this process. The behavioral tests that are used in the ASD animal models studies, are not always of procedural standard. Furthermore, contradictive results have been found. Standardizing procedures is important in this field of research. However, these experiments should be designed in a way that the animal is minimally restricted in performing its natural behavior, therefore Stress-free collection of continuous rodent behaviors and constant environmental conditions are crucial.

ISBS SYMPOSIUM 2: ZUKOWSKA STRESS NEUROSCIENCE SYMPOSIUM

Chairs: VM Klimenko (Russia)

INTRODUCTION: PROFESSOR ZOFIA ZUKOWSKA. Prof. ZOFIA M. ZUKOWSKA (1949-2012) received her M.D. and Ph.D., trained in cardiovascular medicine at the Warsaw Medical Academy (Poland). She pursued post-doctoral training at the NIH, working with such renowned scientists as Irwin Kopin, Scientific Director of NINDS, and Julius Axelrod, a Nobel Laureate. During this research period, her interest in stress and neuropeptides became galvanized. For the 25 years, she was a professor (and, later Chair) of the Department of Physiology and Biophysics at Georgetown University, before moving to the University of Minnesota as the Director of Stress Physiology Center. Her research examined how stress affects cardiovascular and metabolic health and diseases, and the role of peptides, in particular neuropeptide Y (NPY), a sympathetic neurotransmitter and stress mediator. She was the first to determine that NPY mediates stress-induced prolonged vasoconstriction and vascular mitogenic and pro-atherosclerotic effects (via Y1 receptors) and potent angiogenic actions (via Y2 receptors), establishing the role of NPY in ischemia, retinopathy, tumors and obesity. Professor Zukowska (or Zosia, as she was known and admired by many) was a good friend and a strong supporter of the ISBS, serving as a regular plenary speaker at our conferences. Her scientific vision, extraordinary creativity, kindness to colleagues, and the talent to be daring, continue to inspire all her ISBS colleagues and their research. This regular ISBS symposium continues Zofia's scientific legacy in the field of biological psychiatry of stress.

MOTOR ACTIVITY DURING SWIMMING AND WALKING IN THE TAAR5 KNOCKOUT MICE, AV Goriainova, DS Kalinina, RR Gainetdinov, PE Musienko, Institute of Translational Biomedicine, St. Petersburg State University, Sechenov Institute of Evolutionary Physiology and Biochemistry RAS, Pavlov Institute of Physiology RAS, St. Petersburg, Sirius National Technical University, Neuroscience Program, Sochi, Russia

INTRODUCTION: Trace amines (TA) are biogenic substances, which structurally and metabolically are similar to classical monoamines, but their concentration is about 100 ng/g of tissue. Nevertheless, TA and their receptors called trace amine associated receptors (TAARs) may modulate different functions of nervous systems. Particular interest to them in recent years is due to their ability not only modulate the action of monoamines and can be expressed together with their transporters and receptors. Today 15 types of trace amine associated receptors have been identified, but their role in sensorimotor functions is not fully understood [1]. This study investigates the role of the type 5 receptor (TAAR5) in motor control in various types of locomotion. METHODS: The work was carried out on mice with a knockout gene (TAAR 5 KO) encoding the expression of this receptor (n = 7) and WT mice (n = 6). Behavioral tests were performed after implantation of recording electrodes into m. tibialis anterior (L_TA) of the left hind limb and recovery period. Locomotion was assessed during walking on a flat surface, on a regular horizontal ladder (1 cm between rungs) and under conditions of water immersion (swimming). In all tests we used the same parameters of installations - 50 cm long and 10 cm wide. The swimming installation was filled water of a temperature of 37 °C and was 25 cm deep. We analyzed the locomotor parameters as the duration of the phases of the gait cycles (swing, stance), the duration of retraction (extension) and protraction (flexion) during swimming, and the duration of intra- and inter- burst interval of L_TA. RESULTS AND DISCUSSION: It was found that the duration of L_TA bursts was shorter ($p < 0.05$) in knockout mice relative to wild-type, while the intervals between bursts did not differ in both groups. At the same time, we observed a decrease in the duration of the retraction phase ($p < 0.05$) in TAAR5-KO mice under water immersion conditions, although during walking on a flat surface the phases of the cycle did not differ in both groups. The results of the horizontal ladder did not show significant differences. Based on the data obtained, it can be assumed that TAAR5 can specifically affect muscle activity and the characteristics of the locomotor cycle under various conditions of locomotion, especially it may depend on of the gravity. RESEARCH SUPPORT: This work was performed within project ID: 73025317 of the St. Petersburg State University, St. Petersburg, Russia.

EXPLORING THE CONSEQUENCES OF A SINGLE SOCIAL DEFEAT STRESS ON ACCUMBAL DOPAMINE IN MALE AND FEMALE RATS. VV Nemets, VA Zavyalov, PA Chepik, RR Gainetdinov, EA Budygin, St. Petersburg State University, Institute of Translational Biomedicine, St. Petersburg, Russia; Wake Forest School of Medicine, Department of Neurobiology and Anatomy, Winston-Salem, NC, USA

FEATURES OF AUTONOMOUS REGULATION OF THE CARDIOVASCULAR SYSTEM IN ELDERLY UNDER STRESS. VP Nesterov, AI Burdygin, KB Ivanov, SV Nesterov, Sechenov Institute of Evolutionary Physiology and Biochemistry RAS, St. Petersburg, Russia

INTRODUCTION: The use of the piezopulsometric method developed by us (RF Patent for invention, 2020) for a non-invasive study of the functional state of the cardiovascular system (CVS) in an elderly man after physical trauma made it possible to reveal signs of a negative stress response of muscle effectors (ME) CVS to this impact. The combined carrying out of contour and spectral analyzes of variable parameters of pulse arterial pressure (PAP = PP) of blood expanded the range of assessment of cardiohemodynamic parameters (CGD) and made it possible to identify the physiological mechanisms underlying the changes in these parameters. In this work, we used an individual approach to the analysis of CHD parameters and their variability in a particular patient, which is recognized as relevant in our time. METHOD: The basis of the applied method is a computer complex, which includes synchronously functioning piezoelectric sensors and an interface converter. Local changes in PP are visualized on the monitor in the form of graphs of the dependence of the rate of change in the VPP value on time (t), which makes it possible to analyze with high accuracy the dynamics of changes in the amplitude-time parameters of such graphs based on calculated points. A feature of our development is the use of point B - an absolute positive extremum, which non-invasively assesses the contractility of the left ventricular myocardium (LVM) and on which the reflected pulse wave RW (reflected wave) is never superimposed, which significantly increases the accuracy of assessing the CHG indicators, compared with other methods. The parameters VmaxPP [mm Hg / s], SAP [mm Hg] and TNN [ms] were used as parameters for the non-invasive assessment of the effectiveness of the systems of autonomic regulation of ME CVS. RESULTS AND DISCUSSION: It has been shown that the impact of acute post-traumatic pain on the first day of observation causes a negative stress reaction in the ME CVS, provoking an abnormal increase in the contractility of the LV myocardium (the maximum rate of increase in pulse blood pressure - VmaxPP: before injury - 643 ± 71 mm Hg / s, after injury - 2117 ± 173 mm Hg / s). An even greater

increase was revealed when comparing the values of the dicrotic index (DIx): before the injury - 36 ± 9%, after - 375 ± 11% (an increase of 10 times!). The reason for this growth may be the excessively high total accumulation of mediators of sympathoadrenal regulation from the activated neurohumoral system, near the adrenergic receptors of the sarcolemma of cardiomyocytes (CM). This may result from a rapid release of norepinephrine from sympathetic efferents in addition to the increased release of humoral catecholamines from the adrenal cortex, which is common in the elderly. This conclusion follows from the redistribution of HA and ACh activities revealed during the examination. It was shown that the variability of all the main studied parameters of CGD, caused by GC exposure before injury in the ULF range, significantly decreased as a result of trauma, and this decrease was accompanied by an increase in the regulatory activity (variability of parameters) of parasympathetic efferents in the HF range. The released mediator of the autonomic nervous system (ANS), acetylcholine (ACh), plays an important cardioprotective role, inhibiting the contractile function of BM and thereby reducing the load on the heart.

EFFECTS OF GLIBENCLAMIDE ADMINISTRATION ON COGNITIVE FUNCTIONS OF RATS IN NORMOGLYCEMIA. AS Zubov, TV Tiutiunnik, MN Karpenko, VM Klimenko, Institute of Experimental Medicine, St. Petersburg State University, St. Petersburg, Russia

INTRODUCTION: Glibenclamide (GD) is a sulphonylurea-based blood glucose-lowering drug used as a treatment for type 2 diabetes worldwide. However, the effect of GD on CNS and in particular on cognitive function is still poorly understood. MATERIALS AND METHODS: The experiments were carried out on 20 male Wistar rats. At the age of 4 months the cognitive functions were tested with Morris water maze and Y-maze. At 7 months of age, the rats were divided into two groups - Group 1 (daily intraperitoneal (i.p.) administration of GD at a dose of 50 μg/kg for 30 days, n=10) and Group 2 (daily i.p. administration of sodium chloride at a dose of 1 ml/rat for 30 days). At the age of 8 months, the maintenance of cognitive function was also checked using the Morris water maze and the Y-maze. Data are presented as Me (qn; qc), and Wilcoxon or Kruskal-Wallis test followed by Newman-Keuls rank test were used. RESULTS: The residence time in the Morris water maze was found to be statistically insignificant, p = 0.09, in rats aged 4 months (41.7 (31.4; 45.9) seconds) and in the same rats aged 8 months (37.9 (26.7; 41.3) seconds). The administration of GD according to the chosen scheme led to an increase in the residence time in the platform area (45.1 (38.9; 53.3) seconds) in the Morris water maze compared to the control (37.85 (26.72; 41.29) seconds), p = 0.014. When tested in the Y-maze, there was a reduction in the % alternation of burrows at 8 months of age (51.1 (37.6; 70.7)) compared to the same rats at 4 months of age (66.03 (65.0; 72.7)), p = 0.0001. Also, administration of GD increased the % alternation of burrows (74.8 (58.5; 86.1)) compared to control animals at young and older ages, p = 0.0001, p = 0.004 respectively. Thus, the introduction of GD leads to improved spatial learning and memory.CONCLUSIONS: Intraperitoneal administration of GD at a dose of 50 μg/kg for 30 days resulted in improvement of cognitive functions in 8-month-old rats. RESEARCH SUPPORT: The reported study was funded by RFBR, project number 20-015-00168.

THERAPEUTIC EFFECT OF HESPERIDIN ON THE INFLAMMATORY RESPONSE AND OXIDATIVE STRESS INDUCED BY A TRAUMATIC BRAIN INJURY IN RATS, YL Yang, MA Tikhonova, TG Amstislavskaya, KT Lu, Novosibirsk State University, Novosibirsk, Russia, National Chia-Yi University, Chia-Yi, National Taiwan Normal University, Taipei, Taiwan

INTRODUCTION: Traumatic brain injury (TBI) is one of the most prevalent causes of morbidity and mortality all over the world. However, there are no effective pharmacological approaches aimed at neuroprotection in brain injury, correction of the effects of trauma and restoration of lost nerve cells (neuroregeneration). Hence, the search for drugs of neuroprotective action and drugs-inducers / modulators of neurogenesis that would be beneficial at TBI is an urgent task. Hesperidin (C28H34O15) is known as a flavanone glycoside, richly found in the citrus fruits. It possesses the anti-oxidant, anti-inflammatory, and anti-carcinogenic activities. Moreover, herperidin elicits neuroprotective effect through attenuating the free radicals formation, modulating neurotransmitter systems and various inflammatory cytokines, it significantly reduces the capillary permeability which is critical to brain edema formation. Here we studied the effects of hesperidin on a model of a closed neurotrauma in rats. METHODS: A conventional weight drop device was used to induce focal impact in a rat for inducing TBI. Hesperidin was administered at doses of 25, 50, or 100 mg/kg immediately after TBI. Three days after TBI, rats were sacrificed and brain samples were taken for subsequent determination of the levels of inflammatory markers and oxidative stress. To assess the content of HO-1, COX-2, and iNOS in hippocampal homogenates, we used standard methods for total protein isolation and Western blotting with specific antibodies. In addition, the levels of lipid peroxidation in the frontal cortex and hippocampus were determined according to the content of malondialdehyde (MDA) using ELISA. RESULTS AND DISCUSSION: On the third day after the trauma, the expression of inflammatory markers (HO-1 (Heme Oxygenase-1), COX-2 (Cyclooxygenase 2), iNOS (inducible nitric oxide synthase)) was prominent. All doses of hesperidin used in the experiment significantly reduced the neuroinflammatory response to the

level of control (sham-operated) animals. Similarly, the hesperidin administration significantly decreased the levels of lipid peroxidation marker (MDA) in both frontal cortex and hippocampus of the rats after TBI. Hence, the results confirm the expected therapeutic effects of hesperidin in TBI through diminishing the oxidative stress and neuroinflammation in the brain. RESEARCH SUPPORT: The study was partially supported by Russian Science Foundation (grant No. 20-65-46006).

THE EFFECTS OF MAFEDINE ADMINISTRATION ON BRAIN ELECTRICAL ACTIVITY AFTER BRAIN TRAUMA IN RATS. Yul Sysoev, VA Prikhodko, RT Chernyakov, RD Idiyatullin, PE Musienko, SV Okovityi, St. Petersburg State Chemical and Pharmaceutical University, Laboratory of Neuroprosthetics, Institute of Translational Biomedicine, St. Petersburg State University, Pavlov Institute of Physiology RAS, St. Petersburg State Research Institute of Phthisiopulmonology, Ministry of Healthcare of Russian Federation, St. Petersburg, Russia

INTRODUCTION: The search for and development of new neuroprotective drugs as well as suitable methods for their preclinical efficacy evaluation are a priority for current biomedical research. Alpha-2 adrenergic receptor agonists such as mafedine and dexmedetomidine are a highly appealing group of drugs capable of reducing neurological deficit resulting from brain trauma and vascular events in both experimental animals and human patients. Thus, our aim was to assess the effects of mafedine on brain electrical activity in a controlled cortical impact model of traumatic brain injury (TBI) in rats. The functional status of the animals was assessed by electrocorticography (ECoG) using ECoG electrodes chronically implanted in different cortical regions. MATERIALS AND METHODS: To model TBI, a craniectomy was performed in the left frontal region above the sensorimotor cortex, centered at 2.0 mm rostral and 1.5 mm left lateral from the bregma. A steel guide tube carrying a piston with a diameter of 3 mm and a stroke length of 4 mm was positioned over the cranial opening. To produce brain injury, the piston was actuated by a 50 g weight sliding down the guide tube from a height of 10 cm. The removed bone flap was then placed back, and the electrodes were implanted and fastened with screws. Electrodes FP1 and FP2 were placed in the secondary motor cortex area, C3 and C4, the hindlimb primary motor cortex are, and O1 and O2, the primary somatosensory cortex area above the hippocampus. Cortical electrical activity was recorded on post-TBI days 3 and 7 using a Neuron-Spectrum-1 EEG system (Neurosoft, Russia). Corticogram fragments up to 5 min long corresponding to awake, resting state with no locomotion, exploratory and/or grooming behavior were analyzed in Neuron-Spectrum.NETω software (Neurosoft, Russia). For amplitude analysis, mean overall wave amplitudes were calculated. Spectral analysis included the calculation of mean wave amplitudes and rhythm indices for each of the δ (0,5-4,0 Hz), θ (4,0-8,0 Hz), α (8,0-14,0 Hz), and β frequency bands (low-frequency, LF — 14,0-20,0 Hz, and high-frequency, HF — 20,0-35,0 Гц). Rhythm indices were calculated as total duration percentages of signals registered in the δ, θ, α, and β frequency bands. Cross-correlation analysis included the calculation of cross-correlation coefficients (CCr) for the following electrode pairs: FP1-FP2, C3-C4, and O1-O2 (horizontal), and FP1-C3, FP2-C4, C3-O1, and C4-O2 (vertical). RESULTS: Intraperitoneal mafedine sodium administration at 2,5 mg/kg 1 h after TBI and daily for the next 6 days restored interhemispheric functional connections in remote brain regions, and intrahemispheric connections within the unaffected hemisphere at post-TBI day 7. CONCLUSION: Our results confirm the previously described neuroprotective activity of mafedine sodium, and suggest that ECoG registration and analysis are a viable method for the evaluation of drug efficacy in experimental animal models of TBI. RESEARCH SUPPORT: this work was a part of the Saint-Petersburg State University project No. 51134206. Keywords: traumatic brain injury, neuroprotection, electrocorticography, rats, mafedine.

Day 2. Mon, May 17, 2021

Small Hall, Oktiabrskaya Hotel, 10 Ligovsky Prospect, St. Petersburg

SYMPOSIUM 3: CLINICAL STRESS NEUROSCIENCE AND NEUROLOGY

Chairs: VA Rozanov (Russia) and D Kozic (Serbia)

MULTIPARAMETRIC NEUROIMAGING MODALITIES IN DETECTION OF SUBTLE BRAIN CHANGES IN AGING. D Kozic, University of Novi Sad Faculty of Medicine, Novi Sad, Serbia

INTRODUCTION: Healthy brain aging occurs as a result of numerous interconnected structural, chemical and functional brain changes, and, in turn, can lead to a decline in cognitive function. Modern imaging modalities may detect disturbances in connection among crucial brain regions during healthy and pathologic aging. METHODS: Magnetic resonance volumetry is a diagnostic modality that detects the atrophy of specific brain areas. Quantification can be performed via segmentation of the brain parenchyma, in BrainMagix's SurferMagix module (Hermoye et al., 2014). Multivoxel magnetic resonance spectroscopy is able to detect subtle neurometabolic changes, while MR perfusion may

detect brain regions of decreased blood supply. Diffusion tensor imaging is able to reveal disturbance of neuronal connectivity network. The study group was composed of 40 healthy patients who were, based on age, divided in two groups, younger with average age 26,75 +/-2,47 SD and older group which averaged 68,5 +/-5,26 SD years. RESULTS AND DISCUSSION: Reduced N-acetyl aspartate on magnetic resonance spectroscopy in different brain regions can be detected in healthy aging. Radial diffusivity is the most sensitive technique to reveal neuronal connectivity network disturbance, while reduced total gray matter volume and thalamic volume were most prominent during aging ($p < 0,0001$).

THE USEFULNESS OF STRESSING PEOPLE IN VOCATIONAL TRAINING, Ph Fauquet-Alekhine, J Bleuze, H Mouret, Ch. Lenoir, Ph Kessler, SEBE-Lab, Department of Psychological and Behavioural Sciences, LSE, London, UK; Laboratory for Research in Science of Energy, INTRA Robotics, West Catholic University, Angers, France

INTRODUCTION: The literature reports a lot about how stress can be managed in order to reduce it while it provides too little about how to increase stress intensity. This aspect is not insignificant insofar as an individual's ability to manage stress often depends on training: training develops the individual's habituation to the effect of stressors (Fauquet-Alekhine & Erskine, 2021). This is precisely the objective of training through full scale high-fidelity simulation, bit it confronts the difficulty of generating acute stress with the characteristics and intensity of the real operating situation (Sigwalt et al., 2020). METHODS: Based on several operational experiences from different professions regularly confronted with episodes of high-intensity acute stress, we present a method to identify on which factors of stress (or stressors) action must be undertaken to create situations of controlled intense acute stress. Then we present an example of an application and conclude with the limitations and difficulties associated with creating intense acute stress through simulation. RESULTS AND DISCUSSION: According to the transactional model of Lazarus and Folkman (1984, 1986), stress is a transaction between the subject and the environment, a transaction associated with the perception that external solicitations exceed the subject's ability to respond, thus compromising the well-being of the subject. Therefore, professions that regularly face (or may be confronted with) high-intensity acute stress in a real operating situation must develop their habituation to these stressors. To confront professionals under conditions as close as possible to the real operating situation, they are engaged in training using full-scale high-fidelity simulators (Fauquet-Alekhine and Pehuet, 2016); examples: fireman, fighter pilot, airliner pilot, nuclear reactor pilot, robot pilot for intervention on accident, anesthesiologist, surgeon. To create the stress conditions sought in a simulated situation, a method was developed by Fauquet-Alekhine et al. (2012) to identify all the factors of the contextualized situation that could be perceived as a constraint or threat on the one hand, and resources on the other. Actions are then considered to transform the effect of these factors and make them either neutral, or more intense in terms of stress, or less effective in terms of resources. A comparison of the estimation of the effect of these factors (stressful effect, resource effect or neutral effect) on a radar-type diagram with 3 poles (stressor-resources-neutral), so-called the "3-level qualitative scale", between the two conditions (estimations before and after the implementation of actions) are a predictive assessment of the overall effect of the actions envisaged in order to make the simulated situation more stressful. The identification of these factors can be conducted, for example, by using the categorization of stressors of Leka et al. (2003, 2010), and by considering the stimuli of sensory receptors (VAKOG). Example - application at INTRA robotics. The simulated situation involves sending a team to a contaminated and irradiant premise located high up in an industrial building using a small, robot with caterpillars. The aim is to achieve visual and radiological recognition using the robot's on-board metrology at bridles to connect refrigerant pipes. Among the stressors identified, trainers adjust the intensity of 3 stressors: 1) the difficulty of piloting related to the environment through complicating the movement of the robot by adding obstacles, 2) the difficulty of protecting from radioactive contamination and irradiation by increasing the values measured by the metrology via a radiological simulator, 3) the difficulty of concentrating when working in CBRN clothing by increasing external solicitations of pilots (i.e. frequent radio contacts from simulated colleagues who may be involved in this type of situation). Despite this, during the debriefing of the simulation training session, the trainees explained that they had perceived moderate level of stress. This finding is not surprising because, on the one hand, reproducing the stress of the real operating situations in a simulated situation is not always possible (Baker et al., 2017; Clarke et al., 2014; Fauquet-Alekhine & Erskine, 2021), and, on the other hand, professionals placed in this type of situation already trained and therefore accustomed to the exposure of this sort of stressors. To go further, one solution would be to expose the trainees to real operating situations in order to train them. However, it seems difficult to envisage killing someone to train anesthesiologists or surgeons, or even to melt down a nuclear reactor to train reactor pilots or robot pilots on accident. These extreme situations are confronted with practical but also ethical considerations. The solution is therefore to accept the gap between the simulated situation and the actual operational situation by considering that the debriefing will allow a projective perspective that will prepare the trainees for future real operating situations on the basis of simulated situations. RESEARCH SUPPORT: This work was supported by the Groupe INTRA robotics.

THE PATIENT'S OWN BONE MARROW-DERIVED STROMAL CELLS: DISEASE MODIFIERS IN (NEURO)DEGENERATIVE DISORDERS, J de Munter, Maastricht University, Maastricht, Netherlands

A COMMUNICATIVE EDUCATION SUPPORT BY ICT FOR SOCIAL DEVELOPMENT IN CHILDREN PLAYING AT DIFFERENT REAL SPACES ONE ANOTHER, M Ohta, F Tomoto, M Koshiba, Graduate School of Science and Technology for Innovation, Yamaguchi University, Yamaguchi, Department of Pediatrics, Saitama Medical University, Saitama, Graduate School of Information Sciences, Tohoku University, Tohoku, Japan

INTRODUCTION: The corona virus crisis has been facilitating education utility of Information and Communication Technology (ICT) which must alternatively support children's peer social development in the internet virtual space. Meanwhile, the limited communication media comparing to the real one has been reported about some psychiatric etiology risks, e.g. net-game addiction and withdrawal at home. Considering these backgrounds, we designed one ICT educational solution and evaluated the trial with children participants who were playing at different places one another. METHODS: We online-connected two sets of PC displays (50 inches) and web video cameras by a meeting system between the city children's center and the gymnasium over a distance of 200 meters. Each team of the child volunteers were suggested a physical game play, named "Choshu Five" after the regional samurai legend. As the game rule, when a samurai fighter at one terminal swung the sword, multiple children at another terminal were simultaneously asked to jump to avoid the sword edge. Each response was judged whether the avoidance gesture was correct or not. RESULTS AND DISCUSSION: Several tens of children aged 3 to 11 years old, males more than females, played the game voluntarily. In most cases, their playing skills improved dependently on the duration. Supposedly, the youngest girl could perform her response accurately. The generation who played for the longest time resulted in the fifth grade of primary school. Although the frozen behaviors were frequently seen when the stimulator's sword moved unexpectedly, a few individuals could perform responses variably. Despite poor sound specifications in the current communicative system, children seemed to mutually solve with their own adaptive devisal. Further ICT amelioration with multiple image and sound dimension may complement real-space socialization even in restricted communicative states.

CONFERENCE PRESENTATION: AUTOMATED COGNITIVE AND BEHAVIORAL SCREENING OF INDIVIDUAL MICE LIVING IN SOCIAL GROUPS, REDUCING STRESS COMPONENT. D Verma TSE Systems GmbH, Bad Homburg, Germany

A large part of data variability observed within or across labs is caused by unpredictable changes in the lab environment, experimenter's interference, or differential conditions in testing- and housing. To combat such problems, TSE Systems introduced a standardized home cage testing system (IntelliCage) to automatically test group-housed animals within their social environment. The system requires no experimenter's interference and allows high-throughput behavioral phenotyping over several days or weeks. IntelliCage allows a transfer of validated behavioral paradigms into automated setup, as comparative studies revealed the effects on learning and memory processes similar to the findings from e.g., Morris Water Maze or Vogel Conflict Test. Studies using behavioral flexibility- and response-inhibition tasks proved that IntelliCage assess reliably executive functions. Transferring of established behavioral paradigms to IntelliCage has shown to significantly reduce inter- and intra-lab-variability.

SYMPOSIUM 4: ZNRC ZEBRAFISH NEUROSCIENCE SYMPOSIUM

Chair: AV Kalueff (Russia, USA, China)

LASER IRRADIATION FOR MODELING TRAUMATIC BRAIN INJURY IN ADULT ZEBRAFISH, NA Maslov, EO Tsibulskaya, MA Tikhonova, AV Kalueff, YL Yang, TG Amstislavskaya, Novosibirsk State University, Novosibirsk, Russia; National Chia-Yi University, Chia-Yi, Taiwan; Khristianovich Institute of Theoretical and Applied Mechanics SO RAS, Novosibirsk, Russia

INTRODUCTION: Traumatic brain injury (TBI) is one of the most prevalent causes of morbidity and mortality all over the world and apparently has consumed an enormous social cost and economic burden. Development of pharmacological treatment of such damage and achievement a more in-depth understanding of the pathogenesis of TBI requires appropriate injury model. Thus, new methods, which have means of precise control over the damage caused, are still in demand. Here, we studied the potential of using laser irradiation induced injury for such tasks. METHODS: Zebrafish was chosen as an animal model. The variety used in experiments has transparent skin on top of the head. Thus, visible laser radiation could penetrate it without beam distortion. The scull bones are also significantly transparent, and only scatter laser light. It allows to selectively heat brain surface to temperatures high enough to cause hyperthermia or protein denaturation. The experimental setup included a laser diode

(power – 500 mW, wavelength – 405 nm), and aiming system consisting of video camera and 3D translation stage. The radiation of laser diode was focused in 0.1 mm spot on the surface of anesthetized zebrafish telencephalon. The effect was controlled by the irradiation time (2-4 s) and applied laser power. RESULTS AND DISCUSSION: The described above system allowed us to cause closed TBI to the specimen under study. The result of exposure could be observed even visually by changing the color of the affected area. TBI-like disturbances in the brain tissue were confirmed with a neuromorphological study of the samples using histological staining with hematoxylin & eosin or Nissl staining for neuronal loss. 30 minutes after the injury the expression of transcriptional factor HIF1alpha elevated in the zebrafish telencephalon in proportion to the time of exposure to laser irradiation. Notably, both 2- and 4-second-long duration of laser treatment produced a significant increase in HIF1alpha expression as compared to sham operated controls. Thus, the method of laser irradiation induced injury is suggested as an adequate and useful tool for TBI research and preclinical screening of treatment approaches. RESEARCH SUPPORT: This research was supported by Russian Science Foundation (grant No. 20-65-46006).

EFFECTS OF LASER-INDUCED TRAUMATIC BRAIN INJURY ON BEHAVIORAL AND MORPHOLOGICAL CHARACTERISTICS IN ZEBRAFISH, AA Bashirzade, AS Belova, AA Akopyan, VY Babchenko, MA Tikhonova, AV Kalueff, TG Amstislavskaya, Novosibirsk State University, Khristianovich Institute of Theoretical and Applied Mechanics SO RAS, Novosibirsk, Russia

INTRODUCTION: Traumatic brain injury (TBI) is a lesion of the central nervous system of complex and heterogeneous genesis while the development of new approaches and animal models for TBI research and treatment is an urgent task. Here we studied a novel laser-induced TBI model in zebrafish to evaluate TBI-related behavioral disturbances and morphological alterations in the telencephalon. METHODS: TBI was produced using focused laser radiation. Zebrafish telencephalon was lesioned with the laser beam of a 405 nm wavelength and an optical power of 50-100 mW within 1-6 sec. Behavioral phenotyping was performed using the Novel tank test and group formation test - Shoaling test. Neurogenesis in the brain was assessed using the immunohistochemical analysis. Staining protocol for new-born neurons (BrdU+NeuN+ neurons) was applied and the expression of HIF-1α protein and neurotrophic factor BDNF were measured. Neurodegenerative changes in the brain after TBI were estimated using Nissl staining. The measurements were carried out in dynamics – 30 min; 1, 3, 5, or 7 days after the lesion. RESULTS AND DISCUSSION: Unilateral lesion of the dorsomedial telencephalon with a laser power of 50 mW or 100 mW for 2 s produced a power-dependent increase in anxiety in the Novel tank test 1 day after injury. The total time spent in the upper part of the tank by the experimental groups (50 mW or 100 mW) was significantly reduced compared to controls ($p < 0.001$). Similar results were obtained with the frequency of entries to the upper half of the tank. As for social behavior of zebrafish exposed to laser irradiation at both powers (50 mW or 100 mW), the average distance between fish in shoals was augmented ($p < 0.05$). There were no statistically significant differences in behavioral indices on the 3rd, 5th, or 7th days after the trauma. The protein expression of BDNF peaked on the 3rd day after TBI, while the protein expression of HIF-1α peaked on the 1st and 3rd days. Both parameters reached control values on the 7th day after TBI. The results of the study suggest the laser-induced TBI model in zebrafish as an adequate and useful tool for neurotrauma research. It can be applied for investigating the pharmacological approaches aimed at neuroprotection in brain injury, correction of the effects of trauma and restoration of lost nerve cells, in particular, for preclinical studies of neuroprotective drugs and inducers / modulators of neurogenesis. RESEARCH SUPPORT: This research was supported by Russian Science Foundation (grant No. 20-65-46006).

PERSPECTIVES OF STUDYING PSYCHEDELIC SUBSTANCES ON ZEBRAFISH (*Danio rerio*), NA Krotova, KA Demin, KA Derzhavina, TO Kolesnikova, AV Kaluleff, Institute of Translational Biomedicine, St. Petersburg State University, Institute of Experimental Medicine Almazov National Medical Research Centre, Ministry of Healthcare of Russian Federation, St. Petersburg, Russia, School of Pharmacy, Southwest University, Chongqing, China; Neuroscience Program, Sirius University, Sochi, Granov Russian Research Center of Radiology and Surgical Technologies, Ministry of Healthcare of Russian Federation, Pesochny, Russia

The study of hallucinogenic drugs is becoming an important part of biomedical research in psychiatry. Preclinical and clinical studies suggest psychedelics as a promising treatment for depression, anxiety, addiction and other conditions. For example, psilocybin treatment has been shown to reduce anxiety and improve mood in terminal cancer patients as well as reduces symptoms in patients with treatment-resistant depression. Studies with the well-known hallucinogen LSD (lysergic acid diethylamide) have shown stimulation of synaptogenesis and neurogenesis. Mood improvement after LSD and psilocybin therapy has also been shown. Preclinical studies have also shown improvement of cognitive abilities, reduction of depression-like behavior and increase in cortical plasticity after psychedelic drug exposure in animal models. Zebrafish (Danio rerio) is becoming a popular model to study psychoactive drugs

effects by virtue of its high genetic and physiological homology to the human body. Zebrafish is a useful model for testing hallucinogenic drugs due to its high genetic and physiological homology with human. Mescaline and phencyclidine administration change the swimming pattern of zebrafish, increase in top activity and decrease in immobility, whereas LSD administration decrease anxiety-like behavior in the zebrafish. As a consequence, zebrafish is a promising and valuable model for screening psychedelic drugs due to its high sensitivity to behavioral effects of these compounds.

MODELING MEMORY IMPAIRMENT EVOKED BY ACUTE PREDATOR ODOR STRESS IN ADULT ZEBRAFISH, VV Kurashenko, TO Kolesnikova, DS Galstyan, AV Kalueff, Institute of Translational Biomedicine, St. Petersburg State University, Institute of Experimental Medicine, Almazov National Medical Research Centre, Ministry of Healthcare of Russian Federation, St. Petersburg, Russia; School of Pharmacy, Southwest University, Chongqing, China; Neuroscience Program, Sirius University, Sochi, Granov Russian Research Center of Radiology and Surgical Technologies, Ministry of Healthcare of Russian Federation, Pesochny, Russia

INTRODUCTION: Mounting clinical and experimental data indicates that stress strongly affects memory and learning. The Zebrafish (Danio rerio) is a promising aquatic model organism for cognitive neuroscience research and become useful tool for study of correlation between memory and anxiety-related states. The aim of this study was to evaluate zebrafish short-term memory in conditioned place aversion (CPA) test followed predator odor-induced stress. METHODS: A total of 22 wild type naïve short-fin zebrafish housed in groups of 20 in the 3.5-L tank according the standards of zebrafish care were used in the study. Conditioned place aversion test represented a rectangular glass tank (14 height×25 length ×12 width cm) divided into two halves. Black and white plastic cover was glued on the outside of each part of the tank. Low voltage (0.1 mV/cm of water) electric current were negative stimuli for zebrafish avoiding dark part of the test. Zebrafish were trained in conditioned place aversion test for 4 hours. Predator water was added in the experimental tank, and fresh clear water was added in the control tank. Next day, zebrafish behavior was recorded for 5 min and latency, frequency and duration of dark part entries were analyzed. Behavioral data was assessed using RealTimer (Krasnogorsk, Russia) software. RESULTS AND DISCUSSIONS: Overall, we did not find any significant difference between experimental and control zebrafish groups. Our results suggest that acute predator water exposure did not affect zebrafish short-term memory, probably because this stimulus was insufficient to increase anxiety level and cause cognition deficit in zebrafish. Nevertheless, further study of anxiety and their effects on memory and cognitive function in zebrafish are needed. RESEARCH SUPPORT: The research was supported by the Russian Science Foundation (RSF) grant 19-15-00053. The laboratory is supported by SPSU state budgetary funds ID 73026081, Almazov National Medical Research Centre, and Russian Scientific Center of Roentgenoradiology.

CHRONIC BEHAVIORAL EFFECTS OF ACETYLSALICYLIC ACID IN ADULT ZEBRAFISH, VV Zakharova, DS Galstyan, TO Kolesnikova, KA Demin, AV Kalueff, Institute of Translational Biomedicine, St. Petersburg State University, Institute of Experimental Medicine, Almazov National Medical Research Centre, Ministry of Healthcare of Russian Federation, St. Petersburg, Russia; School of Pharmacy, Southwest University, Chongqing, China; Ural Federal University, Ekaterinburg, Neuroscience Program, Sirius University, Sochi, Russia Granov Russian Research Center of Radiology and Surgical Technologies, Ministry of Healthcare of Russian Federation, Pesochny, Russia

INTRODUCTION: Cyclooxygenase (COX) is one of the main enzymes in the biosynthesis of thromboxanes and prostaglandins which can take part in neuroinflammation processes associated with many neurodegenerative and mental illnesses such as Alzheimer's disease, Parkinson's disease, depression and schizophrenia. There are two main types of enzymes: COX-1 and COX-2. Inhibition of COX-2 is the main mechanism of action of non-steroidal anti-inflammatory drugs aimed at reducing inflammation, however, COX-1 also is actively involved in inflammation processes. Based on this, the aim of our study was to evaluate the behavioral effects of chronic treatment with acetylsalicylic acid (AC), as a COX-1 and COX-2 inhibitor in adult zebrafish. METHODS: A total of 54 adult short-fin wild type zebrafish were used for this study. Fish were divided into 3 groups: 5 mg/L, 1 mg/L and control group, and exposure in water solution of AC for 1 week. AC was dissolved in 1 ml of dimethyl sulfoxide (1 ml of this solution was also added to the tank with the control group). The novel tank test was used to assess zebrafish behavior for 5 minutes. Behavioral data were calculated using Noldus EthoVision XT11.5 software. Statistics were analyzed using the Kruskal-Wallis (KW) test followed by Dunn's post hoc test for significant KW data. Statistical significances between the considered parameters were set at $P<0.05$. RESULTS AND DISCUSSION: As a result, chronic exposure at dose of 5 mg/L increased zebrafish activity, showing high values of distance traveled and cumulative duration of mobility state, and demonstrated a higher frequency and duration of top entries compared to the control and 1 mg/l group. Also, 1 mg/L treated fish showed higher duration of mobility and compared to control group. Thus, our results demonstrate that chronic exposure to acetylsalicylic acid induces dose-depending anxiolytic-like

effects in zebrafish. We consider that the further study of the effects of cyclooxygenase in the brain are needed for medical practice in the field of psychiatry. RESEARCH SUPPORT: The research was supported by the Russian Science Foundation (RSF) grant 19-15-00053. The laboratory is supported by SPSU state budgetary funds ID 73026081, Almazov National Medical Research Centre, and Russian Scientific Center of Roentgenoradiology.

PROLONGED CHRONIC UNPREDICTABLE STRESS IN THE ZEBRAFISH: EFFECTS ON BEHAVIORAL AND NEUROCHEMICAL ALTERATIONS PRODUCED BY FLUOXETINE, EPA AND LPS, MV Seredinskaya, TO Kolesnikova, DS Galstyan, KA Demin, NA Krotova, NP Ilyin, KA Derzhavina, DV Sorokin, AV Kalueff, Institute of Translational Biomedicine, St. Petersburg State University, Institute of Experimental Medicine, Almazov National Medical Research Centre, Ministry of Healthcare of Russian Federation, St. Petersburg, Russia; School of Pharmacy, Southwest University, Chongqing, China; Granov Russian Research Center of Radiology and Surgical Technologies, Ministry of Healthcare of Russian Federation, Pesochny, Neuroscience Program, Sirius University, Sochi, Russia

INTRODUCTION: Long-term recurrent stress is a common cause of neuropsychiatric disorders. To explore the heterogeneous effects of stress, we developed a Prolonged Chronic Unpredictable Stress (PCUS) model on zebrafish (Danio rerio) based on rigorous 11-week CUS protocol. We examined the effects of 3-week exposure to the traditional antidepressant selective serotonin reuptake inhibitor (SSRI) fluoxetine and compared with putative positive and negative neuromodulators (the neuroprotective omega-3 polyunsaturated fatty acid/ PUFA-eicosapentaenoic acid, EPA) and the proinflammatory agent lipopolysaccharide, LPS), as well as their combinations with fluoxetine. METHODS: Experimental fish were exposed to different stressors daily for 11 weeks. On day 57, the cohort of stressed fish was divided into six groups: the group continued to be exposed to chronic stress only, or the groups exposed to chronic fluoxetine, eicosapentaenoic acid (EPA), lipopolysaccharide (LPS), fluoxetine+EPA and fluoxetine+LPS for the last 3 weeks. Behavioral and cognitive phenotypes were tested in the novel tank test (NTT), shoaling test (ST), and conditioned place aversion (CPA). The following monoamine levels in the brain were evaluated: norepinephrine (NE), serotonin (5-HT), dopamine (DA), and their metabolites (5-HIAA), 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA). Data were analyzed using the Kruskal-Wallis (KW) test, followed by Dunn's post-hoc test for pairwise group comparisons. RESULTS AND DISCUSSION: In the NTT the EPA, fluoxetine+EPA and fluoxetine+LPS exposure has substantially decreased the zebrafish swim velocity. Stress, EPA and the LPS exposure lower the time on top of the tank vs. control and fluoxetine-treated groups. Stress exposure also increased the latency to enter the top vs. both control and fluoxetine groups, while LPS increases it only by comparison to fluoxetine-treated group. At last, exposure to fluoxetine + LPS decreased the number of top entries. In the CPA model no behavioral alterations were observed in experimental vs. control groups, but the ECUS group spent more time in light than intact fish, just like fluoxetine-treated, fluoxetine+EPA and fluoxetine+LPS groups. In ST, ECUS stress and LPS exposure both reduced the mean distance between fish. In addition, stress exposure reduced the distance between fish compared to all other groups except LPS. In contrast, fluoxetine + LPS exposure increased the mean distance between fish in this test compared to all other groups. Fluoxetine exposure also decreased shoal cohesion compared with EPA and LPS, while fluoxetine+EPA increased distance between fish compared with LPS. As for the neurochemical analysis, we were able to find pronounced differences in the levels of serotonin, dopamine and norepinephrine. Thus, fluoxetine decreased the 5HIAA/serotonin ratio, while fluoxetine+EPA increased 5HIAA levels, with no change in serotonin turnover. We found differences between fluoxetine and fluoxetine+EPA, which decreased 5HIAA levels compared with the stress group, whereas fluoxetine+EPA decreased 5HIAA levels compared with the LPS group.Interestingly, fluoxetine + LPS strongly decreased brain serotonin levels compared with ECUS, fluoxetine alone, fluoxetine + LPS, and LPS groups. In addition, the fluoxetine+LPS group increased serotonin turnover compared with the fluoxetine, EPA, LPS, and fluoxetine+EPA groups. Chronic stress and LPS exposure increased levels of norepinephrine. Fluoxetine+LPS group increased dopamine turnover (DOPAC/dopamine ratio) compared to EPA and LPS groups, with no other effects observed between the experimental groups. Given the constantly evolving, and sometimes opposite, behavioral patterns in many behavioral axes (except anxiety), further studies are needed to better understand the exact interplay between these factors, warranting further CUS protocols with differing numbers of stressors, their severity, and modeling duration. RESEARCH SUPPORT: The research was supported by the Russian Science Foundation (RSF) grant 19-15-00053. The laboratory is supported by SPSU state budgetary funds ID 73026081, Almazov National Medical Research Centre, and Russian Scientific Center of Roentgenoradiology.

BEHAVIORAL EFFECTS OF FLY AGARIC (*AMANITA MUSCARIA*) EXTRACT IN ADULT ZEBRAFISH, YuM Kositsyn, KA Derzhavina, AASh Khaibaev, KI Nechesanova, AV Kalueff, Institute of Translational Biomedicine, St. Petersburg State University Institute of Experimental Medicine, Almazov National

Medical Research Centre, Ministry of Healthcare of Russian Federation, St. Petersburg, Russia; School of Pharmacy, Southwest University, Chongqing, China

INTRODUCTION: Fly agarics (Amanita muscaria) have been used in ancient medicine due to its hallucinogenic and dissociative properties. Also, fly agarics contain a number of alkaloids such as ibotenic acid, muscimol (panterine), and muscasone, which effects on the central nervous system. Ibotenic acid is a neurotoxin, whose structure resembles the glutamic acid and activates NMDA receptors. Muscimol has a strong psychoactivating action and it works primarily by blocking the GABA B receptors. Since, in modern translational medicine, mushroom psychoactive substances have established themselves as potential highly effective drugs, the aim of this study was to evaluate acute behavioral effects of fly agaric Amanita muscaria in adult zebrafish. METHODS: Adult (4–6 months old) wild-type zebrafish (approximately 50/50 male/female ratio) were used in experimental (n=16) and control (n=12) groups. 24 g of Amanita muscaria was brewed in 250 mL of boiling water, kept in room temperature overnight, then filtered and used as aqueous extract for exposure. Zebrafish were exposed for 20 minutes with the fly agaric extract in 300 mL plastic beakers and tested in novel tank test (NTT) for 5 minutes to asses stress-related behavior and motor activity. Top duration (s) and frequency, duration (s) and frequency of freezing behavior, total distance traveled (cm) were calculated using Noldus EthoVision XT 11.5 software. Statistical data were analyzed by the Mann-Whitney (U) non-parametrical test. Statistical significance was set at $P<0.05$. RESULTS AND DISCUSSION: Amanita muscaria aqueous extract exposure decreased distance traveled, top frequency in experimental fish compared to control. Also, increasing meander and not-moving state were shown in fly agaric treatment fish. Moreover, lethal concentration (40 grams per 250 ml of water LD70) were also determined. Thus, aqueous extract of Amanita muscaria is likely to have sedative-like properties, highlighting the potential effects of fungal metabolites and serving as a potential substance for the development of new drugs. Additionally, since in many countries Amanita muscaria is a legal drug, an increase in poisoning and mortality is predicted, and, accordingly, the study of toxic effects on CNS is required. RESEARCH SUPPORT: The research was supported by the Russian Science Foundation (RSF) grant 19-15-00053. The laboratory is supported by SPSU state budgetary funds ID 73026081, Almazov National Medical Research Centre, and Russian Scientific Center of Roentgenoradiology.

CHRONIC EFFECTS OF ESTRADIOL VALERATE IN ADULT ZEBRAFISH: A PILOT STUDY, AASh Khaibaev, KA Derzhavina, DV Sorokin, TO Kolesnikova, KA Demin, AV Kalueff, Institute of Translational Biomedicine, St. Petersburg State University, Institute of Experimental Medicine, Almazov National Medical Research Centre, Ministry of Healthcare of Russian Federation, St. Petersburg, Neuroscience Program, Sirius University, Sochi, Russia; School of Pharmacy, Southwest University, Chongqing, China

INTRODUCTION: Estradiol, belongs to the group of estrogen steroid hormones and is one of the most common and active in the family. It plays an important role in the regulation of menstrual cycle and the function of the female reproductive system. Estradiol is responsible for the development of female reproductive tissues and secondary sexual characteristics. It is considered the main sex hormone in women and is presented in small amounts in men. Estradiol valerate is an estrogenic drug that is used in the hormonal therapy of menopausal symptoms and low estrogen levels in women, as well as hormonal contraceptives. As for latter, estradiol valerate is available as a combined estradiol-containing oral contraceptive (COCs), one of the side effects of which is the appearance of depressive-like states. The aim of present study was to evaluate chronic effect of estradiol in adult zebrafish. METHODS: A total of 38 adult wild type short-fin zebrafish were divided into control (n=17) and experimental (n=21) groups. Zebrafish behavior was assessed in novel tank test (NTT) after 7-day chronic exposure in 0.4 or 0.2 mcg/l of estradiol valerate. Behavioral endpoints studied included latency (s) and durations of top entries, time spent in the upper half of the tank (s), duration (s) and frequency of freezing bouts and total distance moved (s). RESULTS AND DISCUSSION: Chronic estradiol exposure did not alter behavioral parameters in the novel tank test. Thus, we found, that chronic exposure in estradiol valerate did not cause anxiety- and depressive- like state. Nevertheless, further studies of the development of depressive-like states in zebrafish with higher doses and longer exposure time as perspective new aquatic model of depression, are needed. RESEARCH SUPPORT: The research was supported by the Russian Science Foundation (RSF) grant 19-15-00053. The laboratory is supported by SPSU state budgetary funds ID 73026081, Almazov National Medical Research Centre, and Russian Scientific Center of Roentgenoradiology.

ACUTE AND CHRONIC EFFECTS OF DESOGESTREL, ORAL CONTRACEPTIVE, IN ADULT ZEBRAFISH IN NOVEL TANK TEST: A PILOT STUDY. DV Sorokin, AASh Khaibaev, KA Derzhavina, TO Kolesnikova, KA Demin, AV Kalueff, Institute of Translational Biomedicine, St. Petersburg State University, Institute of Experimental Medicine, Almazov National Medical Research Centre, Ministry of Healthcare of Russian Federation, St. Petersburg, Neuroscience Program, Sirius University, Sochi, Russia; School of Pharmacy, Southwest University, Chongqing, China

INTRODUCTION: Desogestrel is widespread over-the-counter hormonal contraceptive drug with progestagenic action. Depression is the most common side effects of contraceptive drug. The main goal of our study was to identify acute and chronic effects of desogestrel in adult zebrafish (Danio rerio). METHODS: Short-fin wild type zebrafish were used for this study. All fish were experimentally naive and housing according to the standards of zebrafish care. In Experiment 1, we evaluate acute behavioral effects of 75 mcg/L of desogestrel. Zebrafish behavior were assessed using 5-min novel tank test following 20-min pre-exposure in tested substance. In Experiment 2, zebrafish were exposed to 1.5 mcg/L of desogestrel for 7 days. In Experiment 3, zebrafish behavior was tested after 7-day treatment with 3 mcg/L of desogestrel. Behavioral parameters, including frequency and duration (s) of entries to upper half of the tank, frequency and duration (s) of freezing behavior, as well as distance moved (cm) and frequency and duration of high-mobile states, were measure using Noldus Ethovision XT11.5 software. Data were analyzed using Mann–Whitney (U) test for non-parametrical data. RESULTS AND DISCUSSION: Acute treatment with desogestrel decreased time spent top in experimental group compared to the control, as well as frequency of high-mobile state, indicating anxiety-like phenotype. We did not find any statistically significant differences between both chronic doses and control groups. Given that zebrafish is a promising tool for modeling depression and anxiety-like states, further study of the chronic effects of higher doses of desogestrel or its combinations is needed. RESEARCH SUPPORT: The research was supported by the Russian Science Foundation (RSF) grant 19-15-00053. The laboratory is supported by SPSU state budgetary funds ID 73026081, Almazov National Medical Research Centre, and Russian Scientific Center of Roentgenoradiology.

THE ROLE OF COMBINED ORAL CONTRACEPTIVES (COC) IN THE DEVELOPMENT OF DEPRESSIVE- LIKE BEHAVIOR IN ADULT ZEBRAFISH: A PILOT STUDY, KA Derzhavina, AASh Khaibaev, DV Sorokin, TO Kolesnikova, KA Demin, AV Kalueff, Institute of Translational Biomedicine, St. Petersburg State University, Institute of Experimental Medicine, Almazov National Medical Research Centre, Ministry of Healthcare of Russian Federation, St. Petersburg, Neuroscience Program, Sirius University, Sochi, Russia; School of Pharmacy, Southwest University, Chongqing, China

INTRODUCTION: Combined oral contraceptives (COC) are widespread and freely sold drugs, which common side effects on nervous system include headache, mood change and, often, depression. Desogestrel is third-generation progestin structurally similar to levonorgestrel used in combination with estrogen. Here, we used desogestrel + estrogen combined oral contraceptive to develop the new model of affective pathogenesis in zebrafish. METHODS: A total of 40 short-fin wild type zebrafish were used for this study. All fish were experimentally naive and fed twice a day. Two experiments were performed with different concentrations of drugs. Novel tank test was used to assess zebrafish behavior for 5 min after 7-day exposition in desogestrel (1.5 mcg/L) + estrogen (0.2 mcg/L) and desogestrel (3 mcg/L) + estrogen (0.4 mcg/L), respectively in Experiment 1 and Experiment 2. We analyzed the latency (s) and number of top entries, time spent in the upper half (s), duration (s) and frequency of freezing bouts, duration (s) and frequency of high-movement state using Noldus EthoVision XT 11.5 software. Data was analyzed using the Mann-Whitney (U) non-parametrical test. Significance was set at $P<0.05$. RESULTS AND DISCUSSION: No statistically significant differences were observed in any study. Desogestrel and estrogen combination did not alter any behavioral endpoints in the studied doses, thus did not induce anxiety and depressive-like state in adult zebrafish. Perhaps, the dose was insufficient or more prolonged exposure time are needed. However, similar desogestrel doses cause an acute effect in zebrafish in another study, so the further studies in the combination with estrogen are needed to understand exact behavioral phenotype. RESEARCH SUPPORT: The research was supported by the Russian Science Foundation (RSF) grant 19-15-00053. The laboratory is supported by SPSU state budgetary funds ID 73026081, Almazov National Medical Research Centre, and Russian Scientific Center of Roentgenoradiology.

ACUTE BEHAVIORAL EFFECTS OF CELEBREX, A SELECTIVE INHIBITOR OF COX-2, IN ADULT ZEBRAFISH, M Nerush, DS Galstyan, KA Demin, TO Kolesnikova, AV Kalueff, Institute of Translational Biomedicine, St. Petersburg State University, Institute of Experimental Medicine, Almazov National Medical Research Centre, Ministry of Healthcare of Russian Federation, Granov Russian Scientific Center for Radiology and Surgical Technologies, St. Petersburg, Russia; School of Pharmacy, Southwest University, Chongqing, China; Ural Federal University, Ekaterinburg, Neuroscience Program, Sirius University, Sochi, Russia

INTRODUCTION: It is well known that inflammation is one of the key factors in development of mental illness. Cyclooxygenase 2 (COX-2) takes an important role in the mechanisms of inflammation. The aim of the present study was to evaluate the acute behavioral effects of celebrex, a selective inhibitor of COX-2, in adult zebrafish. METHODS: A total of 36 adult short-fin wild-type zebrafish were used for this study. All fish were divided into 3 groups: 25 mg/L and 10 mg/L of celebrex and control group. The novel tank test (NTT) was used to assess zebrafish behavior for 5 minutes. Prior to testing, zebrafish were

exposed in a 0.25-L plastic beaker containing drug for 20 minutes. Celebrex was dissolved in 0.25 ml of dimethyl sulfoxide solution (0.25 ml of DMSO was also added to the beaker with the control group). Behavioral parameters, such us frequency, duration and latency of top entries, distance moved, frequency and duration of freezing bouts, were calculated using Noldus EthoVision XT11.5 software. Statistical data were analyzed using the Kruskal-Wallis (KW) test followed by Dunn's post-hoc test for significant KW data. Statistical significances between the considered parameters were set at $P<0.05$ in all tests. RESULTS AND DISCUSSION: The results of our study demonstrated that zebrafish exposed to the maximum dose (25 mg/L) of celebrex showed decreasing in the number of top entries and distance moved, as well as increasing frequency and cumulation duration of freezing behavior compared to the control group. At the same time, we didn't find statistically significant differences between dose 10 mg/L and control group. However, compared to 25 mg/L, fish showed lower cumulative duration of freezing. Decrease top frequency, distance moved as well as the frequency and duration of freezing can be an indicator of anxiety in fish, however, given the low values of the high mobile, we can conclude that high doses of aspirin had a sedative effect on fish. RESEARCH SUPPORT: The research was supported by the Russian Science Foundation (RSF) grant 19-15-00053. The laboratory is supported by SPSU state budgetary funds ID 73026081, Almazov National Medical Research Centre, and Russian Scientific Center of Roentgenoradiology.

ACUTE BEHAVIORAL EFFECTS OF MV-007, BETA-ALANINE DERIVATE, ON ZEBRAFISH BEHAVIOR IN CONDITIONED PLACE AVERSION TEST AND NOVEL TANK TEST, UV Menshikova, TO Kolesnikova, DS Galstyan, AV Kalueff, Institute of Translational Biomedicine, St. Petersburg State University, Institute of Experimental Medicine, Almazov National Medical Research Centre, Granov Russian Scientific Center for Radiology and Surgical Technologies, St. Petersburg, Russia; School of Pharmacy, Southwest University, Chongqing, China; Ural Federal University, Ekaterinburg, Neuroscience Program, Sirius University, Sochi, Russia

INTRODUCTION: With the growing life expectancy globally, cognitive deficits represent an urgent unmet problem in biomedicine. Nootropic drugs are a specific class of psychotropic medication that improve cognitive function and reduce cognitive deficits in humans and animals. Since the discovery of piracetam, the most well-known and widely used nootropic drug, many piracetam-like substances have been synthesized. However, with the rapidly ageing human population and low efficiency of contemporary compounds, there is also an urgent need in novel nootropic drugs. Here, we evaluate acute effect of MV-007, beta-alanine derivate, on zebrafish behavior in the conditioned place aversion test (CPA) and novel tank test (NTT). METHODS: A total of 32 short-fin wild type zebrafish housing according to the standards of zebrafish care were used for the study. Novel tank test represents a rectangular plastic tank divided into top and bottom parts. Frequency, duration of top entries and freezing bouts, as well as total distance moved and duration of high-mobile state were calculated for experimental and control fish. Conditioned place aversion test representing a rectangular glass tank (14 height×25 length ×12 width cm) divided into two halves. Black and white plastic cover was glued on the outside of each part of the tank. Low voltage (0.1 mV/cm of water) electric current were negative stimuli for zebrafish avoiding dark part of the test. Prior to testing, fish were pre-exposed with 700 mg/L of MV007 in plastic breaker for 20 min and then were tested in novel tank test for 5 min. Zebrafish behavior was recorded by camera and assessed using Noldus EthoVision XT 11.5 software. Then, zebrafish were trained in conditioned place aversion test for 4 hours. Next day, zebrafish behavior was recorded for 5 min and latency, frequency and duration of dark part entries were analyzed. RESULTS AND DISCUSSION: No statistically significant differences between experimental and control groups in the novel tank test were observed. However, acute MV-007 exposure significantly increase latency to enter to the dark part of the tank. Thus, MV-007 is likely to have nootropic-like properties in zebrafish, thus may be a perspective agent for mental disorders treatment in human. RESEARCH SUPPORT: The research was supported by the Russian Science Foundation (RSF) grant 19-15-00053. The laboratory is supported by SPSU state budgetary funds ID 73026081, Almazov National Medical Research Centre, and Russian Scientific Center of Roentgenoradiology.

NEUROPEPTIDE SYSTEMS MODULATE POST-STRESSOR RESPONSE IN ZEBRAFISH (*DANIO RERIO*), PP Khokhlov, AA Blazhenko, AD Devyashin, LK Khnychenko, ER Bychkov, SV Kazakov, AA Lebedev, PD Shabanov, Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia

INTRODUCTION: Zebrafish is well known as a successful model organism for behavior studies and particularly stress investigation. However certain molecular and cellular mechanisms are unclear, especially in fish and other lower vertebrates [1]. The aim of our studies was to evaluate roles of «food intake chain» neuropeptides in stress response in zebrafish.
METHODS: Zebrafish of 500 mg weight and 18-25 mm length (male and female) have been used in all experiments. The exposure to predator (Cychlasoma sp., Cychlidae, Percifornes) has been used for

imaging of stress conditions. Then experinental fish have been anaesthetized and brain structures and tail muscle has been obtained and homogenized with «Cryomill» (Retsch, Germany). After homogenizing suspended samples have been analyzed by means of ELISA kits. Cortisol in tail muscle, ghrelin, orexin and corticotropin-releasing hormone in brain structures have been measured. The concentrations of neuropeptides were measured by means of ELISA test kits (ghrelin fish, orexin fish, CRH fish, Phoenix, USA). The quantitative measurements have been made with reader «Synergy 2» (Biotek, USA). RESULTS: The stress effect has been detected by cortisol measurement in tail muscle. Predator exposure have resulted to significant increase of cortisol concentration. The cortisol level has been significantly decreased after ghrelin antagonist administration compared to control animals. So we have used the level of cortisol in tail muscle as an indicator of post-stressor condition. We have used forebrain (up to eye orbit), midbrain (space between eyes' orbits) and hind brain (from eye orbit up to operculum). The exposure to predator has resulted in the changes of distribution of ghrelin, orexin and CRH. The influence of stressor factors has led to changing in distribution of neuropeptides in brain sections. After predator exposure ghrelin concentration has been significantly decreased in hindbrain and at the same time has been increased in fore- and midbrain. CONCLUSIONS: Ghrelin, orexin and certain others signaling neuropeptide signaling systems which are known to regulate food intake in Danio rerio (zebrafish) at the same time take part in response to stress conditions. We may hypothesize about ghrelin production in brain structures in zebrafish. Blocking of ghrelin signaling system results in decrease of response to stress. Furthermore we may propose the ghrelin, 0rexin and CRH signaling systems to be targets for stress effects' correction. Key words: zebrafish, Danio rerio, ghrelin, orexin, corticotrophin-releasing hormone, cortisol, stress.

CORTISOL CONCENTRATION IN ZEBRAFISH (*DANIO RERIO*) AFTER STRESS EXPOSURE AND PHARMACOLOGICAL SUBSTANCIES ADMINISTRATION, AA Blazhenko, PP Khokhlov, IYu Tissen, ER Bychkov, AS Devyashin, SV Kazakov, VA Lebedev, AA Lebedev, SN Proshin, PD Shabanov, Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia

INTRODUCTION: When a human is stressed, corticotropin-releasing hormone containing cells in the hypothalamus are activated, and this leads to the release of CRH, which acts on corticotropic cells in the anterior pituitary to stimulate the release of adrenocorticotropic hormone (ACTH) into circulation. ACTH acts on the adrenal cortex to stimulate glucocorticoid release (corticosterone in rodents, cortisol in humans and Danio rerio). Cortisol mediates adaptive functions to facilitate coping with the stress in humans.According to the literature cortisol is a biomarker of stress also in D. rerio. METHODS: In our study 68 specimen Danio rerio, one speciman of predator Cichlasomanicaraguensis have been used. The fish has been kept at a normal room temperature (22-23 ºC) with standard feeding time (twice per day). The level of cortisol has been tested by ++ELISA test. During experiment a fish has been firstly placed in a beaker with a dissolved pharmacological substance, then has been transferred into a tank with predator. In the end of experiment it has been put into a novel tank for 6 min. Surgically the tail muscle has been taken. After that the material for ELISA test has been made (Cortisol, ELISA kit). RESULTS AND DISCUSSION: In the Control (intact fish) group the level of cortisol has been 0.346 ± 0.035ng/ mg of protein. After predator exposure its level has been changed to 0.720 ± 0.052ng/ mg of protein. After CRF administration in intact fish the level of cortisol has been 0.896 ± 0.068ng/ mg of protein. After [D-Lys3]-GHRP-6 administration in intact fish the level of cortisol has been 0.356 ± 0.043. And after [D-Lys3]-GHRP-6 administration and predator exposure the cortisol level has been changed to 0.357 ± 0.029ng/ mg of protein. The level of cortisol after CRF exposure has been0,896 +/- 0,068 ng/ mg of protein. CONCLUSION: Exposure to a predator increased the level of cortisol in the D.rerio tail practically twice. After the exposure to CRF the cortisol level increased more than 2 times. The ghrelin antagonist [D-Lys3]- GHRP-6 did not significantly change the level of cortisol in the intact fish, but reduced the level of cortisol which has been increased by exposure to a predator. Key words: cortisol, CRF, Danio rerio, stress.

ZEBRAFISH EEG UNDER VARIOUS TYPES OF ANESTHESIA: A PILOT STUDY. MA Gubaydullina, SL Khatsko, AV Kalueff, Ural Federal University, Yekaterinburg, Russia; Southwest University, Chongqing, China

INTRODUCTION: Brain function is in a tight connection with animal behavior, so the influence of various psychoactive substances affects brain electrical activity. Among the others, alcohol and caffeine contain in various foodstuffs and induce prominent neurotropic effects. Furthermore, these compounds extremely influence the procedure of electroencephalography. Hence, we noninvasive EEG apparatus for zebrafish (Danio rerio), high-potential aquatic organism, standardized this method by using alcohol and caffeine. The main purpose of this study was to evaluate the action of distinct anesthesia methods (cold water and eugenol solution) on EEG. METODS: The experiments utilized 50 wild type adult zebrafish with 50/50 male-female ratio. All fish were kept in 40 L tanks filled with filtered water in accordance with zebrafish care standards. Experimental groups included fish anesthetized with 100

μg/100 ml eugenol solution (n=5), +2°C - +7°C cold water (n=5), fish treated with alcohol in hyperactive (0.25%) dose anesthetized with cold water (n=5) and eugenol solution (n=5), fish treated with alcohol in hypoactive (1%) dose anesthetized with cold water (n=5) and eugenol solution (n=5), fish treated with caffeine in hyperactive (5 mg/L) dose anesthetized with cold water (n=5) and eugenol solution (n=5), and fish treated with caffeine in hypoactive (100 mg/L) dose anesthetized with cold water (n=5) and eugenol solution (n=5). Electroencephalography (EEG) included 3 electrodes application to the zebrafish head in the midbrain region. Brain rhythm frequencies were defined in the range of 0.5-30 Hz. RESULTS AND DISCUSSION: Both anesthetics induced the pronounced increase in slow high-amplitude rhythms (delta and theta) in zebrafish. However, cold water anesthesia caused prevailed both low-frequency and high-frequency beta rhythms in comparison with eugenol anesthesia, probably indicating lesser anesthetic effect. Alcohol in dose of 0.25% exhibited decreased delta and theta rhythms and increased alpha and both (high/low-frequency) beta rhythms under cold water, and increased share of low frequency rhythms and the same changes with alpha and both beta rhythms under eugenol solution. Caffeine at a high dose caused seizures, resulting in a high-amplitude dominant part of the delta under both anesthetics. Low dose caffeine reduced delta and increased alpha rhythms under both anesthetics, increased theta rhythm under eugenol and decreased theta rhythm under cold anesthesia. Thus, eugenol displays higher potential for anesthesia than cold water, as far as EEG assessment reveals the increase in alpha and theta rhythms. On the contrary, cold water anesthesia induces higher beta rhythm share in total EEG than under eugenol solution, which is close to wakeful state. Above all, the method presented here stands to advance the utility of the adult zebrafish in the study of nervous disorders as an efficient alternative to the electroencephalography performed in mammalian models and human patients.

ANHEDONIA MODELS IN ZEBRAFISH: ARE WE THERE YET? MS de Abreu, F Costa, ACVV Giacomini, KA Demin, EV Petersen, DB Rosemberg, AV Kalueff, Laboratory of Cell and Molecular Biology and Neurobiology, Moscow Institute of Physics and Technology, Moscow, Neuroscience Program, Sirius University, Sochi, Russia; Bioscience Institute, University of Passo Fundo, Passo Fundo, RS, Graduate Program in Biological Sciences, Federal University of Santa Maria, Santa Maria; Brazil; School of Pharmacy, Southwest University, Chongqing, China

Central nervous system (CNS) disorders are a major cause of disability, including the loss of pleasure - anhedonia. Animal experimental models are commonly used to better understand the mechanism involved in anhedonia and to develop novel therapies for this disability. The zebrafish (Danio rerio) is a powerful model to assess pathobiological mechanisms of anhedonia. Here, we critically discuss the use of zebrafish models for studying mechanisms of anhedonia and for developing novel therapies of this disability, and its translational implications.

ISBS SPECIAL TALK: NEUROPROSTHETICS OF MOTOR AND VISCERAL FUNCTIONS, PE Musienko, Institute of Translational Biomedicine, St. Petersburg State University, Pavlov Institute of Physiology RAS, St. Petersburg, Sirius National Technical University, Neuroscience Program, Sochi, Russia

SYMPOSIUM 5: CONSOLIDATED POSTER SESSION PART 1

Chairs: AV Kalueff (China, Russia, USA) and VM Klimenko (Russia)

EFFECTIVENESS EVALUATION OF GROOMING MICROSTRUCTURE INDICATORS TO IDENTIFY DEPRESSIVE BEHAVIORAL FEATURES OF TAAR1-KO AND TAAR5-KO MICE, AL Manasyan, SA Apryatin, EM Turkeeva, VM Klimenko, Institute of Experimental Medicine, St. Petersburg, Russia

Introduction: Trace amine receptors TAAR1 and TAAR5 belong to the class of orphan G-protein coupled receptors. TAAR1 is expressed in glial cells and neurons, as well as in peripheral organs and tissues. It has been shown that TAAR1 is an important link in dopaminergic and serotonergic neurotransmission. Its functional impairment leads to depressive conditions. The TAAR5 receptor is used as a molecular target in the treatment of mental and other disorders (schizophrenia, depression, etc.). The potential role of TAAR5 in modulating cognitive functions in various functional disorders of the brain has been shown. TAAR5-KO are known to be less susceptible to stress and have low levels of anxiety. It is known that the microstructure of grooming changes under stress and depressive conditions in rodents. Thus, the study of depressive behavior is of great research interest for understanding the microstructure of grooming and its patterns. The aim of this work is a comprehensive analysis of TAAR1 and TAAR5 knockout mice grooming microstructure (total duration, frequency, latency, and other indicators) and the selection of the most informative parameters for anxiety and depressive states identifying. METHODS: The study was carried out on TAAR1-KO (n = 17) and TAAR5-KO (n = 12). Laboratory animals of each line were genotyped and divided into two groups with the WT and KO genotypes. Grooming indicators

were analyzed in the tests "Open field" (OF). In this study, three main indicators of grooming were assessed: latency (in seconds) to start grooming (LG), number of grooming acts (NB), and total time (in seconds) spent on grooming (TS). Also, for all groups, the total number of stages (NS), the average duration (in seconds) of one stage (TS/NS) and the average duration (in seconds) of a single grooming act (TS/NB) were calculated. TS/LG depression ratio was proposed to assess depressive states. RESULTS AND DISCUSSION: In the OF test, there are traditional indicators of grooming (TS, LG, etc.). significantly differed in TAAR1-KO mice in comparison with the “wild type” mice. The latency of the onset of grooming was almost 2 times higher in TAAR1-KO mice than in the WT group. In addition, the same group significantly demonstrated shorter stages, a sharp decrease in the frequency (TS/NB) and duration of grooming. The depression ratio (TS/LG) values were significantly different in both groups. The average number of acts and stages did not differ significantly in both groups. In contrast, TAAR5-KO mice not prone to anxiety and depression were characterized by a longer time spent on grooming against the background of a longer average duration of a single act and a greater number of grooming stages. Depression ratio (TS/LG) values were also increased in comparison with “wild type”. The number of acts, the average duration of one stage and the grooming latency did not differ significantly. It was shown that mice with depression symptoms were characterized by a later onset of grooming (LG), spent less time both on grooming itself and on its patterns, and, as a consequence, more reduced grooming activity and intermittent nature of its stages. The mean values of the TS/LG coefficient in the more depressed TAAR1-KO mice decreased in comparison with the WT group. TAAR5-KO mice showed the opposite effect (antidepressant behavior), which was expressed in fuller and more complete grooming and an increase in the mean values of the depression ratio (TS/LG). Thus, TAAR1-KO mice demonstrated depressive changes in the parameters of grooming microstructure in the OF test, while TAAR5-KO mice, on the contrary, demonstrated antidepressant behavior. In this regard, the search for TAAR1 receptor agonists and TAAR5 antagonists is an urgent scientific target for the development of new effective antidepressants. The proposed and characterized of depression ratio (TS/LG) can be used to grooming microstructure analyze in the study of depressive behavioral rodents characteristics. A decrease in TS/LG values may indicate the presence of depressive symptoms in rodents.

THE RESEARCH FOR DIAGNOSIS OF STRESS USING TGI TECHNIQUE, K Oda, M Koshiba, Graduate School of Science and Technology for Innovation, Yamaguchi University, Yamaguchi, Department of Pediatrics, Saitama Medical University, Saitama, Graduate School of Information Sciences, Tohoku University, Tohoku, Japan

INTRODUCTION: The number of patients with chronic pain is on the rise, and currently 13% of the population in Japan is affected. It has been reported that the intensity of pain changes due to stress. On the other hand, we examined to evaluate the stress by evaluating the pain. It is recommended to use a thermal pain threshold for pain assessment, but there is a risk of burns and it is necessary to stimulate the pain at the lowest possible temperature. Therefore, we made a prototype probe using the thermal grill illusion (TGI) technique, and the decrease in the threshold value by TGI was confirmed, and the change of the pain level due to stress was evaluated. METHODS: We recruited 7 healthy adult participants for this study. A probe with three areas of 2.2×3.8 [mm] in parallel was fabricated. The temperatures on both sides were fixed conditions at 28 (TGI condition) or 32 (not-TGI condition) degrees Celsius, and the thermal pain threshold was measured by center area. The pain sensitivity before and after the stress load by 2-Back-test was evaluated. RESULTS AND DISCUSSION: The pain threshold at TGI conditions was lower than not-TGI conditions. The averages of pain threshold temperatures at TGI and non-TGI conditions were 43.4 and 46.9 degrees Celsius, respectively. The pain threshold temperatures after stress became higher compared with before. This study may suggest that TGI condition enables us to safely diagnose both our pain and stress.

INTER-AND TRANSGENERATION INHERITANSE OF CHEMICAL AND PSYCHOLOGICAL STRESS IMPACTS. EPIGENETIC MECHANISMS, EL Patkin, SG Tsikunov, Institute of Experimental Medicine, St. Petersburg, Russia

Exposure to chronic chemical or/and Psychosocial stress, either repeated severe acute or moderate sustained stress, is one of the strongest risk factors for the development of psychopathologies such as post-traumatic stress disorder and depression. Chronic stress is linked with several lasting consequences, particularly to the stress endocrine system, also disturbing intermediate phenotypes such as brain structure and function, immune function, and behavior. Genetic predisposition confers a proportion of the risk, the most relevant molecular mechanisms determining susceptible or resilient to the effects of different types of stress and trauma may be epigenetic. Epigenetics refers to the mechanisms that regulate or at least modulate genomic information by dynamically changing the patterns of transcription and translation of genes. A growing body of data points to the specific role of epigenetic modifications in response to chemical, traumatic and chronic stress. Moreover, the picture is complicated by the fact that different types of stressful influences can act simultaneously, and in different

ways, depending on the period of ontogenesis. Thus, a better understanding of epigenetic changes is needed by further investigations in longitudinal studies beginning very early development, when the main epigenetical reprogramming takes place. Chronic stress and trauma are associated with several lasting biological changes, particularly of the stress endocrine systems. Thus, it is important to study epigenetic changes upon endocrine disrupting chemicals such as bisphenol A, and to trace how such agent, enduring stress and trauma can lead to permanent changes in the structure of several brain regions and their epigenetic status. Epigenetic changes refer to the mechanisms that regulate genomic information by altering the accessibility of DNA to transcriptional regulators by: (i) post-translational modifications of histone proteins,(ii) the addition of chemical groups most commonly at cytosine-phosphate-guanine (CpG) sites (e.g. methylation, hydroxymethylation, or other modification), or (iii) the binding of non-coding RNAs to specific sequences in DNA. Epigenetics thus provides a mechanism by which the environment can have a global and lasting influence on the expression of genes in an individual following stress exposure, with epigenetic processes believed to underlie associations of disease burden, environmental risk, and individual phenotype. Several lines of evidence suggests that epigenetic modifications may be sustained during cell division (for example due to asymmetric chromosome divisions) and possibly transmitted across generations. The strongest evidence for epigenetic transgenerational inheritance comes from animal studies of parental transmission but depending on maternal or paternal transmission. Stress occurring early in development can cause dramatic effects on physiology and behavior. However, additional studies of how different types and lengths of stress lead to epigenetic changes are required as well as of combined effects of mentioned different types of stress. Changes to gene expression by epigenetic modifications are prominent gene and environment interactions that are an important aspect of future chronic stress and trauma research. It is necessary to take into consideration that epigenetic inheritance transmission to next generation (intergeneration) or transgeneration (further generations) depends on paternal or maternal transmission. For mechanistic understanding, tissue specificity of these epigenetic changes must be addressed and understood. Overall, more research in this area will lead to a better understanding of stress-induced epigenetic effects and mechanisms as well as their potential moderation, allowing for their therapeutic exploitation and the development of new interventions and treatments.

INFLAMMATION AND OXIDATIVE STRESS PERIPHERAL INDICATORS AS BIOMARKERS OF EARLY DIAGNOSIS OF CHRONIC CEREBROVASCULAR INSUFFICIENCY, OS Tumashova, ZM Muruzheva, IS Ivleva, MN Karpenko, VM Klimenko, Institute of Experimental Medicine, St. Petersburg State Chemical Pharmaceutical University, St. Petersburg, Russia

INTRODUCTION: Chronic cerebrovascular insufficiency (CCI) is the most common vascular pathology of the brain. Solving the problems of early diagnosis and prevention of CCI is one of the priorities due to the high prevalence of CCI, the substantial medical and social consequences, as well as the significance of this disease as a risk factor for stroke. This study aims to identify peripheral biomarkers for the diagnosis of CCI at the pre-symptomatic stage of the disease. SUBJECTS AND METHODS: The study involved 20 patients with dyscirculatory encephalopathy (DE), including 4 men (20%) and 16 women (80%), aged 50 to 83 years, the median was 74.5 years (73.0; 81.0). Among them, 15 (75%) patients were diagnosed with "stage 2 dyscirculatory encephalopathy", 5 (25%) – "stage 3 dyscirculatory encephalopathy". The duration of the disease varied from 3 to 25 years, the median-15 (10; 16) years. The control group consisted of 12 healthy volunteers. The Montreal Cognitive Assessment (MoCA) and the Mini-mental State Examination (MMSE) were used for the study of cognitive functions. The content of cytokines (IL-1β, IL-6, IL-8, IL-10, TNF) in the blood was determined by ELISA. The lactate, pyruvate, malondialdehyde (MDA) levels, as well as the activity of catalase, glutathione-S-transferase, and glutathione reductase were determined by the colorimetric method. RESULTS AND DISCUSSION: When assessing cognitive functions on the MoCA in patients with CCI, the median was 21 (18; 24) points. The average score for MMSE was 26 (24; 28) points. The level of IL-1β and IL-8 in the CCI group was significantly higher than in the control group and amounted to (5.4 ± 0.9 pg/ml) and (3.7 ± 0.6 pg/ml) vs (3.0 ± 0.5 pg/ml) and (1.0 ± 0.2 pg/ml), respectively ($p<0.01$). The level of MDA in the serum of patients with CCI was also significantly higher than in the control group - (3.4 ± 0.1 pg/ml) vs (2.9 ± 0.1 pg/ml), respectively ($p<0/05$). The level of IL-10 in the CCI group was lower than in the control group - (3.3 ± 0.6 pg/ml) versus (5.0 ± 0.3 pg/ml), respectively ($p<0.01$). The levels of IL-6 and TNF in the CCI group were (1.1 ± 0.4 pg/ml) and (2.6 ± 0.3 pg/ml) and did not differ from the control group - (0.8 ± 0.2 pg/ml) and (2.1 ± 0.3 pg/ml). CONCLUSION: The IL-1β, IL-8, IL-10 levels, and MDA in the blood have potential diagnostic significance for early diagnosis of CCI. The serum IL-1β level has a potential prognostic significance for identifying individuals with a high risk of developing grade III CCI among patients with grade II CCI.

DEXAMETHASONE INCREASES ACTIVITY OF CALPAIN- 2 IN THE HIPPOCAMPUS AND CORTEX, TV Tyutyunnik, AS Zubov, MN Karpenko, VM Klimenko, St. Petersburg State University, Pavlov Department of Physiology, Institute of Experimental Medicine, St. Petersburg, Russia

INTRODUCTION: Nowadays many people have degenerative diseases. Some of these health disorders are characterized by progressive neuronal death. Reasons for these CNS conditions research to present day. It's an essential biological problem to modulate growth by surviving neurons. There is a potential target for such therapy for the treatment of some neurodegenerative lesions. Such an object is a protein GAP-43 which participates in neurodegeneration, plasticity and the axon's growth. It was shown that in a single injection of the synthetic glucocorticoids, specifically dexamethasone, increased level of the RNA and protein GAP-43 in CNS. However, as well that protein is a substrate of protease, calpain-2 which even be able to lead to apoptosis and cell death. That enzyme cleavage GAP-43 by a specific site Ser41. Additionally, establishing fragments of the target protein, forming after that cleavage, can inhibit the calpain-2. Therefore, it's necessary to explore how the injection of glucocorticoids influences the activity of calpain-2. METHODS: In the experiment, there were used two groups of rats: control (n=4) and experimental (n=4). The experimental group was administrated the single injection of dexamethasone in a dose of 8 mg/kg. The control group was administrated the single injection of a saline solution in the value of 1 ml a rat. After 18 hours animals were decapitated and the hippocampus and cortex were analyzed. The activity of calpain -2 in these structures was measured by the method polyacrylamide gel electrophoresis (PAGE) with adding casein. Data is shown as m $\pm$ SEM using the statistical Mann–Whitney U test. RESULTS AND DISCUSSION: It turned out that the level of activity of calpain-2 in the hippocampus enhances in the experimental group (3.5 ± 0.3) in 1.5 times (p=0.02) relatively control group (2.3 ± 0.1). Also, the level of activity of calpain-2 increases in the cortex at rats getting an injection of dexamethasone (1.5 ± 0.0) in 1.5 times (p=0.006) relatively control (1.0 ± 0.1). Thus, the dexamethasone injection in a dose of 8 mg/kg induces the calpain-2 activation. Consequently, dexamethasone -mediated increase of the GAP-43 production is able to form its split residuals. So, the probable neuroprotective effect of dexamethasone requires further investigations.

AGE-DOSE-DEPENDENT ANALGETIC EFFECT OF A TYPE 2 VASOPRESSIN RECEPTOR AGONIST, 1-DESAMINO-8-D-ARGININE-VASOPRESSIN, IN A MODEL OF ACUTE THERMAL RAT PAIN, AA Nikitina, VA Maistrenko, SG Belokoskova, SG Tsikunov, Institute of Experimental Medicine, St. Petersburg University of the Ministry of the Interior of Russian Federation, St. Petersburg, Russia

INTRODUCTION: Arginine-vasopressin (AVP) is known to be involved in pain modulation (Yang J. et al., 2006, 2007). The role of activation of type 1 receptors by AVP in this process has been established (Zubrzycka M. et al., 2005; Juif P.E. et al., 2013). The role of type AVP 2 receptors (Avpr2) has been little studied. In the tail flick test the agonist Avpr2, 1-desamino-8-D-arginine-vasopressin, DDAVP, with a single injection into the ventricles of the brain increased the threshold of nociceptive reaction in rats (Kordower J.H. et al., 1984). DDAVP in intranasal administration caused analgesia in volunteers in conditions of mechanical pain (Pohl J. et al., 1996); reduced the severity of spondylogenic pain (Belokoskova S.G., et al., 2016). There is no data on the effect of DDAVP in intranasal administration on acute thermal pain in rats. The aim of the study was to assess the effect of Avpr2 agonist, DDAVP, with course intranasal administration on nociceptive sensitivity in the model of acute thermal pain in rats of different ages. METHODS: The study was carried out on 79 mature male rats of Vistar aged four and nine months (the original body weight of 220 ± 25 g), contained in standard conditions of vivarium. They simulated acute pain by thermal irritation of the tail skin when immersed in hot water. The stimulus was applied to the tip of the tail when immersed in a container with water heated to a temperature of 52 ± 0.1° C. The time, in seconds, of flicking the tail out of the water was considered the threshold of nociceptive response (TNR). Each animal used 6-fold measurements determined the average values of TNR before and after the introduction of DDAVP. The method of block randomization of animals four and nine months divided into 4 groups. Group 1 (intact control) included 10 young and 10 adult rats; Group 2 consisted of 10 young and 10 adult rats that received saline; Group 3 – 10 young and 10 adult rats who received low doses of DDAVP; Group 4 – 8 young and 9 adults who received high doses of DDAVP. DDAVP was administered intranasally once a day for 5 days in 2 dose ranges: in small doses – 2 ng once, 10 ng per course and in large doses – 2 μg once and 10 μg per course. Saline was administered according to the peptide regimen. Before and after the administration of the test substances, the mean values of the tail-flick latency (TFL) and the percentage of analgesia were determined. The percentage of analgesia (% A) was calculated using the formula: A = [P – B] / [30 – B] X100%, where A is the percentage of analgesia or % of the maximum possible effect; P – latent period of reaction in seconds after drug administration; B – latency period before drug administration; 30 s – maximum exposure time in seconds (Anjaneyulu M. et al., 2004; Jinushi K. et al., 2018). Statistical analysis was performed using Student's t-test and one-way analysis of variance. Differences were considered significant at $p < 0.05$. RESULTS AND ITS DISCUSSION: In rats at the age of 4 months, DDAVP, administered in high doses, increased the TNR and % A ($p = 0.023$; $p = 0.024$, respectively). In rats at the age of 9 months, DDAVP did not affect the TNR and % A ($p > 0.05$, $p > 0.05$, respectively).

Thus, DDAVP in young rats, when administered intranasally at high doses (2 μg / day, 10 μg / course), increased the TNR and % A. The revealed age-related and dose-dependent moderate analgesic effect of DDAVP could be due to a number of factors. It is known that the representation of Avpr2 in the rat brain depends on the age of the rodents. In rats in the neonatal period, the expression of the Avpr2 gene was detected in the forebrain, olfactory bulb, hippocampus, cerebellum, cochlea of the middle ear, choroidal plexus and vascular endothelium in adult rats - only in the hippocampus and cerebellum (Ostrowski N.L. et al., 1992; Hirasawa A. et al., 1994; Kato Y. et al., 1995; Furuta H. et al., 1998; Chen Q. et al., 2000; Vargas K.J. et al., 2009; Muramoto K. et al., 2011). It is generally accepted that the tail withdrawal reflex is realized mainly at the spinal level (Olkhovik Yu.A. et al., 2015). Probably, when administered intranasally in large doses, DDAVP increased the activity of the antinociceptive system of the rat brain, which had an inhibitory effect on the spinal mechanisms of the reflex. It is known that AVP is involved in modulating stress responses (Gagliese L. et al., 2000). A decrease in nociceptive sensitivity in rats after moderate stress exposure has been shown (Butler R.K. et al., 2009). It cannot be ruled out that DDAVP, activating stress responses, caused stress analgesia. Analysis of the effect of DDAVP on the content of adrenaline, norepinephrine, dopamine, serotonin, BDNF, GDNF and the levels of whole genome DNA methylation in blood and brain will clarify the contribution of peptide activation of the antinociceptive system and stress reactivity to the modulation of the nociceptive response by the peptide.

DEVELOPMENT OF ANHEDONIA IN ADULTS AND YOUNG FEMALE RATS AFTER VITAL STRESS, NK Apraksina, TV Avaliani, SG Tsikunov, Institute of Experimental Medicine, St. Petersburg University of the Ministry of the Interior of Russian Federation, St. Petersburg, Russia

INTRODUCTION: One of the psychoemotional disorders arising from exposure to stress associated with a threat to life is anhedonia. The severity of the decrease or loss of the ability to receive pleasure, loss of motivation for activity and activity in achieving the goal are determined by the individual psychopathological characteristics of the individual and age-related changes in the perception of pleasure among them. The aim of the study was to assess the dynamic of the development of anhedonia caused by vital stress depending on the age of female rats. METHODS: Study performed on the young (5 months -group A) and adult (14 months- group B) female rats of Wistar weigh 200-350 gram (n=40). The control was the indicators of animals before psychogenic trauma (group A1, group B1). The psychogenic trauma in a group of female rats was modeled being placed in a terrarium to tiger python, where one of them is the victim of predator food (Tsikunov et al., 2016). Severity of depressive component behavior in stressed rats was verified in a test for sucrose preference. The basal level of preference, the ratio of consumption of 1% sucrose solution to the total volume of fluid you drink per day in percentage was determined and correlated with indicators of preference after stress. Reduction of more than 50% of sucrose consumption was believed anhedonia. To detect statistically significant differences applied univariate analysis of variance for repeated measures and Student's T-test for dependent samples corrected for multiple comparisons. RESULTS AND DISCUSSIONS: The control groups A1, B1 of animals showed a basal preference for sucrose solution. We did not establish a correlation between metabolic changes in terms of changes in body weight, water and feed intake and the level of sucrose preference. A significant change in the preference for sucrose solution after vital stress was found both group (0,84 ± 0,08 vs. 0, 15 ± 0,01; p.005)- groups A and in group B (0,75 ± 0,06 vs. 0,09 ± 0,01; p.005) compared to the control. The revealed changes were observed largely in-group B in 50% of animals; in contrast to 20% kkin-group, A. Hedonic changes observed within 9 days after stress in the experimental groups were wavy in nature. In adult female rats, the manifestation of anhedonia persisted later, compared with young animals that underwent vital stress. Thus, the life-threatening psychogenic effect leads to the development of anhedonia in both young and adult female rats. The most pronounced and long-term hedonic changes caused by vital stress are characteristic of older animals.

BLOOD PLASMA BUTYRYLCHOLINESTERASE ISOFORMS ACTIVITY IN MILD COGNITIVE IMPAIRMENT, VV Khizha, DE Zaitsev, MF Balluzek, AB Shishkin, SV Symina, DS Vasilyev, DI Kozlova, Sechenov Institute of Evolutionary Physiology and Biochemistry RAS, St. Petersburg Clinical Hospital RAS, St. Petersburg, Russia

INTRODUCTION: The activity of different butyrylcholinesterase (BChE) forms (typical, atypical and minor) was investigated for amnesic mild cognitive impairment (a-MCI) further diagnostic usage. METHODS: 21 patients aged 56±21 years with verified MCI were included in to this study. The control group (CG) consisted of 27 patients without memory and attention impairment (51±23 years). The activity of BChE forms was determined by the modified Ellman’s method in combination with inhibitory analysis. The analysis was performed in 96-well plates in the presence of a synthetic substrate - butyrylthiocholine (BTCh). RESULTS AND DISCUSSION: The general activity of BChE in CG was 1513±54,4 pmol of substrate/mg protein×min with the maximum input (51%) of typical BChE (769,8±25,9). Activity of atypical BChE was 53% (409,3±14,2) of the typical form's activity (it was fully compatible with the

literature data), and 27% of total activity. The activity of the minor forms was about 43% of typical BChE activity (333,9±14,3) and 22% of total activity. It was demonstrated that the total BChE activity in relatively healthy people consisted of 50% of the typical form and 50% of atypical and minor isoforms. Just the same time in patients with diagnosed a-MCI the total BChE activity was approximately 35% lower than in CG (987,3±25,1). The maximum input (48%) to the total activity was made by typical BChE (470,2±10,5). The activity of atypical BChE was 69% (324,7±6,3) of the activity of typical BChE and 33% of the total form. The activity of minor forms was 192,4±8.3. This is approximately 41% and 19% of the typical and the total forms activity respectively. Based on the results of our study, we can conclude that a decrease of the typical and minor forms of BChE activity as well as an increased input of atypical BChE to the total activity can serve as a diagnostic criterion for the a-MCI pathological changes development evaluation. The obtained data can be used as a basis for the creation of a diagnostic test system. Completed with partial financial support from RFBR 18-515-57001, 13-04-00388, 19-015-00232. The study was carried out within the framework of the state task AAAA-A18-118012290373-7.

CHANGES IN THE BRAIN EXPRESSION OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR GENES IN THE RAT MODEL OF TEMPORAL LOBE EPILEPSY, AA Kovalenko, MV Zakharova, AP Schwarz, AV Dyomina, TB Melik-Kasumov, OE Zubareva, Sechenov Institute of Evolutionary Physiology and Biochemistry RAS, St. Petersburg, Russia; Institute of Physiology NASB, Minsk, Belarus

Despite intensive research, approximately 30% of patients with temporal lobe epilepsy suffer from pharmacoresistant forms of the disease. The role of gut-brain interactions in the pathogenesis of neurological diseases is widely discussed. Peroxisome proliferator-activated receptors (PPARs) are considered to be a key element of these interactions, and PPARs agonists are considered promising for epilepsy therapy due to their neuroprotective and anti-inflammatory effects. However, the PPARs gene expression in the animal brain in epilepsy models have not been fully elucidated. This research aims to study the expression of different PPAR genes in the rat ventral and dorsal hippocampus and temporal cortex in the lithium-pilocarpine model of temporal lobe epilepsy. Lithium-pilocarpine seizures were induced in Wistar rats aged 7-8 weeks by administration of LiCl solution (i.p., 127 mg/kg) and then, after 24 hours, pilocarpine (PC, i.p., fractional administration of 10 mg/kg every 30 min before reaching stage 4 severity of seizures on the Racine scale or to a maximum dose of 40 mg/kg). Half an hour before the first injection of PC, methylscopolamine was administered (i.p., 1 mg/kg). The control rats were injected with saline and LiCl. The relative gene expression of 3 types of PPARs (Ppara, Ppard, Pparg) was measured by quantitative RT-PCR in the latent (3 and 7 days after PC-induced seizures) and the chronic (60 days after PC administration) phase of the model. During the latent phase of the lithium-pilocarpine model, we observed a decrease in Ppara mRNA production and an increase in Ppard gene expression in the ventral region of the rat hippocampus. In the temporal cortex, we also found a decrease in Ppara gene expression in the latent and chronic phases of the lithium-pilocarpine model. Pparg gene expression did not change significantly in the studied brain regions. Thus, the mRNA expression of PPARs changes after pilocarpine-induced seizures. The results suggest that Ppara mRNA downregulation may have epileptogenic effect, while changes in Ppard gene expression may represent one of the compensatory mechanisms. Supported by RFBR project No. 20-515-00020.

PLASMA BDNF CONTENT IN CHILDREN WITH VARIOUS FORMS OF AUTISM SPECTRUM DISORDERS, EM Malsagova, ZM Muruzheva, SG Belokoskova, MN Karpenko, SG Tsikunov, Institute of Experimental Medicine, St. Petersburg University of the Ministry of the Interior of Russian Federation, St. Petersburg, Russia

INTRODUCTION: Autism spectrum disorders (ASD) are a heterogeneous group of mental development disorders, including diseases and conditions with similar clinical manifestations in the form of impaired ability for social interaction, verbal and non-verbal communication, stereotyped behavior, leading to social maladjustment (Simashkova N.V., 2015; APA, 1994). The study of the pathogenesis and pathophysiology of ASD remains relevant. Neurotrophins are involved in the growth, development, and regulation of brain functions. BDNF (brain-derived neurotrophic factor) and related TrkB receptors potentiate neurogenesis, angiogenesis, synaptic plasticity and neuronal survival, affect learning and memory (Lasek-Bal A. et al., 2015). In the developing central nervous system, the content of BDNF is at a low level and increases as it matures (Maisonpierre P.C., 1990). There is a relationship between the content of BDNF in the brain and the concentration in the blood (Pan W. et al., 1998; Karege F. et al., 2002). However, the role of BDNF in the pathogenesis of ASD is unclear. The data on the content of BDNF in the blood of children with ASD are contradictory. It is set to increase in the level of the neurotrophin in blood (Wang M. et al., 2015; Barbosa A.G. et al., 2020), and decline (Katoh-Semba R. et al., 2007). The aim of this work was to study the concentration of BDNF in the blood of children with various clinical forms of ASD. METHODS: The study was conducted on 78 patients with ASD, including 58 boys and 20 girls aged 3 to 12 years with an average age of 6.3 ± 0.3 years. The inclusion criteria for

patients with the study was compliance with the identified clinical manifestations of ICD-10, rubrics F84.0–F84.8. All subjects were divided into 5 groups. Group 1 included 43 children with early childhood autism (F84.0); Group 2 – 18 children with atypical autism (F84.1); Group 3 – 11 patients with other pervasive developmental disorders (with elements of autism) (F84.8); Group 4 – 6 patients with Asperger's syndrome (F84.5). Group 5 (control) consisted of 4 typically developing (TD) controls, 2 boys and 2 girls aged 4 to 7 years, with an average age of 6.5 ± 1.0 years. The CARS scale was used to assess the severity of the clinical manifestations of ASD. BDNF content in blood plasma was measured by ELISA (ELISE kit manufactured by Abcam ab212166). The normality of data distribution was checked using the Shapiro-Wilk test, the significance of differences between the two groups was established using the t-test for unequal variances, between three or more groups – ANOVA, followed by the Tukey test. The presence of statistical dependences was determined by calculating the Spearman's correlation coefficient. Differences were considered significant at $p < 0.05$. RESULTS AND ITS DISCUSSION: All 78 children with ASD had lower plasma BDNF levels than in TD ($t = -7.6$, $p = 0.00001$). In group 1, the content of BDNF was higher than in group 2 ($p = 0.03$) and lower than in group 5 ($p = 0.03$). In group 2, BDNF levels were lower than in groups 1 and 5 ($p = 0.03$, 0.002, respectively); in group 4 – lower than in group 5 ($p = 0.029$). The BDNF content in group 3 did not differ from that in group 5 ($p = 0.069$). The BDNF content in all 78 children with ASD did not depend on gender ($t = -0.69$, $p = 0.49$), age ($R = -0.15$), and disease severity ($R = 0.18$). A weak was found between the content of BDNF and the severity of the disease in children in group 2 ($R = 0.24$, $p < 0.05$). Thus, in all children with ASD, the BDNF content in the blood plasma was reduced as compared to the TD. In children with early childhood autism and atypical autism, Asperger's, the levels of neurotrophin were lower than in TD. In children with atypical autism, the BDNF content was lower than in children with early childhood autism. In the group of children with other general developmental disorders, the concentration of BDNF in the blood did not differ from its level in TD. The BDNF content in all children with ASD did not depend on gender, age, and severity of the disease. A weak relationship was found between the content of neurotrophin and the severity of the disease in children with atypical autism. Analysis of BDNF content in blood plasma in children with different forms of ASD reflects the different role of neurotrophin in their pathogenesis. In children with atypical and early childhood autism, that is, with non-symptomatic forms of ASD caused by congenital and often genetic pathology, a decrease in the level of neurotrophin reflected the presence of pronounced disorders in the neurotrophic supply of the brain. There were no changes in the BDNF content in children with other general developmental disorders, that is, with a symptomatic form of ASD caused by residual organic brain lesions. Thus, the analysis of the content of neurotrophin in blood plasma can be used for the differential diagnosis of non-symptomatic and symptomatic forms of ASD. The results obtained reflect the prospects of using techniques that activate BDNF expression in the brain in children with non-symptomatic forms of ASD.

NEUROBEHAVIORAL EFFECT OF THE NEWLY FORMULATED DRUG AS AN AGONIST OF SEROTONIN RECEPTORS [2,5-DIMETHOXY-N-[(2-METHOXYPHENYL)METHYL]ANILINE], TZ Mbutho, AV Zhdanov, VA Shevyrin, OV Kuprianeova, SL Khatsko, AV Kalueff, Ural Federal University, Yekaterinburg, Russia; Southwest University, Chongqing, China

INTRODUCTION: Stress is common physiological reaction of all living organisms to environmental alterations. In vertebrates, the main stress triggers are glucocorticoids, the hormones of adrenal gland. Interestingly, there is an obvious correlation in vertebrate species between stress response and the skin color (Khan et al., 2016). Hence, we assessed cortisol level in terms of acute stress procedure in genetically modified zebrafish strains (GloFish®), which tissues express fluorescent proteins closely related to pigments. METHODS: The experiment utilized 79 zebrafish of adult wild type and four GloFish® strains with 50/50 male-female ratio, spread out across five different 40-L tanks filled with filtered water in accordance with zebrafish care standards. The stressing procedure included 30 minutes predator exposure in 2L tanks, contained 10 ml solution of conspecific alarm substance (CAS). Hence, the control groups included unstressed wild type/WT (n=8), green fluorescent protein/GFP (n=8), red fluorescent protein/RFP (n=8), red + green fluorescent protein (orange)/RFP+GFP (n=8), and blue fluorescent protein/BFP (n=8) zebrafish. The acutely stressed fish were also reassigned to above mentioned strains: WT (n=8), GFP (n=8), RFP (n=8), orange (n=7), and BFP (n=8). The cortisol level was analyzed by ELISA under 415 nm detecting light beam wave length. RESULTS AND DISCUSSION: Basic cortisol was significantly lower in GFP and orange fish than in WT, and RFP fish cortisol level tended to be lower than in WT ($p=0.09$). Under acute stress, the orange fish exhibited less prominent stress response than WT, GFP, and BFP fish. Additionally, RFP fish tended to be more stressed than orange fish ($p=0.08$). Furthermore, paired comparisons between stressed and unstressed fish revealed no differences between stressed and unstressed orange fish. Hence, the results point at the remarkable stability of stress level in orange (RFP+GFP) zebrafish, as cortisol level had not changed even after 30 minutes of constant predator exposure and additional CAS influence. This evidence supposes to be the result of anti-stress effect, caused by combined expression of two fluorescent protein genes. However, the specific physiological mechanism of such genetic influence is still to be studied. RESEARCH SUPPORT: Ural Federal University, Yekaterinburg, Russia.

BEHAVIORAL ASSESSMENT OF DIFFERENT GLOFISH® ZEBRAFISH STRAINS IN THE NOVEL TANK TEST (NTT): A PILOT STUDY. AS Starodvorskaya, GO Maslov, CR Shakirova, KN Zabegalov, AV Kalueff, Ural Federal University, Ekaterinburg, Institute of Translational Biomedicine, St. Petersburg State University, Russia; Southwest University, Chongqing, China

INTRODUCTION: GloFish® are commercially available, genetically engineered fish strains of various species with high potential for laboratory experiments. These strains contain the genes of different fluorescent proteins (FP), which make their body bloom under normal light, or glow, absorbing specific light wavelengths. According to the studies, fluorescent proteins likely influence the behavior of transgenic fish strains (Sackermann et al., 2010). Here, we used GloFish® strains, based on prominent model organism zebrafish (Danio rerio), to evaluate the neurobehavioral effects of fluorescent protein genes in novel tank test (NTT). METHODS: A total of 102 adult zebrafish with 50/50 male-female ratio, including wild type (WT) zebrafish (n=26) and four GloFish® strains, was kept in different 40-L tanks per each group filled with filtered water in accordance with zebrafish care standards. Colored strains included green (GFP) (n = 22), red (RFP) (n =18), orange (RFP+GFP) (n =18) and blue (BFP) (n = 18) colored fish. Behavioral measurement included 5 min videorecordings in the novel tank test (NTT). The key behavioral endpoints were time spent in the top half of the tank (s), top entries, latency to top and bottom half (s), freezing frequency, freezing total duration (s), freezing latency (s), erratic movement frequency, erratic movement latency (s). RESULTS AND DISCUSSION: There were no significant differences in the frequency of erratic movements between WT, GFP, RFP and BFP. Although, RFP+GFP moved erratically less frequent than RFP and WT. Furthermore, the latency to first erratic movement in RFP+GFP group was significantly longer than in RFP and BFP. GFP and RFP+GFP swam at the top half significantly longer than RFP and WT. BFP also spent more time at the top, than RFP. Additionally, RFP+GFP entered the top half more frequently than WT and RFP, when GFP did it more frequent than RFP. RFP+GFP, GFP, and BFP latencies before the first top entry were shorter than in WT, as GFP and RFP+GFP entered in the top half earlier than RFP, and RFP+GFP did earlier than BFP. GFP and RFP+GFP had the longest latency to bottom half entry, than three other groups. Thuswise, the orange (RFP+GFP) strain by most NTT indices, such as erratic movements, top duration, top frequency, top latency, bottom latency (Egan et al., 2009). The green fish (GFP) had also tendency to anxiolysis, based on significant differences. However, red fish (RFP) behavior was close to wild type. Hence, obtained data indicated remarkable anxiolytic behavioral pattern in green and orange GloFish®.RESEARCH SUPPORT: Ural Federal University, Ekaterinburg, Russia.

EFFECTS OF EXTRACTS OF INONOTUS OBLIQUUS FUNALLIA TROGII AND GANODERMA APPLANATUM ON ZEBRAFISH BEHAVIOR IN THE NOVEL TANK TEST: A PILOT STUDY. MS Chernykh, AA Ermoshin, SL Khatsko, AV Zhdanov, AV Kalueff, Ural Federal University, Yekaterinburg, Russia; Southwest University, Chongqing, China

INTRODUCTION: Mushrooms, as plants, have been used in folk medicine for centuries. Even though mushrooms are hard to cultivate and to use them as cure, due to some toxic components, they have a high pharmacological potential. In that manner, the search for safer and abundant mushroom types, containing a huge number of physiologically beneficial compounds, is relevant. The studies, related to mushroom active compounds derivation and toxicology of such extracts, are important to expand our knowledge of mushrooms' therapeutic properties. The efficient model object for such tasks is zebrafish, which has proven itself in many biological disciplines, due to its relative availability and various physiological similarities with humans. METHODS: The experiment involved 73 wild-type short fin adult zebrafish. All fish were experimentally naive with 50/50 male-female ratio and kept in a 30L aquarium filled with filtered water in accordance with Danio rerio care standards. Animal behavior was assessed in the novel tank test (NTT), based on anxiety-like hallmarks. The NTT included 5-minute video recordings of control and experimental groups exposed to the extracts from the fungi of 3 types, derived with petroleum (C7H7BrMg) and diethyl esters (C4H10O) with the ratio of 500 ml mushroom's tissue to 1L of extractant. The experiment included intact animals, control (n(C7H7BrMg)=8 and n(C4H10O)=7), Inonotus obliquus extract (n(C7H7BrMg)=8 and n(C4H10O)=7), Funallia trogii (n(C7H7BrMg)=7 and n(C4H10O)=6), and Ganoderma applanatum (n(C7H7BrMg)=8 and n(C4H10O)=6). The statistical analysis was processed by Statistica 12 software with nonparametric Mann-Whitney U-test followed by Bonferroni correction. RESULTS AND DISCUSSION: extracts of Funallia trogii (C7H7BrMg) and Inonotus obliquus (C4H10O) induced the significant decrease in the number of top entries in comparison with intact animals. Besides, fish treated with C7H7BrMg, Funallia trogii (C7H7BrMg), and Inonotus obliquus (C4H10O) extracts exhibited increased number and total duration of freezing vs experimentally naïve fish. In addition, Inonotus obliquus (C4H10O) significantly altered the total duration of freezing relatively to the C4H10O treated control. Additionally, Ganoderma applanatum (C7H7BrMg) treated group displayed the significant reduction in the number of erratic movements vs. the intact fish. The experiment showed significant differences between fish, treated with two fractions of all studied

mushroom species, and experimentally naïve fish, but not the control, except for the distinctions with Inonotus obliquus (C4H10O) group by the total duration of freezing. Thus, the isolated extracts (C7H7BrMg and C4H10O) of studied mushroom species do not significantly affect the zebrafish behavior of due to the strong influence of the extractants themselves. The selected extractants are highly toxic and can significantly affect the condition of animals. The further study assumes the lyophilisation of mushroom tissue followed by the dose-dependent effect analysis and the investigation of biochemical and biomolecular effects of such extracts. RESEARCH SUPPORT: Ural Federal University, Yekaterinburg, Russia.

INVESTIGATION OF THE LINKAGE OF FIN LENGTH AND SKIN COLOR WITH NEUROBEHAVIORAL PHENOTYPES IN ZEBRAFISH. PART I: THE NOVEL TANK TEST. KN Zabegalov, AA Bashirzade, YY Babchenko, TG Amstislavskaya, AV Kalueff, Ural Federal University, Yekaterinburg, Scientific Research Institute of Physiology and Basic Medicine, Novosibirsk, Russia; Southwest University, Chongqing, China

INTRODUCTION: The different gene groups, responsible for limb/fin formation and color protein (pigment) expression are closely related to nervous system development and functioning in vertebrates of different taxons (Philippidou & Dasen, 2013; Nusslein-Volhard & Singh, 2017). In terms of laboratory neurobiological screening, zebrafish (Danio rerio) is suitable and one of the less expensive species. Hence, we used four zebrafish phenotypes of the common wild type forebears and divided them by fin length and skin pigmentation for the assessment of their basic behavioral hallmarks in novel tank test (NTT). METHODS: The study utilized 80 fish, reassigned to four different groups, contained in 40-L tanks filled with filtered water in accordance with current zebrafish care standards. Groups included dark-colored shortfin (n=20) and longfin (n=20) fish, as well as light-colored shortfins (n=20) and longfins (n=20). The behavior was recorded within 5 min for each fish of each experimental group in novel tank test (NTT). NTT basic endpoints were top tank half entries, top half duration (s), distance moved in the whole tank (m), and total velocity (m/s). Statistical analysis was proceeded between four previously mentioned groups, and included two paired comparisons: longfins with shortfins, and dark-colored with light-colored fish. RESULTS AND DISCUSSION: Longfins revealed the significant increase in top frequency and top half duration in comparison with shortfin fish. The result corresponds to previously published study, where shortfins spent the most time at the bottom of the tank, and were more active in there (Rosemberg et al., 2011). The skin color related comparison also included top half alterations. Thus, light-colored fish spent more time in the top half than dark-colored fish. Besides, there is substantial data on zebrafish skin pigmentation role in behavioral patterns. Thereby, close related to our study's light-colored fish, golden zebrafish displays anxiolytic-like behavior and high locomotor activity in novel tank test (Audira et al., 2020). In terms of multiple comparison between four groups, significant differences in top half indices were observed. Dark-colored longfins, light-colored longfins, light-colored shortfins entered the top half more frequent than dark-colored shortfins. As well as dark-colored longfins and light-colored longfins spent more time in the top half than dark-colored shortfins. It is unknown weather pigmentation or fin length are exact reasons for behavioral changes in zebrafish, though multiple comparison between groups revealed the probable combined influence of fin-formation and skin color genes in dark shortfins. Either way, a genome wide research could be accelerated the understanding of color/structural genes involvement in CNS functioning and behavior in vertebrates. RESEARCH SUPPORT: Scientific Research Institute of Physiology and Basic Medicine, Novosibirsk, partially Ural Federal University, Yekaterinburg, Russia.

CHANGES IN EXPRESSION OF SUBUNITS OF NMDA RECEPTORS IN THE STRIATUM IN A RAT MODEL OF PARKINSON'S DISEASE, KK Sitdikova, VD Dergachev, EE Yakovleva, ER Bychkov, PD Shabanov, Institute of Experimental Medicine, St. Petersburg, Russia

INTRODUCTION: ***N***-methyl-D-aspartate (NMDA) receptors play a significant role in the development of various neurodegenerative disorders, such as Parkinson's disease (PD). Interactions between glutamate and dopamine in the striatum, which play important roles in motor control, are thus altered in PD. Antagonists of the NMDA type of glutamate receptors alleviate some of the motor symptoms of PD but these beneficial effects are accompanied by unwanted side effects. For a better understanding of processes underlying in PD genesis we need to know more about changes in NMDA receptor expression in the brain after dopaminergic neuronal degeneration. The aim of this study was to estimate the expression level of genes GluN2A, GluN2B, GluN2C, GluN2D subunits of glutamate NMDA receptors in striatum after 6-OHDA injection. METHODS: Rats were anesthetized and positioned in a stereotaxic frame. A stainless steel guide cannula was implanted at the following coordinates: posterior -0.6 mm from bregma, lateral +1.2 mm from sagittal suture, ventral -3.5 mm from surface of the scull. 6-OHDA injected intracerebroventricularly in a dose of 1.5 mg/kg 15 days prior to the experiment. Control animals were injected with saline.The animals were given intraperitoneal injections of desipramine (25 mg/kg) 30 min prior to 6-OHDA to prevent the uptake of the neurotoxin into noradrenergic nerve terminals or

saline infusions in the treated and control rats, respectively. In three weeks animals were decapitated, the brains were rapidly removed from the skulls and placed on an ice-cooled glass plate. Striatum were dissected from the brain. Tissues frozen in liquid nitrogen and stored at -70C until analysis. To estimate the degree of dopamine denervation, dopamine (DA), 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) contents in supernatants of the striatum were measured by HPLC with electrochemical detection. RNA was isolated from striatum using «RNA-EXTRAN» kit (Syntol, Russia) and DNA was obtained by performing a reverse transcription reaction. Real-time PCR was conducted to examine the expression level of genes GluN2A, GluN2B, GluN2C, GluN2D subunits of glutamate NMDA receptors. Kit «PCR mix» (Syntol, Russia) was used. Statistical data processing was carried out in the GraphPad Prism 6.0program.The significance among groups was evaluated with the one-way ANOVA test. RESULTS AND DISCUSSION: Administration of 6-OHDA in our study resulted in a marked reduction in the DA, DOPAC and HVA contents in the striatumin 6-OHDA group as comparedto sham-operated control group. In addition, there were significant increases in DOPAC/DA and HVA/DA ratios in the striatum. This is probably related to compensatory increase of functional activity of DA-ergic system. In rats given 6-OHDA expression genes GluN2A, GluN2B and GluN2C subunitsof NMDA receptor was decreased in striatum more than 2 times (32%for GluN2A,46%for GluN2B 31% for GluN2C), expression of GluN2D subunits was not significant change. CONCLUSION: These results demonstrate the sensitivity of GluN2A, GluN2B and GluN2C subunits expression to degeneration of dopamine terminals in striatum. Key words: parkinsonism, GluN2A, GluN2B, GluN2C, GluN2D subunits NMDA-receptor.

STRESS AS A MOTIVATOR OF COGNITIVE DISSONANCE AFFECTING BEHAVIOR IN THE SYSTEM OF DISTANT EDUCATION, LV Shabanov, SV Marihin, AA Lebedev, St. Petersburg Military Institute of National Guard of Russia, Pushkin Leningrad State University, Institute of Experimental Medicine, St. Petersburg, Russia

INTRODUCTION: The article considers stress as a motivational trigger that often affects the quality of the educational space. According to the authors, the transition to remote methods created an internal virtualization conflict for both the teacher and the student. Stress and related behaviors were ignored by the support team. If visual's or audio's perception can still compensate for the situation of mutual physical absence in the classroom, then tactile-follower (which require real physical contact to assimilate information) can no longer cope with the density of the information flow, which immediately affects their performance. This is a kind of challenge not only to the teacher or his students, but also to the entire educational environment. METHODS: The stress caused by the constantly changing situation in the modern communication system, which builds fast and complex configurations, is today complemented by specific communication gaps in the form of distance education. This is a new and progressive line of cognitive conflict, when social deprivation of contacts occurs with an obvious excess of information flows. Moreover, teachers in the context of the COVID-19 pandemic shift personality dominants to reduce contact, and therefore to their own activities. RESULTS AND DISCUSSION: With the advent of the distant factor, the educational environment was rapidly virtualized. But few of the techno specialists have calculated how much the virtuality coincides with the psychological qualities of the personality involved in this space. So, visual's or audio's perception, as well as mixed (digital and logical) types on both sides of the teacher-student communication, were able to find compensating compromises. But the kinesthetic pupils present in the teams of teachers and students (as well as mixed types) showed that without tactile contact, the process of transmitting and assimilating information, despite all its effectiveness, is resultantly low. Such virtuality causes nothing but stress and frustration barriers. Key words: stress, virtuality of the educational environment, cognitive dissonance.

SEARCH FOR ANTIHYPOXIC DRUGS AMONG NEW COUMARIN DERIVATIVES, AF Safonova, OM Rodionova, AO Kashirin, ER Bychkov, AA Lebedev, PD Shabanov, Institute of Experimental Medicine, St. Petersburg, Russia

INTRODUCTION: The article is devoted to the study of anti-hypoxemic properties of new coumarin derivatives in the models of hypoxemic hypoxia with hypercapnia, hemic hypoxia and histotoxic hypoxia. METHODS: Hypoxemic hypoxia with hypercapnia was modeled as follows: mice were placed in hermetic 200 cm3 jars one in a jar. Hemic hypoxia was reproduced in mice by single subcutaneous introduction of sodium nitrite in a dose of 230 mg/kg. Histotoxic hypoxia was caused in mice by intraperitoneal introduction of sodium nitroprusside in a dose of 20 mg/kg. Coumarin derivatives under lab codes IEM-2266 and IEM-2267 were dissolved in distilled water with addition of twin-80, and injected intraperitonealy in the doses 25 and 50 mg/kg 45 minutes before placing the mice to the model conditions. Increased life time of an animal compared with the control served as the criterion of antihypoxic effect of the studied substances. RESULTS AND DISCUSSION: In hypoxemic hypoxia with hypercapnia test the compound IEM-2267 in doses of 25 and 50 mg/kg increased mice life time by 26 and 34% respectively in comparison with control. In hemic hypoxia model, the positive effect was seen

with IEM-2266 in a dose of 50 mg/kg which increased life time of animals by 45% in comparison with control. In histotoxic hypoxia model IEM-2266 in a dose of 25 mg/kg and IEM-2267 in a dose of 50 mg/kg increased life time up to 117% and 123% respectively. The coumarin derivatives IEM-2266 and IEM-2267 relieved the course of acute hypoxia and increased life time of animals in the models of hypoxemic hypoxia with hypercapnia, hemic hypoxia and histotoxic hypoxia. Key words: hypoxemic hypoxia with hypercapnia, hemic hypoxia, histotoxic hypoxia, coumarin derivatives.

STUDY OF EMOTIONAL BEHAVIOR AND DESACYL-GRELIN CONTENT IN RAT BRAIN AFTER PSYCHOEMOTIONAL STRESS, VA Raptanova, AA Lebedev, SG Tsikunov, PP Khokhlov, AG Pshenichnaya, IYu Thyssen, ER Bychkov, VA Lebedev, NS Efimov, KE Gramota, PD Shabanov, Institute of Experimental Medicine, St. Petersburg Medico-Social Institute, St. Petersburg, Russia

INTRODUCTION: The work is devoted to the analysis of the elements the reactivity of grelin system in the model of psychogenic stress. In recent years, it has been shown that the ghrelin brain system is not limited only to the regulation of energy balance and eating behavior. Along with other peptide regulatory systems, it plays an important role in the mechanisms of stress, reward and addiction. Therefore, the elements of this system should be considered primarily as molecular targets of pharmacological action in order to correct the states of addiction and post-stress disorders. METHODS: To produce psychoemotional stress, we used an acute single traumatic situation in male Wistar rats. The animals were placed in the tiger python, one animal died as a result of its nutritional needs, the rest of the rats experienced the death of a partner. In rats, course intranasal administration of the ghrelin or ghrelin antagonist [D-Lys3] -GHRP-6 within 7 days (20 μl, 1 mg/ml) after the presentation of the python and emotional behavior were studied. Then animals were decapitated, and the brain structures were isolated. Aliquots of the brain structures suspensions were examined for the content of desacyl-ghrelin (DAG) using a highly sensitive enzyme-linked immunosorbent assay (ELISA). RESULTS: In rats, course intranasal administration of the ghrelin antagonist [D-Lys3] -GHRP-6 within 7 days after the presentation of the python in the “elevated plus maze” test caused an anxiogenic effect: the time spent in the light sleeve decreased compared to other groups. Ghrelin, on the contrary, had an anxiolytic effect, the time spent by the animals in the light arm reached the values of the control groups, while the locomotor activity of the animals increased. In the open field test, the ghrelin antagonist [D-Lys3] -GHRP-6 and ghrelin did not have a significant effect on animals. In the "resident" test in stressed animals, the ghrelin antagonist [D-Lys3] -GHRP-6, like ghrelin itself, reduced the communicative activity as compared to the control groups. Ghrelin also led to the manifestation of aggression in stressed rats. DAG was detected in all studied brain structures: amygdala, hippocampus, and hypothalamus. The highest concentration of DAG was noted in the hypothalamus ($p < 0.05$), which may serve as an indirect confirmation of the data on the presence of ghrelin-containing neurons in the nuclei of the hypothalamus. After exposure to stress, a sharp decrease in the level of DAG was observed in all studied brain structures (8–12 times, $p < 0.01$): amygdala, hippocampus, and hypothalamus. CONCLUSION: Psychoemotional stress completely suppresses the content of desacyl-ghrelin of the brain in rats, which may be based on both a disturbance of the central mechanisms of limbic regulation. Intranasal administration of the ghrelin or ghrelin antagonist [D-Lys3] -GHRP-6 within 7 days (20 μl, 1 mg/ml) after the presentation of the python and emotional behavior were studied.Key words: stress, desacyl-grelin, emotional behavior, rat.

DEVELOPMENT OF EROSIVE INFLAMMATION IN THE STOMACH MUCOSA AFTER EXPERIMENTAL EMOTIONAL STRESS, VA Raptanova, PS Bobkov, SG Tsikunov, AV Droblenkov, Institute of Experimental Medicine, St. Petersburg Medico-Social Institute, St. Petersburg, Russia

INTRODUCTION: Reactive changes in the tissues of the gastric mucosa, subject to deep erosive post-stress disorders, have not been targeted in experimental models. Meanwhile, the practice of stress modeling to establish the effectiveness of therapeutic effects suggests the expediency of obtaining new and informative criteria for assessing the degree of its disturbance and therapeutic effect. METHODS: In order to establish the features of changes in the structure of the gastric mucosa, the inner part of the gastric mucosa in its cardiac part was examined in 2 groups of sexually mature male rats (5 animals weighing 200-220 g): intact and after acute single stress. For this, rats in the amount of 20-22 individuals were placed in a terrarium (1.2 x 0.7 x 1 m volume) to a tiger python weighing about 35 kg. The python strangled and swallowed one of the animals, the other rats watched this, being together with the python in the cage in a situation of unavoidable psychogenic stress. On the 4th day of rats after decapitation, stomachs were removed, which were fixed in 10% formalin solution. In horizontal paraffin sections of the gastric mucosa, at a distance of 0.02 mm from the junction of the esophagus into the stomach, after staining with hematoxylin and eosin on an area of 0.015 mm2, the height of superficial and dimple mucous cells (as having different degrees of differentiation), the height of the pit stroma, and superficial, dimple mucocytes and stroma of the fossae, as well as the number of dead mucocytes. To clarify the differentiation of epithelial cells, they were stained with alcian blue (Biovitrum, Russia). Morphometry

was performed using the Imagescope software (Electronic Analysis, Russia). The data were processed using the GraphPad PRISM 6.0 (USA) statistical software package and the Mann – Whitney nonparametric test, determined after the median, upper and lower quartiles were established.
RESULTS AND DISCUSSION: In intact rats, the gastric dimples along the section, visually, did not differ significantly in height and contained a narrow lumen. Dimple mucocytes showed signs of less differentiated cells than superficial ones, differing from each other in height and area ($p < 0.0001$). There were single dead cells, altered by the type of apoptosis. Viable mucocytes contained a large oval or rounded nucleus with a distinguishable nucleolus and small areas of accumulations of mucus secretory inclusions located near the superficial part of a well-developed cytoplasm. A thin continuous mucous border was stained above the surface of the epithelial layer. Fibroblasts and capillaries were located in the stroma of the dimples. As a result of a short-term experience of psychogenic stress, the relief of the surface of the mucous membrane along the cut of the stomach became uneven, the lumen of the dimples became wider, and the mucocytes became much smaller in height and area. The largest part of the cytoplasm of mucocytes was occupied by accumulations of mucous inclusions; the width of the mucous border increased. The nucleus of mucous cells became smaller and more colored than in the control. In the epithelium, the number of dead cells increased sharply, some of which, having lost their connection with the rest of the cells of the layer, were found on the surface. The height and area of the stroma of the dimples decreased significantly. The mucosal stroma (especially) and the epithelium (to a lesser extent) were diffusely infiltrated by lymphocytes. CONCLUSIONS: The short-term experience of psychogenic stress in the experimental model is expressed by erosive inflammation of the gastric mucosa, the death of many mucocytes, as well as an increase in mucus production by viable mucocytes.
Key words: gastric mucosa, stress, python.

EXPERIMENTAL STUDY OF THE EMOTIONOGENIC EFFECTS OF PEPTIDES OF THE KISSPEPTIN GROUP, LA Magarramova, AA Lebedev, AG Pshenichnaya, VA Lebedev, PD Shabanov, Institute of Experimental Medicine, St. Petersburg, Russia

INTRODUCTION: Kisspeptin, encoded by the Kiss1 gene, is a key factor in the regulation of reproductive development and function. The Kiss1 gene encodes 145 amino acid proteins that are proteolytically processed to produce 54 amino acid peptides, called kisspeptin-54, and several other smaller peptide fragments. Centrally administered kisspeptins stimulate the secretion of GnRH and gonadotropins in prepubescent and adult animals. Buserelin is a synthetic analog of the gonadotropin-releasing hormone. It competitively binds to gonadotropin-releasing hormone receptors in the cells of the anterior pituitary gland. With initial or intermittent administration, buserelin stimulates the release of gonadotropins (LH and FSH) by the pituitary gland, which, in turn, causes a short-term increase in the level of sex hormones in the blood plasma. Constant use leads to a blockade of the gonadotropic function of the pituitary gland. Yohimbine hydrochloride is a alpha-blockers, selectively blocks central and peripheral presynaptic alpha2-adrenergic receptors. In large doses, it has the ability to block postsynaptic alpha-adrenergic receptors. Improves erectile function, improves mood, can increase anxiety. The purpose of this work was to studyemotional and exploratory behavior in rats during intranasal and intraperitoneal administration of peptide. MATERIALS AND METHODS: The experiments were performed on 40 male Wistar rats with an initial mass of 200-220 g. The animals were kept in groups of 7 individuals in separate cells under artificial 12-hour lighting and a temperature of 22 ± 2oC. All animals received water, with free access to dry, standardized food. To achieve this goal, we used a battery of behavioral tests: "Open field", "Elevated plus maze", "Intruder-resident", the Porsolt test. The sample for each group of animals was at least 7 rats. 15 minutes before the study of behavior in the tests, animals were administered intranasally with Kisspeptin-10 and Buserelin 20 μl (10 μl in each nostril). Kisspeptin-10 and Yohimbine hydrochloride were administered intraperitoneally. The obtained data were processed statistically using the software package "Statistica v.10" using the Student's t-test for independent samples. RESULTS AND DISCUSSION: In the "Elevated plus maze" test, the peeking out time significantly ($p < 0.05$) increased in animals that were administered Kisspeptin-10 intraperitoneally compared to intraperitoneal administration of Yohimbine hydrochloride. In the "Intruder – resident" test, the animals that received Kisspeptin-10 intranasally increased the probability of the number of acts of defensive behavior compared to the control group. In the groups of animals that were administered Buserelin intranasally, the probability of acts of communicative behavior increased in comparison with the control group. The groups of animals that received intraperitoneal Kisspeptin-10 compared to the group of animals that received intraperitoneal Yohimbine hydrochloride increased the number of acts of protective behavior. In the Porsolt test, the time and amount of active swimming significantly increased ($p < 0.01$) in the groups of animals administered intranasally with Kisspeptin-10 compared to the control group. There were also significant differences in the number of acts of active swimming between the group of animals that were administered Kisspeptin-10 intranasally and intraperitoneally. Also, in animals that were administered intraperitoneal Kisspeptin-10, compared with intraperitoneal administration of Yohimbine hydrochloride, the amount of active swimming increased. A decrease in immobilization was found in animals after intraperitoneal administration of Yohimbine hydrochloride and Kisspeptin-10 compared to

the control ($p < 0.05$). Key words: kisspeptin-10, buserelin, yohimbine, elevated plus maze, intruder – resident.

ANTIHYPOXIC EFFECT OF NEW COUMARIN DERIVATIVES IN THE MODEL OF ACUTE HYPOBARIC HYPOXIA IN RATS, AO Kashirin, EN Selina, IB Krylova, NR Evdokimova, ER Bychkov, VA Polukeev, PD Shabanov, Institute of Experimental Medicine, St. Petersburg, Russia

INTRODUCTION: It is known that hypoxia followed by oxidative stress contributes to the development of metabolic disorders and the occurrence of various pathologies such as hypertension, cardiovascular, respiratory and neurodegenerative diseases. The search for highly effective substances with antihypoxic activity for the pharmacological correction of disorders arising from oxygen deficiency is an urgent task. Coumarins represent an important type of naturally occurring and synthetic oxygen-containing heterocycles. They have special benzopyrone structure enables their derivatives interact with a diversity of enzymes and receptors in organisms, and thereby exhibit wide specter of pharmacological activities: anti-coagulant, anti-tumor, anti-inflammatory, enzyme inhibition properties, as well as anti-oxidant effects and scavenging of reactive oxygen species. Now synthetic derivatives continue to attracted strong scientific interest due to their potent pharmacological activities and less toxicity. In our department, new coumarin derivatives have been synthesized - 7-alkoxycoumarin IEM-2266 and 4-aminocoumarin IEM-2267. It has been shown that they have mild tranquilizing and anti-stress effects. The aim of the present study was to investigate the antihypoxic properties of IEM-2266 and IEM-2267 on the model of acute hypobaric hypoxia. METHODS: The experiments were performed on male Wistar rats weighing 200-220 g. IEM-2266 and IEM-2267 were injected once intraperitoneally at a dose of 25 mg/kg, the reference drug Mexidol - at a dose of 100 mg/kg one hour before hypoxia. Control animals were injected with an equal volume of solvent. The antihypoxic activity of the drugs was evaluated by the rat lifespan on the simulated altitude equivalent to 11000 m in animal pressure chamber, as well as by the effect on individual hypoxic resistance (altitude threshold and resistance to hypoxia expressed in scores). RESULTS AND DISCUSSION: In the acute hypobaric hypoxia model IEM-2266, IEM-2267 and Mexidol increased the lifespan of the rats at the altitude 11,000 m in 2.4, 5.4 and 4.9 times respectively versus control. Altitude threshold in control was 10,95±0,21 km. IEM-2266 increased the altitude threshold up to 11,67±0,14 km, IEM-2267 – up to 12,44±0,10 km and Mexidol – up to 12,33±0,19 km (differences versus control are statistically significant at $p<0.05$). The individual resistance to hypoxia expressed in scores was 6,4±0,7 in control and 10,7±0,5 with Mexidol treatment. IEM-2267 demonstrated the same activity as Mexidol. IEM-2266 increased the individual resistance in scores by 36% compared with control. Thus, coumarin derivates IEM-2266 and IEM-2267 showed a positive antihypoxic activity. Efficiency of IEM-2267 was higher than IEM-2266 and comparable with Mexidol. Both coumarine derivatives can be further studied as potentially drugs with antihypoxic properties. Key words: coumarin derivatives, hypobaric hypoxia, Mexidol.

THE EFFECT OF ACUTE MENTAL STRESS ON THE EXCHANGE OF MONOAMINES IN THE MESOCORTICAL AND NIGROSTRIATAL SYSTEMS OF THE RAT BRAIN, IV Karpova, SG Tsikunov, DV Kritskaya, LK Khnychenko, AA Lebedev, ER Bychkov, IYu Thyssen, SS Pyurveev, PD Shabanov, Institute of Experimental Medicine, St. Petersburg, Russia

INTRODUCTION: Prefrontal cortex and ventral tegmental area, mesocortical dopaminergic structures, as well as striatum, nigrostriatal dopaminergic structure, are referred to brain formations that are highly sensitive to stressful events. One of the most adequate models of acute psychogenic stress in animals is the death of a partner upon presentation of a predator. Despite a number of publications of the consequences of acute psychogenic stress on the functioning of the neurochemical systems of the central nervous system, there is a clear deficit in studies of the dynamics of changes in the content and metabolism of monoamines in stress-reactive dopaminergic structures of the brain. The aim of this study was a comparative analysis of the content of dopamine, norepinephrine, serotonin and their metabolites in the prefrontal cortex, striatum, and ventral tegmental area in rats on days 3, 7, and 14 after the acute psychogenic stress of the death of a partner upon presentation of a predator. METHODS: 28 male Wistar rats were studied. Acute single traumatic situation was used. A group of rats was placed in a tiger python terrarium. One animal died as a result of its nutritional needs, the rest of the rats experienced the death of a partner. The content of dopamine, serotonin and their metabolites in the brain structures was carried out by high performance liquid chromatography with electrochemical detection (HPLC / ED). The rat brain samples were taken after decapitation on ice on days 3, 7, and 14 after presentation of the predator. RESULTS: Changes in the content of dopamine (DA), serotonin (5-HT) and their metabolites dioxyphenylacetic (DOPAC), homovanillic (HVA), and 5-hydroxyindoleacetic (5-HIAA) acids in the prefrontal cortex, striatum, and ventral tegmental area were found on the 7th and 14th days after the presentation of the predator. No significant changes in the content of the studied mediators and their metabolism were found on the 3rd day after the stressful event. Differences with control group were

noted in the ventral tegmental area only on the 7th day after the stress exposure; in the striatum and prefrontal cortex differences were noted only on the 14th day after the presentation of the predator. At the same time, an increase in the activity of dopamine and serotonin systems was noted in the ventral tegmental area. The opposite changes were noted in the striatum and prefrontal cortex: a decrease in the activity of the DA and 5-HT systems. In the ventral tegmental area, there was an increase in the DOPAC/DA ratio and an increase in the serotonin metabolite 5-HIAA, which reflects an increase in the activity of dopamine and serotonin. In the prefrontal cortex, the DOPAC content and the DOPAC/DA index decreased. The 5-HIAA content in the prefrontal cortex and the 5-HIAA/5-HT value also significantly decreased. The ratio of DOPAC/DA decreased in the striatum in comparison with the value 7 days after the stress exposure. CONCLUSION: Changes in the content of mediators and their metabolism after presentation of a predator develop gradually: increase of the dopamine and serotonin activity in the ventral tegmental area was noted on the 7th day after presentation of the predator, decrease in their activity in the striatum and prefrontal cortex – only on the 14th day, reflecting the development of depressive states and post-traumatic stress disorder. Key words: stress, predator, dopamine, serotonin, mesocortical system, striatum.

PHARMACOLOGICAL ANALYSIS OF THE IMPACT OF GHRELIN AND OREXIN ON GAMBLING BEHAVIOR, KE Gramota, AA Lebedev, ER Bychkov, VA Lebedev, IYu Thyssen, ND Yakushina, SS Pyurveev, PD Shabanov, Institute of Experimental Medicine, St. Petersburg, Russia

INTRODUCTION: Mechanism of gambling addiction is considered as an active desire to experience asituation of risk or loss; or as malfunctioning of the process of operant conditioning – from this point gambling is considered as a systematic reproduction of cognitive errors which, in turn,occurs as a result of violations of the internal reinforcement system and its modulation. In this paper, we performed a pharmacological assessment of some parts of the system of internal reinforcement and stress and their impact on gambling. METHODS: To assess gambling behavior of rats, subjects were trained for 28 days for a rodent gambling test method performed in the operant chamber with two arms, each of which had anautomatic feeders installed. The first sleeve of the chamber was set in FR1 mode to dispense 1 unit of food reward for each selection of this chamber. The second arm was set to dispense 3 reward units in a VR5 mode: randomly, with a probability of dispensation at 1:5. The animals were tested daily, in cycles of 5 days with 2 days-off. The test lasted 10 minutes at each day. The results were assessed according to a ratio of selections between the first and the second sleeves for each test. RESULTS: Analysis of the gambling behavior test results at the intact animals has shown that the distribution of subjects on the basis of risk preference is heterogeneous. Thus, the animals were divided into two subgroups based on the individual risk preference: the 1st group preferred the second sleeve and were considered “risk prone”, and the 2nd group of animals who preferred the sleeve with a fixed small delivery of food and considered “risk-aversive”. Serotonergic agonist fluoxetine and dopaminergic antagonist haloperidol reduced the number of risky choices in a situation of different probabilities of reinforcement for a subgroup of subjects with an initially increased risk preference by 9% and 11%, respectively ($p<0.05$ compared to the baseline level in both cases). At the same time, the serotonin 5-HT1A receptor agonist buspirone reduced the number of risky choices in all subjects, regardless of their initial risk preference. Administration of the 5HT1A serotonin receptor agonist buspirone relieved the effects of ghrelin receptor agonist GHSR1A L-692585. The ghrelin receptor antagonist [D-Lys3] -GHRP-6 and the orexin receptor antagonist OX1R SB-408124 reduced the number of risky choices in a situation of different probability reinforcement for a subgroup of subjects with an initially increased risk preference. Ghrelin itself had no effect on risk preference in subjects with initially normal and initially elevated risk preference. CONCLUSION: Thus, the results demonstrate the mutual influence of a different mediator systems of the brain and their influence on the decision-making process in conditions of uncertainty. It is shown that the key systems that regulate behavior in the conditions of uncertainty are the dopaminergic and serotonergic systems of the brain, which mediate their action through the activation of D2 and 5HT1A receptors respectively. Orexin and ghrelin, in turn, may be consideredadjuvants and their function is to modulate the effect of the dopaminergic firing and its impact on the formation of behavior. Key words: gambling, brain, dopamine, serotonin, neuropeptides, orexin, OX1R, OX2R.

OREXIN BRAIN OX1R mRNA INCREASES IN RISK-PRONE RATS IN A MODEL OF GAMBLING, KE Gramota, EA Sexte, AA Lebedev, ER Bychkov, MI Airapetov, IYu Thyssen, VA Lebedev, SS Pyurveev, PD Shabanov, Institute of Experimental Medicine, St. Petersburg, Russia

INTRODUCTION: Orexin and its receptors are involved in the mechanisms of pathological craving for alcohol and psychoactive drugs. The orexin system is also involved in the mechanisms of non-chemical forms of addiction:binge eating and gambling. Gambling as an object for study is of particular interest. In the international classifiers (ICD 10 and DSM-5) it stands out as a separate disease, is one of the non-chemical forms of addiction and has all the characteristics in the traditional understanding of this term: the development of tolerance (addiction), the development of addiction itself and the corresponding

withdrawal syndrome. Despite the general recognition of gambling addiction as an independent disease, there are no unified or generally accepted approaches to the treatment of this condition, as there is not a single drug registered for this indication. The most objective way to assess the degree of manifestation of a subject's gambling in laboratory conditions is the IOWA gambling task method, which is based on placing the subject in a situation of unpredictable or partially predictable choice with heterogeneous reinforcement and subsequent assessment of the subject's ability to act rationally in conditions of unpredictable choice to maximize his own benefit. In recent years, the IOWA gambling task has been used in animal experiments. In our laboratory, a version of the model of this test in a three-arm maze in rats was developed. The aim of this study was to study the level of orexin receptor mRNA in emotiogenic brain structures in risk-prone rats in a gambling addiction model. METHODS: For three weeks, the rats were trained in a three-arm maze using the food reinforcement (sunflower seeds). During the first five days, at the end of the 1st arm, the animals received 1 seed, at the end of the 2nd arm, 2 seeds, and at the end of the 3rd arm, 3 seeds. In the following days, the reinforcement was differentiated: each entry in arm 1was reinforced with 1 seed, each second entry in arm 2 was reinforced with 2 seeds and every third entry in arm 3 was reinforced with 3 seeds. Thus, when visiting the 1st arm, the amount of reinforcement was minimal, and the probability of its delivery was maximal. The entry to the 3rd arm was reinforced as much as possible, but with the lowest probability. We compared group of rats that prefer to receive a high reward, but with a low degree of probability with the group of rats that prefer to receive a low reward, but with a high degree of probability (100%). The rats were decapitated and the brain structures were isolated. Real time PCR was used to determine the content OXR mRNA in the hypothalamus, hippocampus and striatum. RESULTS: It was shown that the level of OX1R mRNA was significantly increased in the hypothalamus and hippocampus in rats that prefer to receive a high reward, but with a low degree of probability, in comparison with the group of rats that prefer to receive a low reward, but with a high degree of probability (100%). In the prefrontal cortex, on the contrary, no significant changes were observed in the level of OX1R mRNA. When studying the level of OX2R mRNA, no significant changes were observed in the rats prone to risk in the hypothalamus, hippocampus, and prefrontal cortex. CONCLUSION: The data indicate the involvement of OX1R in the hypothalamus and hippocampus in mechanisms mediating gambling. Apparently, this reflects the peculiarities of the inclusion of the orexin system in the mechanisms of gambling addiction when OX1R is mainly involved in, which is more associated with the assessment of the likelihood of reward. This is confirmed by our previous studies on the increase in the level of OX1R receptors in the hippocampus in alcohol withdrawal syndrome in chronically alcoholized rats. when the search for ethanol is activated with a subjectively low probability of reward. Key words: gambling, brain, neuropeptides, orexin, OX1R, OX2R.

A GHRELIN RECEPTOR ANTAGONIST, [D-LYS3]-GHRP-6, REDUCES THE RISK BEHAVIOR IN THE RAT GAMBLING MODEL BY ALTERING THE TURNOVER OF DOPAMINE AND SEROTONIN, KE Gramota, AA Lebedev, IV Karpova, ER Bychkov, ND Yakushina, IYu Thyssen, NS Efimov, VA Lebedev, SS Pyurveev, PD Shabanov, Institute of Experimental Medicine, St. Petersburg, Russia

INTRODUCTION: Gambling as an object for study is of particular interest. In the international classifiers (ICD 10 and DSM-5) it stands out as a separate disease, is one of the non-chemical forms of addiction and has all the characteristics in the traditional understanding of this term: the development of tolerance (addiction), the development of addiction itself and the corresponding withdrawal syndrome. Despite the general recognition of gambling addiction as an independent disease, there are no unified or generally accepted approaches to the treatment of this condition, as there is not a single drug registered for this indication. The most objective way to assess the degree of manifestation of a subject's gambling in laboratory conditions is the IOWA gambling task method, which is based on placing the subject in a situation of unpredictable or partially predictable choice with heterogeneous reinforcement and subsequent assessment of the subject's ability to act rationally in conditions of unpredictable choice to maximize his own benefit. In recent years, the IOWA gambling task has been used in animal experiments. In our laboratory, a version of the model of this test in a three-arm maze in rats was developed. METHODS: The effect of the ghrelin receptor antagonist [D-Lys3] -GHRP-6 on the elements of gambling and monoamine metabolism in the rat brain was investigated. For three weeks, the rats were trained in a three-arm maze using the food reinforcement (sunflower seeds). During the first five days, at the end of the 1st arm, the animals received 1 seed, at the end of the 2nd arm, 2 seeds, and at the end of the 3rd arm, 3 seeds. In the following days, the reinforcement was differentiated: each entry in arm 1was reinforced with 1 seed, each second entry in arm 2 was reinforced with 2 seeds and every third entry in arm 3 was reinforced with 3 seeds. Thus, when visiting the 1st arm, the amount of reinforcement was minimal, and the probability of its delivery was maximal. The entry to the 3rd arm was reinforced as much as possible, but with the lowest probability. Rats that had developed a stable conditional locomotion in the maze were injected intranasally with 0.9% NaCl or D-Lys3-GHRP-6 and studied the behavior. 3 days after testing the rats were re-administered with 0.9% NaCl or D-Lys3-GHRP-6. After 80 minutes, the rats were decapitated and the brain structures were isolated. HPLC was used to determine the content of dopamine, serotonin and their metabolites in the hypothalamus, hippocampus, striatum, and olfactory tubercle (the part of ventral striatum). RESULTS: Intranasal

administration of the ghrelin receptor antagonist [D-Lys3] -GHRP-6 (20 µl, 1 mg/ml) increased the number of entries into the 1st arm (with a high (100%) probability, but less reinforcement). No significant changes were found in the content of dopamine and serotonin after [D-Lys3]-GHRP-6 administration in the hypothalamus. The serotonin content significantly increased in the left hippocampus. The turnover of monoamines in the olfactory tubercle and striatum changed only in the right hemisphere, while the ratio of the content of 5-hydroxyindoleacetic acid to the content of serotonin increased in both structures. In the right striatum, these changes were also accompanied by an increase in the content of serotonin and dopamine metabolites. DISCUSSION: Thus, the ability of [D-Lys3] -GHRP-6 to change the strategy of choice in favor of the greatest probability, but the least amount of reinforcement, is based on an increase in the activity of the dopaminergic and serotoninergic systems in the dorsal and ventral striatum of the right hemisphere of the brain and the serotonin content in the hippocampus of the left hemisphere. Key words: ghrelin, [D-Lys3] -GHRP-6, gambling, dopamine, serotonin.

ANTICONVULSANT PROPERTIES OF THE 1,2-SUBSTITUTED DERIVATIVES OF IMIDAZOLE-4,5-DICARBOXYLIC ACID, SP Foksha, EE Yakovleva, MA Brusina, ER Bychkov, LV Myznikov, LB Piotrovskij, PD Shabanov, Institute of Experimental Medicine, St. Petersburg, Russia

INTRODUCTION: It is known that glutamic acid is the most common excitatory amino acid neurotransmitter of the brain and spinal cord, and it also performs a number of vitally important physiological functions. The use of glutamate receptor antagonists is a topical issue today. The large number of studies indicates a significant anticonvulsant effect of NMDA receptor antagonists, but the application of NMDA ligands remains limited in research. Derivatives of imidazole-4,5-dicarboxylic acid are ligands to the NMDA receptor complex, while they can exhibit a multidirectional effect. The application of new ligands of the glutamate NMDA-receptor complex with anticonvulsant effect on the model of NMDA-induced seizures remains unresolved. However, the application of current NMDA-blockers is limited by their toxic effects - the problem of mild regulation of the NMDA-receptors function is still unresolved according to safety of the therapy. The main aim of the study was to investigate the anticonvulsant effect of new ligands for the glutamate NMDA-receptor complex – imidazole-4,5-dicarboxylic acid derivatives. METHODS: The experiments were performed on male mice weighing 18-25 g. The effects of two derivatives (IEM1574 and IEM2250) of imidazole-4,5-dicarboxylic acid (IDCA), synthesized in the Department of Neuropharmacology of FSBSI IEM were studied. The agents were dissolved in distilled water, adjusted using 0.5 n NaOH to pH=7.0 and was injected into the lateral ventricles of an awake mouse brain in a volume of 5 µl. As a convulsant, an NMDA solution was injected into the lateral ventricles of the brain (Sigma, USA, 5 µg in 5 µl). Test substances were administered in doses of 0.1-1 µmol in 5µl 15-20 minutes before NMDA, after that motor activity and animal behavior, as well as the intensity, duration of convulsions and the frequency of deaths due to introduction of NMDA were registered in each experimental group. RESULTS AND DISCUSSIONS: Referring to our research, it can be concluded, that not everyone IDCA derivatives exhibit anticonvulsant activity of varying degrees of severity in a dose range from 0.1 to 1 mmol, using the NMDA-induced convulsions model. The administration of IEM1574 in doses of 0.2-0.5 mmol reduced the mortality caused by NMDA seizures from 100 to 40%. The mortality rate decreased to 40% and the duration of seizures increased from 50 to 350 seconds after administration of substance 1 in a dose of 0.5 mmol. A dose-dependent effect on increasing the duration of seizures and reducing the percentage of deaths is observed. In addition, sedative and muscle relaxant effects were identified. Substance 1 with a low dissolution of the active substance (suspension type). IEM2250 has a low anticonvulsant activity in this test, reducing the mortality rate of animals in doses of 0.2-05 mmol from 100 to 60-70%, protecting animals from seizures with concomitant sedative and muscle relaxant effects. Subtoxic and toxic effects (increased respiratory rate, heart rate, convulsions and tremors) and 80% mortality were observed with increasing of concentration using substance 2 (in a dosage of 1 mmol). CONCLUSION: Thus, the results of the study confirm the dose-dependent anticonvulsant activity of new antagonists of the glutamate NMDA-receptor complex-1,2-substituted imidazole-4,5-dicarboxylic acids, which indicates the prospects for further development of these substances and the search for new potential anticonvulsants among this pharmacological class. Key words: anticonvulsant drugs, NMDA receptor, imidazole-4,5-dicarboxylic acid derivatives.

BEHAVIORAL EFFECTS OF ANTIDEPRESSANTS ON THE NOVEL TANK STRESS IN ZEBRAFISH, DANIO RERIO, AS Devyashin, AA Blazhenko, VA Lebedev, AA Lebedev, SV Kazakov, PD Shabanov, Institute of Experimental Medicine, St. Petersburg, Russia

INTRODUCTION: The purpose of this research was to study the behavioral effects antidepressants on novel tank stress in Danio rerio. Previously, the effect of the benzodiazepine anxiolytic phenazepam was study in a test for novelty and predator stress [1]. The obtained results showed a decrease in anxiety behavior. The time spent on the top of tank and the number of transitions to the top of the tank were increased. The number of «freezings» was decreased. In this study, we used different groups of

antidepressants as substances that reduce anxiety-phobic reactions in human. MATERIALS AND METHODS: A stress test on novelty situation was used: a fish was placed first in a beaker with a dissolved pharmacological substance. We used clomipramine 0.5 mg/l (TCA), trazodone 0.5 mg/l (SSRI), paroxetine 0.5 mg/l (SSRI) and agomelatin (stimulate MT1, MT2 receptors) 0.5 mg/l. Further a fish was placed in a novel tank for 6 min, where the trajectory, the path length, the number of movements to the upper part of the novel tank, the number and time of the pattern of “freezing” for each min of the experiment were measured. RESULTS: The typical reaction of the zebrafish in the novel tank test was to submersion to the bottom. The effect obtained with administration of antidepressants is comparable of anxiolytics. We observed a significant decrease in the number of «freezing» only in the paroxetine group 27.4 ± 8.1 ($p \leq 0.05$) (control 58.6 ± 21.2). In all groups, the time at the top of the tank significantly increased: clomipramine 24.7 ± 9.7 ($p \leq 0.05$); trazodone 94.2 ± 9.8 ($p \leq 0.05$); paroxetine 229.5 ± 9.9 ($p \leq 0.05$); agomelatine 258.5 ± 13.7 ($p \leq 0.05$) (control 309.4 ± 12.9). Movements to the upper part of the tank significantly differed in the groups: paroxetine 56 ± 7.9 ($p \leq 0.05$); trazodone 45.4 ± 7.4 ($p \leq 0.05$) (control 21.9 ± 8.7); clomipramine 7.4 ± 1.7 ($p \leq 0.05$) differs significantly from the other groups because most of the time the fish was carry out at the top of the tank. The amount of distance covered did not differ significantly in the groups. CONCLUSION: It have been concluded that novelty stress is really response anxiety and phobic reactions in Danio rerio. The use of antidepressants in the example of clomipramine, trazodone, paroxetine, and agomelatin reduces the anxiety of fishes Danio rerio. Danio rerio is a promising model for the study and research for neuropharmacological agents in the study and correction of post-stress disorders. Key words: Danio rerio; novelty stress; behavior; antidepressants.

INTRANASAL ADMINISTRATION OF TYRAMINE LEADS TO REDUCED ANXIETY IN RATS, SA Apryatin, RR Gainetdinov, VM Klimenko, Institute of Experimental Medicine, Institute of Translational Biomedicine, St. Petersburg State University, St. Petersburg, Russia

INTRODUCTION: Trace amines (TA) are the decarboxylation products of amino acids. These reactions take place in various organs and tissues. TA are also found in many foods that are natural psychotropic compounds. The role of trace amines in the control of energy metabolism, as well as cellular immune responses, including interaction with microbiota, biochemical transformations of nutrients in the body, and, as a consequence, in the pathogenesis of alimentary-dependent diseases, has been indicated. One of the classical TA is tyramine (tyrosine metabolite), which can be secreted in the body endogenously, or by microbiota. It has been shown that tyramine activates the TAAR1 receptor; however, the physiological role of the mechanism is not yet well understood. In part, it is due to the predominant action of tyramine as a “false neurotransmitter” in the periphery during systemic administration. The aim of the study was to compare the effect of the route of administration (intranasally and with the diet) of tyramine on various behavioral parameters of Wistar rats. METHODS: The experiment was carried out on Wistar rats 3 months old (n = 32). The rats were divided into 4 groups. Animals from group 1 (n = 8) received the control diet, group 2 (n = 8) received tyramine in the diet for 48 hours (200 mg/kg of body mass/day). Group 3 (n = 8) received saline solution intranasally, group 4 (n=8) received tyramine at a dose of 50 mg/kg of body mass intranasally. Indicators of locomotor activity, anxiety levels, grooming microstructure, and other behavioral changes were investigated by "Open Field" and "Elevated Plus Maze" tests. RESULTS AND DISCUSSION: The locomotor activity levels of rats in the group receiving intranasal tyramine did not change in comparison with the control group in the “Open Field” test. However, the level of anxiety of rats in the "Elevated Plus Maze" test was decreased with intranasal administration of tyramine in comparison with the control group. Indicators of the microstructure of grooming also revealed tendencies towards a decrease in the level of anxiety. In the case of consumption of tyramine with food within 48 hours, the closed arms/open arms ratio in the “Elevated Plus Maze” test essentially does not change, however, the distance covered in closed arms was significantly lower than in the control group. This result may be due to peripheral degradation of tyramine under the influence of intestinal microflora and enzymes of the MAO family in the epithelium of the small intestine or well-known action on the cardiovascular system through modulation of peripheral norepinephrine system. Thus, intranasal administration of tyramine is likely led to its penetration of the brain regions directly where TAAR1 is expressed such as dopaminergic Ventral Tegmental Area and serotonergic Dorsal Raphe, and this action on TAAR1 results in the reduction of anxiety. These results open up prospects for the creation of new anxiolytic treatments.

EFFECT OF HINDLIMB UNLOADING ON HAMSTRING MUSCLE DURING TREADMILL LOCOMOTION IN RATS, A Popov, V Lyakhovetskii, O Gorskii, D Kalinina, PE Musienko, Institute of Translational Biomedicine, St. Petersburg State University, Pavlov Institute of Physiology RAS, St. Petersburg, Russia

EVALUATION OF SEXUAL MOTIVATION IN TAAR1 KNOCKOUT MICE, IS Zhukov, MA Ptukha, IY Tissen, IV Karpova, AB Volnova, RR Gainetdinov, Institute of Translational Biomedicine, St. Petersburg

State University, Institute of Experimental Medicine, St. Petersburg University Hospital, St. Petersburg State University, St. Petersburg, Russia

INTRODUCTION: It is known that the TAAR1 receptor is involved in limbic brain functions and putative reward circuitry. Moreover, other TAARs are expressed in the olfactory system of all studied vertebrate species. Therefore, we can assume that TAARs may play a role in rodent sexual behavior. A comparative behavioral analysis of TAAR1 knockout (TAAR1-KO) and wild type (WT) mice is also important to evaluate potential side effects of future TAAR1-based therapies. In our studies, we used a modified sexual incentive motivation test (SIMT) to evaluate sexual behavior of TAAR1-KO and WT mice. METHODS: 16 TAAR1-KO and 15 WT male mice were tested in SIMT. 10 WT female mice in induced estrous (10 mkg estrogen benzoate, 500 mkg progesterone i.p. 48 and 2 hours before the experiment, respectively) were used as sexual incentive, males were able to observe and smell females, but not reach them due to a permeable wall. Behavior was recorded for 20 minutes. Numbers of approaches as well as time spent close to the incentive were analyzed using Noldus EthoVision XT (Noldus Information Technology, Netherlands). Additionally, we performed measurements of testosterone by an automated ELISA analyzer (Siemens Advia Centaur XP, Germany). RESULTS AND DISCUSSION: Comparative analysis revealed no significant differences in sexual behavior between TAAR1-KO and WT male mice. Moreover, TAAR1 gene knockout did not affect testosterone levels. These data suggest that potential TAAR1 therapies should have a good safety profile in regard to sexual behavior. Further evaluation of sexual behavior in other TAAR-KO mice is being performed.

Day 3. Tue, May 18, 2021

Small Hall, Oktiabrskaya Hotel, 10 Ligovsky Prospect, St. Petersburg

ISBS SPECIAL LECTURE: SUICIDES IN THE PANDEMIC – WHAT KIND OF STRESS ACTUALLY PROVOKES SUICIDAL BEHAVIOR? VA Rozanov, St. Petersburg State University, Bekheterev National Research Center for Psychiatry and Neurology, St. Petersburg, Russia

When recent COVID-19 pandemic has emerged, many psychiatrists and suicidologists all around the world have expressed concerns regarding possible rise of suicides. Such concerns were based on quite reasonable expectations of higher anxiety, depression, alcohol consumption and stress in huge populations. Moreover, many studies during the pandemic, especially in the period of the most severe quarantine, and further, when restrictions were gradually lifted, have revealed growing risk factors of suicide, including above mentioned psychiatric disorders, as well as psychosocial factors like fears to catch an infection personally or by a family member, forced social isolation, global shift to online communications, sedentary lifestyles, dietary deviations, aggression, home violence, etc. However, the design of the most studies (mainly online surveys) made it impossible to evaluate mental health evolution in relation to pandemic. Some studies did manage to provide comparative data by using pre-pandemic measurements. The results appeared to be mixed, for instance on the population level, incidence of depression during pandemic was similar to pre-pandemic period, while percent of people experiencing anxiety had almost doubled. Other studies involving specific working groups, like IT-specialists, did not find elevated anxiety, while the feeling of perceived stress was significantly higher during quarantine and afterwards. In most of the studies anxiety and depression was greater in younger people, women, those with pre-existing mental/physical health conditions and individuals in socioeconomic adversity, while those protected by compensating financial measures were demonstrating better psychological well-being. At the same time clinical observations all around the world and in Russia revealed that psychiatric referrals, including alcohol abuse, depression and suicide attempts appeared to drop shortly after pandemic was announced. Moreover, real-time monitoring of completed suicides in many countries, based both on the national statistics, and on more local regional data have revealed that in the overwhelming number of cases suicides did not rise, on the contrary, rates and numbers either dropped, or remained stable. Thus, at least by the end of the year 2020 there is no marked rise of suicides despite many rather alarmed predictions. Of course, this must not be the reason for complacency, and prevention measures should be promoted and adjusted. However, this quasi-experimental situation rises several questions. Life stress (understood as negative life events accumulation) is a well-studied risk factor of suicides, while pandemic is an example of the most severe stressful situation that is thought to enhance other risks. So, what may be counteracting factors that protect vulnerable individuals? One of the explanations is the vital character of the threat. It may not only produce “pulling together” effect but may oppose and dismiss deteriorating effects of the so-called psychosocial chronic stress, which is the main reason of depression, psychache and suicidal behavior. Acute stress actualizes survival tendencies and pushes self-reflections, frustrations, and even daily hassles into background, returning human populations to vital needs and motivations for survival and self-preservation. This is a good reason for rethinking of the role of stress in suicide. People commit suicide not when all are confronted

by deadly threats and the whole society is united, but on the contrary, when life seems prosperous in general while society is disintegrated, and they are facing inequalities and social injustice. Pandemic is a global factor that changed a lot in our lives and perceptions, including our understanding of occupational stress, academic stress, information stress and perceived stress. More studies are needed to evaluate specific features of stress during pandemic in relation to different demographic and occupational groups and its' importance for suicidal behavior.

SYMPOSIUM 6: PSYCHIATRIC GENETICS: STRESS-RELATED ASPECTS

Chairs: VE Golimbet and AO Kibitov (Russia)

GENE-ENVIRONMENT INTERACTIONS AND THEIR INFLUNCE ON THE RISK AND SEVERITY OF PSYCHIATRIC DISEASES, VE Golimbet, Mental Health Research Center, Moscow, Russia

GENETIC MARKERS OF THE STRESS-REACTIVITY SYSTEMS IN SUICIDAL BEHAVIOR, VA Rozanov, St. Petersburg State University, Bekheterev National Research Center for Psychiatry and Neurology, St. Petersburg, Russia

DNA METHYLATION AS A POTENTIAL MEDIATOR OF EARLY LIFE STRESS EFFECTS ON COGNITIVE PERFORMANCE IN SCHIZOPHRENIA, M Alfimova, Department of Clinical Genetics, Mental Health Research Center, Moscow, Russia

GENETIC STUDIES OF MOOD DISORDERS WITH FAMILY DESIGN: NEW PERSPECTIVES, E Kasyanov, E Kasyanov, Bekheterev National Research Center for Psychiatry and Neurology, St. Petersburg, Russia

THE ASSOCIATION BETWEEN INTERNET ADDICTION AND STRESS IN SOCIAL COMMUNICATION: PSYCHOLOGICAL AND GENETIC FACTORS, AV Trusova, St. Petersburg State University, Bekhterev National Research Center for Psychiatry and Neurology, St. Petersburg, Russia

GENETIC MARKERS OF THE INTERNET ADDICTION RISK: POSSIBLE LINKS WITH CHILDHOOD TRAUMA AND PERSONALITY TRAITS, AO Kibitov, Serbsky National Medical Research Centre on Psychiatry and Addictions, Moscow, Russia

SYMPOSIUM 7: CONSOLIDATED POSTER SESSION PART 2

Chairs: AV Kalueff (China, Russia, USA) and VM Klimenko (Russia)

INVESTIGATION OF THE LINKAGE OF FIN LENGTH AND SKIN COLOR WITH NEUROBEHAVIORAL PHENOTYPES IN ZEBRAFISH. PART II: THE SOCIAL PREFERENCE TEST. KN Zabegalov, AA Bashirzade, TG Amstislavskaya, AV Kalueff, Ural Federal University, Yekaterinburg, Scientific Research Institute of Physiology and Basic Medicine, Novosibirsk, Russia; Southwest University, Chongqing, China

INTRODUCTION: Skin pigmentation and some structural features (e.g., the differences in body parts size) are important markers for social behavior in various vertebrate species. In evolutionary ancient teleost fishes, such as zebrafish, these hallmarks, including skin color and fin length, play an essential role in shoaling behavior and social preference (Stednitz & Washbourne, 2020). In that case, we analyzed zebrafish social behavior in social preference test in the purpose to define the supposed involvement of pigmentation and body part morphological varieties in vertebrate sociality. METHODS: The study utilized 78 adult fish with 50/50 male-female ratio, divided into four groups, contained in 40-L tanks filled with filtered water in accordance with zebrafish care standards. Groups included dark-colored shortfin (n=19) and longfin (n=20) fish, as well as light-colored shortfins (n=19) and longfins (n=20). The behavior was recorded within 5 min for each fish of each experimental group in social preference test (SPT). SPT basic indices included velocity (m/s), total distance moved (m), stranger shortfins' area entries, stranger longfins' area entries, stranger shortfins' area duration (s), stranger longfins' area duration (s), tank center duration (s). Statistical analysis consisted of multiple comparisons between four previously mentioned groups and two paired comparisons: long-fins with shortfins, and dark-colored with light-colored fish. RESULTS AND DISCUSSION: The fish of different fin length demonstrated differences in both, locomotor, and area related behavior. Hence, shortfins moved longer distance and

developed higher velocity than longfins. Regarding stranger area, shortfins and longfins kept closer to the same fin length strangers: shortfins more frequently entered the shortfin strangers' area, and longfins spent more time in longfin strangers' area. Despite the distinct color, the fish of the same fin length spent more time together, as it was studied before. Moreover, the increased locomotion (velocity and total distance moved) of shortfins in comparison with longfins was also observed in that study (Kiesel et al., 2012). Regarding the skin color, light-colored fish had the higher locomotor parameters, such as velocity and distance moved, than dark-colored fish. That coincides with our previous study in novel tank test (NTT) and with current data (Audira et al., 2020). The light-colored fish also kept closer to shortfin strangers, spent more time in their area and enter this area more frequently. The underlying mechanism of such preference is still to be investigated. Multiple comparisons between four group revealed the significant increase in locomotion (velocity and distance moved) in light-colored shortfins vs three other groups. Additionally, dark-colored longfins and shortfins spent less time in shortfin strangers' area, than light-colored shortfins. Almost the same situation was about shortfin strangers' area entries, except for dark-colored shortfins just tended ($p=0.09$) to enter this area less frequently. There was also tendency in less frequent entries to longfin strangers' area ($p=0.08$) in light-colored shortfins relatively to dark-colored longfins. Thus, as light-colored fish in our study is likely of albino mutation, which used to be anxious in novel tank test (Lima et al., 2017), the most apparent reason of shortfin "albino" increased preference to different color strangers is the specific gene interaction between hox genes, inducing fin development, and pigmentation genes, such as slc45a2, slc24a5. RESEARCH SUPPORT: Scientific Research Institute of Physiology and Basic Medicine, Novosibirsk, partially Ural Federal University, Yekaterinburg, Russia

INVESTIGATION THE LINKAGE OF FIN LENGTH AND SKIN COLOR WITH NEUROBEHAVIORAL PHENOTYPES IN ZEBRAFISH. PART III: MIRROR-INDUCED AGGRESSION TEST. KN Zabegalov, AA Bashirzade, TG Amstislavskaya, AV Kalueff, Ural Federal University, Yekaterinburg, Scientific Research Institute of Physiology and Basic Medicine, Novosibirsk, Russia; Southwest University, Chongqing, China

INTRODUCTION: As the part of normal behavioral activity, all vertebrate classes express aggression. However, altered aggressive behavior can be the sign of various impairments, such as intermittent explosive disorders, psychopathic aggression, oppositional defiant disorder and so on (DSM V, 2013). Zebrafish belongs to the ancient vertebrate systematic group, along with shared physiological traits with humans and simply recognized behavioral patterns. So, we investigated the aggression level in zebrafish using mirror-induced aggression test in accordance with their skin pigmentation and the fin length. METHODS: A total of 76 fish, divided into four groups, contained in 40-L tanks filled with filtered water in accordance with zebrafish care standards. Groups included dark-colored shortfin (n=17) and longfin (n=20) fish, as well as light-colored shortfins (n=19) and longfins (n=20). The behavior was recorded within 5 min for each fish of each experimental group in mirror-induced aggression test (MIAT). MIAT locomotor endpoints were assigned to whole tank and the mirror area, including distance moved (m), velocity (m/s), fast moving state (s), and the number of rotations. Aggression-related markers were the time spent in the mirror area (s), and the entry frequency in this area. Statistical analysis consisted of multiple comparisons between four previously mentioned groups and two paired comparisons: long-fins with shortfins, and dark-colored with light-colored fish. RESULTS AND DISCUSSION: Paired comparisons showed differences in locomotion only between longfins and shortfins. Hence, the shortfins moved a larger distance, developed the higher velocity, and had the larger period of high speed in mirror area vs longfins. As for rotations, shortfins rotated more frequently than longfins both in the whole tank and in the mirror area. In addition, shortfins spent more time in front of mirror than longfins. In the color-related paired comparison, aggression-related indices were significantly altered. Thereby, light-colored fish entered the mirror area more frequent, and spent there more time than dark-colored fish. To some extent, the whole data from both paired comparisons correlates with currently published studies (Audira, 2020). Multiple four groups' comparisons revealed differences in all locomotor indices in all zones. Thus, light-colored shortfins moved the longest distance and developed the highest speed among all four groups in the mirror area. Besides, light-colored shortfins exhibit increased distance and total velocity vs dark shortfins in whole tank. Light-colored shortfins also displayed the longer period of fast moving than dark-colored shortfins in the whole tank, and in the mirror area light-colored shortfins has this endpoint increased vs dark-colored shortfins, dark-colored longfins, and with the tendency to the increase vs light-colored longfins ($p=0.051$). Regarding rotations in whole tank, light-colored shortfins rotated more frequently than dark-colored longfins and light-colored longfins, with the tendency to more rotations than dark-colored shortfins ($p=0.062$). In the mirror area light-colored shortfins exhibited more rotations than dark-colored longfins, with tendency to more rotations than light-colored longfins ($p=0.066$). Furthermore, light-colored shortfins spent more time in front of the mirror than dark-colored longfins. Hence, all the results indicate the positive correlation of aggression with low pigmented and shortfin fish. It does not coincide with data from pharmacological aggression studies in zebrafish, where the darker fish was more aggressive (de Abreu, 2021). Most probably, in that case the reason is in deep genetic

influence within CNS development. RESEARCH SUPPORT: Scientific Research Institute of Physiology and Basic Medicine, Novosibirsk, partially Ural Federal University, Yekaterinburg, Russia.

REGENERATIVE MEDICINE CELL QUALITY CONTROL SYSTEM "AICELEX", K Ito, M Koshiba, Graduate School of Science and Technology for Innovation, Yamaguchi University, Yamaguchi, Department of Pediatrics, Saitama Medical University, Saitama, Graduate School of Information Sciences, Tohoku University, Tohoku, Japan

INTRODUCTION: The stem cell therapy has been highlighted in treatment approaches for incurable psychiatric diseases such as autism spectrum disorders. For instance, transplanting stem cells derived from the patient him-/her-self have been reported some radical effects successfully with educational supports. The own stem cell requires to be cultured without canceration, with reliably confirmed its functional prediction. To provide stable, safe and high-quality stem cells from the culture, we developed a cloud diagnostic report system with image processing, named as Aicellex and evaluated this with the human mesenchymal stem cells. METHODS: Microscopic images of the human mesenchymal stem cells cultured at hospitals were obtained via internet and were processed at a cloud computer with three steps; adjustment for uneven illumination, binarization, and automatic quantification of proliferating numbers and each cell diameter. The accuracy of these values were evaluated with the measured one manually. The time lapse profiling of each targeted cell was graphed out in the time-series heat map and visualized clustering in the principal component analysis (PCA). RESULTS AND DISCUSSION: Ten sets of cultured images were automatically quantified each stem cell number, shown in the Aicellex answer as 196 to 265. The accuracy rates of these values compared with the manually quantified were confirmed 91 to 98 % (average: 94,4 %, Standard deviation: 2.2%). The time-lapse heat map comparison in five cells generally discriminated two patterns of cell activities. The profiling by PCA elucidated three groups of clustering patters in the 3D components. Further Aicellex customization with preparing various data bases would open novel tailor made medicine with the own stem cell transplant. RESEARCH SUPPORT: Reiwa Adoption of Strategic Infrastructure Technology Advancement Support Project in FY2020.

SOCIAL BEHAVOIR COMPARISON OF DIFFERENT GLOFISH® ZEBRAFISH STRAINS: A PILOT STUDY. GO Maslov, CR Shakirova, AS Starodvorskaya, KN Zabegalov, AV Kalueff, Ural Federal University, Ekaterinburg, Institute of Translational Biomedicine, St. Petersburg State University, Russia; Southwest University, Chongqing, China

INTRODUCTION: Emerging evidences indicate the pronounced influence of color proteins on animal social behavior (Price et al., 2009). However, specific mechanisms of how color-changing protein affect the social behavior are poorly studied, especially in transgenic organisms with inserted fluorescent protein genes, such as GloFish®. GloFish® animals, including glowing zebrafish (Danio rerio), are ubiquitous and publicly available. Studies with such organism can help to create non-pharmacological models of some sociality related psychological diseases and explore novel neurobiological markers, as far as color related proteins most probably affect neurochemistry and neurogenetics. In this study, we investigated neurobehavioral effects of GloFish® fluorescent proteins on fish social behavior. METHODS: Four GloFish® stains were studied, including green fluorescent protein (GFP) (n=22), red fluorescent protein (RFP) (n=20), orange colored (RFP+GFP) (n=20), blue fluorescent protein (BFP) (n=20) zebrafish, and the wild-type (WT) Danio rerio (n=11) as a control group. All the fish with 50/50 male-female ratio were contained in separated groups in 40-L tanks filled with filtered water in accordance with zebrafish care standards. Behavior assay included 5-min videorecordings in the social preference test (SPT). Behavioral markers include stranger fish side entries, conspecific fish side entries, stranger fish side duration (s), conspecific fish side duration (s), the latency of the first entry to the stranger or conspecific area (s), duration and frequency of biting the edge of stranger or conspecifics fish area (s). RESULTS AND DISCUSSION: The fish from GFP+RFP group revealed decreased number of conspecifics side bites in comparison with RFP and GFP groups. The RFP group spent significantly more time in conspecific area than three other glowing fish strains, but not WT. Besides, the RFP fish had also increased cumulative duration of biting conspecific fish site compared to GFP group. Three previous differences are correlating with other experiments with GloFish (Barlow, 2012), where animals prefer to shoal with conspecifics instead of strangers. In such manner, GFP+RFP group exhibited the longer latency of conspecific fish site biting in comparison to RFP group. Regarding stranger side, WT fish displayed shorter latency to the first bite than RFP and GFP groups. As far as WT strangers include the fish of 3 presented GloFish® strains (red, blue and green), it may correspond to the study, where wild-type females prefered yellow GloFish® males (Howard and Rohrer, 2015). Although, we cannot strictly prove it, as WT sample size was much smaller, than the others were. Even though, we did not obtain multiple differences between groups in stranger side indices, GFP+RFP group has likely lesser need to contact with conspecifics vs. other GloFish® strains, but the RPF fish tended to novel social contacts lesser. No doubt, that this study should be repeated and high throughput analysis of fish brain

structures should be conducted, though fluorescent proteins obviously affect social behavior. RESEARCH SUPPORT: Ural Federal University, Ekaterinburg, Russia.

BIOCHEMICAL ASSESSMENT OF STRESS RESPONSES IN DIFFERENT GLOFISH® ZEBRAFISH STRAINS: A PILOT STUDY, KN Zabegalov, CR Shakirova, GO Maslov, T Mbutho, AS Starodvorskaya, AV Zhdanov, SL Khatsko, AV Kalueff, Ural Federal University, Ekaterinburg, Institute of Translational Biomedicine, St. Petersburg State University, Russia; Southwest University, Chongqing, China

INTRODUCTION: Stress is common physiological reaction of all living organisms to environmental alterations. In vertebrates, the main stress triggers are glucocorticoids, the hormones of adrenal gland. Interestingly, there is an obvious correlation in vertebrate species between stress response and the skin color (Khan et al., 2016). Hence, we assessed cortisol level in terms of acute stress procedure in genetically modified zebrafish strains (GloFish®), which tissues express fluorescent proteins closely related to pigments. METHODS: The experiment utilized 79 zebrafish of adult wild type and four GloFish® strains with 50/50 male-female ratio, spread out across five different 40-L tanks filled with filtered water in accordance with zebrafish care standards. The stressing procedure included 30 minutes predator exposure in 2L tanks, contained 10 ml solution of conspecific alarm substance (CAS). Hence, the control groups included unstressed wild type/WT (n=8), green fluorescent protein/GFP (n=8), red fluorescent protein/RFP (n=8), red + green fluorescent protein (orange)/RFP+GFP (n=8), and blue fluorescent protein/BFP (n=8) zebrafish. The acutely stressed fish were also reassigned to above mentioned strains: WT (n=8), GFP (n=8), RFP (n=8), orange (n=7), and BFP (n=8). The cortisol level was analyzed by ELISA under 415 nm detecting light beam wave length. RESULTS AND DISCUSSION: Basic cortisol was significantly lower in GFP and orange fish than in WT, and RFP fish cortisol level tended to be lower than in WT ($p=0.09$). Under acute stress, the orange fish exhibited less prominent stress response than WT, GFP, and BFP fish. Additionally, RFP fish tended to be more stressed than orange fish ($p=0.08$). Furthermore, paired comparisons between stressed and unstressed fish revealed no differences between stressed and unstressed orange fish. Hence, the results point at the remarkable stability of stress level in orange (RFP+GFP) zebrafish, as cortisol level had not changed even after 30 minutes of constant predator exposure and additional CAS influence. This evidence supposes to be the result of anti-stress effect, caused by combined expression of two fluorescent protein genes. However, the specific physiological mechanism of such genetic influence is still to be studied. RESEARCH SUPPORT: Ural Federal University, Yekaterinburg, Russia.

AGGRESSIVE BEHAVIOR ASSAY OF DIFFERENT GLOFISH® ZEBRFISH STRAINS: A PILOT STUDY. CR Shakirova, AS Starodvorskaya, GO Maslov, KN Zabegalov, AV Kalueff, Ural Federal University, Ekaterinburg, Institute of Translational Biomedicine, St. Petersburg State University, Russia; Southwest University, Chongqing, China

INTRODUCTION: Aggression is an important component of social interactions among animals. However, aggression can cause self-harm and physical injury or death to conspecifics or other species individuals. A huge number of clinical and preclinical studies indicate the pronounced influence of different pigments on behavior, including aggression (Walk et al., 2017, Dijkstra et al., 2017). Hence, to elaborate our knowledge of pigments' role in aggressive behavior, we analyzed several zebrafish Glofish® strains (transgenic derivatives from zebrafish Danio rerio), as an effective and relatively inexpensive model organism, expressing fluorescent proteins, functionally closed to pigments. METHODS: The study utilized adult wild-type WT zebrafish (n=19) and four groups of Glofish®: green fluorescent GFP (n=20), red fluorescent RFP (n=18), orange fluorescent RFP/GFP (n=17), and blue fluorescent protein BFP (n=18) adult zebrafish with 50/50 male-female ratio. Fish were kept in groups of same color in 40-L tank filled with filtered water in accordance with zebrafish care standards. Zebrafish behavior assessment included 5 min video recording in mirror-induced aggression test (MIAT). Major behavioral endpoints were the latency (s) and number of entries in mirror area, time spent in the mirror area (s), duration (s) and frequency of mirror biting, and the latency of mirror biting (s). RESULTS AND DISCUSSION: MIAT observations revealed the significant decrease in the number of entries in the mirror area in RFP/GFP group vs. wild-type group. So, we can suppose that RFP/GFP Glofish® is less aggressive comparing to wild-type fish because aggressive individuals move as close as possible to the mirror image and spend more time in the mirror area (Way et al., 2015). Besides, MIAT observations revealed the significant decrease in the number of mirror bites in RFP/GFP group vs. BFP group. As far as fish is unable to recognize its own mirror image, so it attacks a supposed intruder (Rowland, 1999). Hence, RFP/GFP Glofish® is probably less aggressive than the wild type zebrafish and other blue fluorescent strain. According to these results, the combined presence and functioning of green and red fluorescent proteins (or their genes) in fish presumably affects some brain structures associated with aggressive behavior. In further research, it may be important to observe the genetic and neurochemical basis of such effects. RESEARCH SUPPORT: Ural Federal University, Ekaterinburg, Russia.

HYPOLIPIDEMIC EFFECTS OF KRAMIZOLE ON THE EXPRESSION PDIA2 GENE IN THE RAT'S HYPERCHOLESTEROL DYSLIPIDEMIA MODEL, AV Lizunov, IV Okunevich, GP Kosyakova, LB Piotrovskiy, PD Shabanov, Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia

INTRODUCTION: Atherosclerosis is a chronic multifactorial vascular disease with the atherogenic dyslipoproteinemia (DLP) as a leading risk factor. Research indicates that chronic psychological stress is closely connected with the risk of atherosclerotic diseases. Prevention and treatment of atherosclerosis requires early and intensive pharmacotherapy by means of effective lipid-lowering and anti-atherosclerotic agents, acting as a modulators of molecular mechanisms of the lipid exchange. In order to correct atherogenic DLP, the search for new drugs among aromatic heterocyclic compounds still represents an important biomedical task. In our work we used hypercholesterol model of dyslipidemia on rats to analyze the effect of kramizole injection on the expression of the pdia2 gene, encoding the regulator of secretion of the main LDL protein ApoB: PDIA2. METHODS: We had four groups of rats: intact control group, hypercholesterol diet group, phenophibrate group and cramizole group. During a 30 days we gave an oral injections of kramizole for the kramizole group, phenophibrate (as a reference drug) for phenophibrate group and hypercholesterol diet for kramizole, phenophibrate and hypercholesterol diet groups. Liver tissue samples were used for RNA extraction and following RT-PCR (Real Time PCR) with primers for pdia2 mRNA sequences. RESULTS: We have found, that pdia2 mRNA level was decreased in control group by 600% respectively to the intact group. Pdia2 mRNA level in phenofibrate group was also decreased by 112% respectively to the control group, but increased by 242% in the kramizole group respectively to the control group. CONCLUSIONS: kramizole works like stimulator pdia2 gene expression. That modulating of the expression of antiatherogenic protein gene could be the additional mechanism of the hypolipidemic effect of kramizole. Key words: kramizole, pdia2 gene, atherosclerosis.

THE ROLE OF THE GRELIN SYSTEM IN REDUCING ANXIETY AND STABILITY OF THE PERIPHERAL BLOOD GENOME AFTER VITAL STRESS IMPACT, GP Kosyakova, AG Pshenichnaya, AV Lizunov, VE Mikhailova, IV Kazurov, PV Shalyapin, VA Lebedev, Institute of Experimental Medicine, St. Petersburg State University of Chemistry and Pharmacy, St. Petersburg, Russia

INTRODUCTION: The aim of the study was to study the effect of ghrelin and its receptor antagonist D-[Lys3]-GHRP-6 on behavior and genome stabilization after vital stress. The stress factor is reflected in the destabilization of the genome of mononuclear cells in the peripheral blood of animals. This factor is of not only scientific, but also practical interest: to what extent does vital stress affect behavior and destabilization of the genome of the peripheral blood of animals. In this regard, we continue to study such an informative indicator characterizing the instability of the cellular genome as the frequency of erythrocytes and lymphocytes with micronuclei. METHODS: Mental trauma was caused by a stressful effect, the essence of which was the animal's experience of the circumstances of the death of a partner from the actions of a predator. A group of rats was placed in a tiger python terrarium once. After the action of vital mental stress in rats, two associated behavioral phenomena were observed - a high level of anxiety and an increase in the number of buried balls. This was accompanied by a decrease in communication skills. Peripheral blood from rats was taken from the tail vein, a drop of blood was applied to a glass slide, dried in air, and fixed with 96% ethyl alcohol. Then the staining was carried out according to Romanovsky-Giemsa. To determine the frequency of occurrence of mononuclear cells with micronuclei, at least 10 thousand cells from each individual were analyzed. In the study, only morphologically normal, intact cells were processed. The number of genetically aberrant cells was expressed in ppm. Erythrocyte micronuclei were detected with the Romanovsky-Giemsa dye. The preparations were examined using an OlympusVanox-T microscope. RESULTS AND DISCUSSION: The data obtained on the frequency of erythrocytes and lymphocytes with micronuclei in the group of rats after vital stress with and without drugs are of no doubt of interest. The drug ghrelin, with intranasal course (7 days, at a dose of 10 μg in 20 μl), after presentation of a vital stressor effect, reduced the level of anxiety and normalized compulsive behavior). Despite the low background frequency of occurrence of mononuclear cells with micronuclei, significant differences were recorded between the studied groups of animals. The frequency of micronuclei in rat peripheral blood mononuclear cells after vital exposure without drugs averaged 1.12 ‰, whereas with intranasal administration of ghrelin and its receptor antagonist, ghrelin D-[Lys3]-GHRP-6, it was possible to register a tendency towards a decrease in the frequency of micronuclei in erythrocytes peripheral blood up to 0.6 ‰. Output. Thus, ghrelin and its ghrelin receptor antagonist D-Lys3] -GHRP-6 reduce the manifestation of compulsive behavior and can be considered as correctors of anxiety disorders of an obsessive-compulsive nature, emotional behavior and cognitive disorders caused by vital stress. They also reduce the instability of the genome of mononuclear cells in the peripheral blood, which is expressed in a decrease in the frequency of aberrant cells. The use of intranasal administration of ghrelin and its analogs in the clinic will allow the use of

small doses of substances and thereby reduce their possible toxic effects. Key words: stress, antagonist D-[Lys3]-GHRP-6, peripheral blood, ghrelin, genome, cells.

ANTIPARKINSONIAN ACTIVITY OF NEW N-METHYL-D-ASPARTATE RECEPTOR LIGANDS IN THE ARECOLINE HYPERKINESIS TEST, VD Dergachev, EE Yakovleva, MA Brusina, EV Litasova, ER Bychkov, LB, PD Shabanov, Institute of Experimental Medicine, St. Petersburg State Pediatric Medical University, Kirov Military Medical Academy, St. Petersburg, Russia

INTRODUCTION: Parkinson's disease (PD) is one of the most common neurodegenerative diseases in the population of older patients. Even though long-term combination therapy helps to cope with the main manifestations of PD. It inevitably leads to the appearance of such side effects as drowsiness, hallucinations, dyskinesia, and many others. Therefore, the search for effective antiparkinsonian drugs devoid of the above-mentioned adverse reactions remains an urgent task of modern neuropharmacology. The explored substances are derivatives of imidazole-4,5-dicarboxylic acid. These compounds belong to a fundamentally new class of N-methyl-D-aspartate ligands (NMDA) that are not channel blockers. Their pharmacological effect is realized due to interaction with the NMDA receptor recognition site, which, along with high efficiency, allows us to assume their higher safety, compared to previously existing channel blockers from the NMDA ligand group.The main objective was to studyof the antiparkinsonian activity of new ligands of the glutamate NMDA-receptor complex-1,2-substituted imidazole-4,5-dicarboxylic acids on an experimental model of arecolinehyperkinesis. METHODS: Imidazole-dicarboxylic acid derivatives (IEM2258, IEM2248, IEM2247, and IEM1574) were injected into the lateral ventricles of the mouse brain 10 minutes before arecoline in a volume of 5 µl at doses of 0.1-0.5 µmol, then the latent period, intensity, and duration of tremor were recorded. Amantadine was used as a comparison drug. RESULTS AND DISCUSSION: Preliminary administration of the studied examined substances led to a significant decrease in the intensity and duration of arecoline tremor. The highest inhibitory activity with respect to the intensity and duration of the experimental tremor was demonstrated with the introduction of the compound IEM-2247 (at a dose of 0.1-0.5 mmol, the duration of the latent period of the tremor was 1.7-2.3 times longer than the control one, respectively, the duration of the tremor decreased by 1.5 - 2.5 times).Currently, it is difficult to make a final conclusion on what the differences in effects between the studied substances depend on. Further analysis of the structure-action relationship with respect to the claimed agents and analysis of other components of the antiparkinsonian action of these compounds, in addition to the effect on cholinergic transmission, such as the effect directly on dopaminergic transmission, etc., is necessary. An important fact is that, as blockers of the NMDA receptor recognition site, the substances under study are considered as potentially safer NMDA ligands, compared to previously developed channel blockers, and with established effectiveness have significant prospects in the treatment of Parkinson's disease. CONCLUSION: Based on the results obtained in this work, it is particularly worth highlighting the compound IEM-2247, which, when administered, demonstrated the highest inhibitory activity with respect to the intensity and duration of experimental tremor. The dose-dependent antiparkinsonian activity of imidazole-dicarboxylic acid derivatives is shown,indicating the prospects for the development of these substances and the further search for effective and safe antiparkinsonian agents among the compounds of this class. Key words: parkinsonism, glutamate NMDA-receptor, imidazole-dicarboxylic acid derivatives.

NEW SYNTHETIC COUMARINS DECREASE COMPULSIVE BEHAVIOR IN THE RAT MARBLE TEST, BB Daliev, M Kvasov, AA Lebedev, ER Bychkov, LV Myznikov, LB Piotrovsky, PD Shabanov, Institute of Experimental Medicine, St. Petersburg, Russia

INTRODUCTION: Coumarin derivates are well known pharmacological agents, but many of them have very poor water-solvability. So they have complicacy in clinical practice. Now we are holding on synthesis of new coumarin-held macromolecules, which combine diverse biologically active fragments, which can increase clinical effects of synthetic derivates more than natural coumarins. The aim of the study was to investigate central effects of new species based on coumarin – LVM-99, LVM-S144, IEM-2886 – on compulsive behavior in marble test in rats. METHODS: We used “Marble test” and “Elevated plus maze” to investigate the behavioral reactions in Wistar rats, 180-200 g weight. We had intact group of rats and several groups by 7-9 species. Rats received drugs in the dose 1 - 25 mg/kg intraperitoneally. RESULTS: The experiment demonstrated the decrease in number of buried marbles after injection of coumarin derivates in “Marble test”. The number of buried marbles in control group was 15,17±0,7, but after drug injection the number of buried marbles was decreased ($p \leq 0,05$). The highest anti-compulsive effect realized in 25 mg/kg dosage: 9,85±0,70 buried marbles by LVM-99, 7,70±0,59 buried marbles by LVM-S144, 8,28±0,68 buried marbles by IEM-2886 ($p \leq 0,05$).This indicates the significant depression in compulsivity of rats by drug dose increase. In “Elevated plus maze” we have recorded, that rats have spent less time in the open arm. In control group they spent 55,00±5,24sec, by highest dose (25 mg/kg) of two drugs – LVM-S144 and IEM-288628,43±5,78 sec and 19,67±4,04 sec respectively($p \leq 0,05$). This

fact may be explained as an increase of anxiety in rats by high doses of drugs. DISCUSSION: Obtained results demonstrate the dose-depending effect of new synthetic coumarins on compulsive behavior in marble test. The obtained effects are selective, since no anxiolytic, tranquilizing effect was observed in the "Elevated plus maze" test. Thus, new synthetic derivates of coumarin will be successful drugs in clinical practice, especially in treatment of neurological and psychiatric compulsive disorders and shows the new prospects in their development and further synthesis of successful substances. Key words: coumarin, derivate, compulsivity, marble-test, elevated plus maze, behavior.

NEUROPROTECTIVE EFFECT OF GALANTAMINE IN MALE RAT REPRODUCTIVE FUNCTION UNDER IMMOBILIZATION STRESS, EV Stashina, MA Ganzenko, AO Zelener, RN Magradze, AD Lisovsky, AA Bairamov, PD Shabanov, Institute of Experimental Medicine, St. Petersburg, Russia

INTRODUCTION: Sexual behavior (SB) is the most vulnerable aspect of male reproductive function under stress. Acute and chronic stress influences modify the SB components in a wide range [1]. If sexual activity in rats can be stimulated by acute short-term stressing of animals, then chronic stress, depending on its nature, causes a significant alteration of almost all recorded parameters of SB [2]. In addition to hormonal factors, neurotransmitter systems, including cholinergic mechanisms, are also involved in the mechanisms of SB disruption under stressful influences [1]. At the same time, the state of the cholinergic mediator system during various stressful influences has not been sufficiently studied. Therefore, the aim of this work was to study the protective effect of the anticholation nesterase drug Galantamine in the implementation of sexual function under immobilization stress. METHODS: Young adult male Wistar rats with acquired sexual experience were used in the experiment. Immobilization stress was induced by the method of restriction of movement (restriction) under bright illumination for 6 hours (6 h). Sexual behavior parameters were recorded before stress and 1 hour after stress. The components of sexual activity were recorded visually for 15 minutes [2]. Latent periods and numbers of cages (LpC and NC, respectively), intromissions (LpI and NI), and ejaculations (LpE and NE), as well as parameters of the recovery period (RP) and interejaculatory interval (IEI). In the experiment, one of the two test groups of animals 30 minutes before stressing in order to activate m-cholinergic mechanisms, she was subjected to combined premedication with the anticholinesterase drug galantamine (at a dose 1.0 mg/kg) and the n-cholinergic blocker gangleron (5.0 mg/kg) intraperitoneally. RESULTS: Experimental data indicate that acute stress lasting 6 hours leads to significant damage to the copulatory components of sexual function: the number of NC, NI and NE decreased (by 38.7%, 49.4%, and 24.1%, $P < 0.05$) (Fig. 3). LpC (by 92.3% $P <0.01$) and LpI (by 110.4% $P <0.01$) increased significantly, reflecting the damage to the motivational component of sexual function. The decrease in the number of ejaculations occurred due to the increase in LpE (by 33.1%, $P <0.01$). The opposite situation was observed when cholinotropic drugs were administered before immobilization. Premedication with galantamine and gangleron contributed to the preservation of PP activity at the pre-pressure level - there was an increase in copulatory parameters - SBP, INT and EJC (by 43.3% and 67.5%, 39.6%, $P <0.01$) and a decrease in the time of MEI (by 34.1%, $P <0.01$) and PT (by 25.0%, $P <0.05$), compared with the stressed control group. CONCLUSION: Thus, the data obtained indicate that the preliminary activation of m-cholinergic mechanisms against the background of blockade of n-cholinergic transmission had a pronounced protective effect against both the central motivational and peripheral copulatory components of sexual function under 6-hour stress.

EFFECTS OF IMMOBILIZATION STRESS ON SEXUAL BEHAVIOR OF MALE RATS EXPOSED PRENATALLY TO CHOLINOLYTICS, MA Ganzenko, EV Stashina, AO Zelener, AD Lisovsky, NSh Mamina, AA Bairamov, PD Shabanov, Institute of Experimental Medicine, St. Petersburg, Russia

INTRODUCTION: Influence of different neurotropic drugs at prenatal period is the cause of brain sexual differentiation disorder at neonatal period and behavioral abnormalities at sexually mature age. In some cases, those influences are mediated via brain cholinergic system injury (Levin et. al., 2002; Abreu-Villaca et. al., 2004). The aim of the current work was to study the effect of immobilization stress on the sexual behavior (SB) of male rats subjected prenatally to the action of selective M- and N-cholinoblockers. METHODS: Pregnant female Wistar rats at 9–11, 12–14, and 17–19 days of pregnancy (the group 1, the group 2, and the group 3 correspondingly) were injected with cholinotropic drugs of the central action — methylbenactyzine (MeT) (2.0 mg/kg) and gangleron (GnL) (12.0 mg/kg). Gonadal hormones were analyzed in peripheral blood in some of offspring at the age of 2 months. Influence of immobilization stress lasted 6 hrs on sexual activity with SB test was studied in sexual matured male rats at the age of 100–110 days with acquired sexual experience. RESULTS: Influence of cholinotropic drugs at prenatal period exerted long-term effects on the level of sexual hormones in some of offspring of male rats at the age of 2 months and on the sexual behavior of matured male rats. Testosterone level was significantly decreased in all groups with GnL. The matured male rats from these groups showed less spontaneous sexual activity and slow dynamics of acquisition of sexual experience in comparison with the animals from the control group. The male rats from the group MeT, possessed low spontaneous

sexual activity, showed more fast dynamics of acquisition of sexual experience that was compared with one from the control group animals. Immobilization stress lasted 6 hrs depressed sexual activity in the control group. Quantity of setting, intromissions, and ejaculation was significantly decreased (accordingly on 19.7%, 23.4% and 25.1%, $p<0.05$) as well as increase of SB time components in considerable limits. The male rats from the MeT group showed compared with the control group dynamics of sexual activity after stress exposure, apart from the group 1, which ejaculatory component was decreased more greatly (44.3%). Quite differing data from the control and MeT groups were found in the GnL-treated male rats' offspring: SB motivational components were decreased more then twice at all groups. The ejaculatory component was decreased more then 1.5 time apart from the group 3 (reduction on 27.3%). Sexual activity after stress exposure was totally suppressed in 25% of male rats from the first GnL group. CONCLUSION: Thus, prenatal exposure to cholinergic blockers of N-type and to a lesser degree of M-type exerts long-term effects on sexual hormone level of male rat's offspring and on sexual activity of the matured offspring. Change of cholinergic neuronal activity at prenatal period with cholinotropic drugs of the central action decreases sexual activity and increases behavioral sensitization to stress factors at matured individuals. Key words: immobilization stress, sexual behavior, methylbenactyzine, gangleron.

INFLUENCE OF PRENATAL STRESS ON THE CONTENTS OF DOPAMINE AND SEROTONIN IN THE BRAIN OF RAT FETUS, MA Ganzenko, EV Stashina, RN Magradze, DE Fisenko, AA Bairamov, PD Shabanov, Institute of Experimental Medicine, St. Petersburg, Russia

INTRODUCTION: Stress influences at the late prenatal period can become the reason for disturbance of integrative processes in neuroendocrine brain system at neonatal period and disorder of different functions of an organism at puberty age. The aim of the current work was assessment of influence of prenatal noise stress on the contents of dopamine and serotonin in the brain of rat 3 weeks old fetus and evaluation of the role of the cholinomimetic agent Gangleron (GnL) in the development of the stress reaction. METHODS: The subjects were 20 days old embryos got from 3 groups of rat females: 1 — the control group, 2 — the group of animals subjected to the noise stress (150 dB), 3 — the group of animals injected with GnL (intramuscularly 10 mg/kg) 40 min before the noise stress at the 17th–19th day of pregnancy. On the day 20 of pregnancy fetuses were taken out and decapitated (brain without cerebellum was frozen in the liquid nitrogen). Concentration of dopamine (DA), serotonin (5HT), and its metabolites DOPAC and HIAA in the rat fetus brain measured with HPLC-ED. RESULTS: Prenatal stress led to increase of DA level (on 28%) in the rat fetus brain in comparison the with control group whereas DA turnover was significantly decrease, DOPAC concentration being unchanged. In spite of considerable decrease of 5-HT level (on 36%), 5-HT turnover in the rat fetus brain did not changed due to in parallel decrease of the level of its metabolite HIAA (37.2%). Premedication with GnL significantly changed balance of neuromediators in brain, making closer its level to the control group one. Small increase of DA level and significant decrease of 5-HT level in comparison with the control group was marked. Inter-gender difference in the content of DA and CE was absent. CONCLUSION: Influence of prenatal noise stress at the 17th–19th day of pregnancy changes contents of DA and 5-HT and its metabolites in brain of 3 weeks old rat fetus. Found changes in concentrations of the mediators can appear due to release of corticosteroids and catecholamines into mother's blood as the result of realization of stress-reaction of an organism. GnL, blocking N-cholinoreactive systems of autonomic ganglions, prevents releasing of adrenal gland mediators into blood; thereby mother stress-reaction develops to the less extent. Key words: prenatal noise stress, rat fetus, dopamine, serotonin, brain, neonatal period.

CHOLINERGIC MODULATION OF SEXUAL BEHAVIOR AFTER STRESS: NEUROCHEMICAL CORRELATIONS, EV Stashina, MA Ganzenko, AO Zelener, AD Lisovsky, YaV Kozak, AA Bairamov, PD Shabanov, Institute of Experimental Medicine, St. Petersburg, Russia

INTRODUCTION: According to modern concepts, sexual behavior (SB) control substantially is supported with neuronal mechanisms and is under the control of neuroendocrinal and neurotransmitter systems. Pharmacological modification of activity of the cholinergic and monoaminergic neurotransmitter systems results in change of structure man's SB. The aim of this study was the assessment of cholinergic transmitter system role in neurochemical mechanisms of SB damage after emotional stress. METHOD: Emotional stress was produced with immobilization under bright lighting during 6 h. Two groups of Wistar male rats with the acquired sexual experience were used. The first group was injected with galanthamine (GAL) (1,0 mg/kg, i.p.) 30 mines before the stress. SB parameters were recorded visually within 15 min before and 1 h after the stress. The number of mounts (NM), intromissions (NI), ejaculations (NE), their latency (ML, IL, EL), restoration period (RP) and interejaculatory interval (IEI)) were measured. In repeated test animals of both group after stress and intact rats group were decapitated, brains were taken and immediately frozen in liquid nitrogen for neurochemical research. Determination of concentrations of NE, DA, 5-HT and their metabolites in supernatants of the brain structures (amygdale (Am), hippocampus (Hp), hypothalamus (Ht), nuc. caudatus (NC)) were measured with HPLC using

electrochemical detection. The installation consisted of Beckman System Gold 125 pump and LC-4C amperometric detector. The quantity of the substances was calculated as ng per mg of tissue wet weight. RESULTS: Behavioral tests: 6 h stress inhibited sexual activity: considerable decrease of NM, NI and NE parameters, significantly increased SB temporal components. GAL pretreatment before stress resulted in change of SB parameters in opposite direction - NM, NI, NE were increased (at 43,3%, 67,5%, 39,6% accordingly, $p<0,01$). Temporal parameters and motivational components were reduced- RP (25%, $p<0,05$) and IEI (34,1%, $p<0,01$). Immobilized stress produced sharp unbalance in mediator contents - NE, DA, 5-HT and their metabolites in the limbic system structure in comparison with intact group. Considerable decrease of DA level in Hp (20 times) and in Am (71,9 %, $p<0,01$) was found. The contents of DA metabolites in Hp was also significantly low. NE contents in Hp enlarged 5 times, and in Am was reduced on 71,4%. Similar changes were observed also in the 5-HT level. In Ht at stressed group significant change was only found in NE contents. In contrast to other mediators, the serotonin turnover, mostly in the limbic system, was considerably enlarged. In NC DA was significantly reduced, 5-HT and NE were increased (45,5% and 47,1%, $p<0,05$). GAL pretreatment before stress considerably changed neurotransmitters balance, approaching their status to control values in intact group. The most considerable changes were noted in the DA contents in Hp - increase up to control values. GAL pretreatment did not change the 5-HT level in Hp, but significantly lowered its metabolism index. Rising of DA level (33,5%, $p<0,01$) in Ht was found, though significant changes in DA contents in control group were not observed. The neurotransmitters contents and their metabolites in NC in GAL pretreatment group were close to values of the intact group. CONCLUSION: Thus, GAL pretreatment exerts modulating effect on the neurotransmitters contents in the brain structures, providing neuronal basis of SB, and prevents damaging action of stress upon SB. In our opinion, modulatory effect of GAL on SB, beside direct cholinergic regulation, is mediated also by augmentation of dopaminergic neurotransmitter activity in limbic system and in Ht. Key words: sexual behavior, immobilization stress, galanthamine.

GINSENOSIDES INFLUENCE THE EXPRESSION OF INNATE IMMUNITY GENES IN THE NUCLEUS ACCUMBENS OF BRAIN OF RATS AFTER PROLONGED ALCOHOL INTOXICATION, MI Airapetov, SO Eresko, ER Bychkov, AA Lebedev, PD Shabanov, St. Petersburg State Pediatric Medical University, St. Petersburg State University, St. Petersburg State Chemical and Pharmaceutical University, Institute for Experimental Medicine, Kirov Military Medical Academy, St. Petersburg, Russia

INTRODUCTION: The anti-inflammatory effect of ginsenosides contained in the extract of plants of the genus Ginseng (Panax) has been known for a long time, but the exact mechanisms of their action remain unclear. Long-term ethanol consumption is characterized by the development of neuroinflammation, and the use of ginsenosides reduces the level of neuroinflammation in various models of pathological conditions of the brain in animals. It seems interesting to evaluate the relative content of mRNA of key genes involved in the mechanisms of neuroinflammation in the nucleus accumbens (NAc) of the brain of long-term alcoholized rats after intraperitoneal injections of the amount of ginsenosides isolated from Panax Japonicus extract. MATERIALS AND METHODS: Alcoholization of rats (n=16) with 20% ethanol solution for 2 months. After the abolition of ethanol within 7 days were performed injections of the amount of ginsenosides intraperitoneally (50 mg / kg, n = 8). Control group of rats (n=10) received water. The rats were decapitated, NAc was removed. RNA was isolated using TRIzol (Evrogen, Russia). RT was performed using M-MuLV reverse transcriptase (Evrogen, Russia). Real-time PCR (Mx3005P, Stratagene, USA) was carried out in a mixture containing SYBR Green Mix (Evrogen, Russia) and primers (Beagle, Russia). The data obtained are normalized to the mRNA content of the Gapdh gene. RESULTS: In the group of long-term alcoholization of rats, the level of mRNA of Tlr3 and Trif decreased, but the level of mRNA of Tlr4, Myd88, Ccl2, Tlr4, Infg, on the contrary, increased. The mRNA level of Tlr7, NF-κB, Irf3 remained without significant changes throughout the experiment. Injections of the sum of ginsenosides (50 mg/kg) led to an increase in the level of Tlr3 mRNA by 3 times and to a decrease in the level of Myd88 mRNA by a factor of 1,6 in comparison with the group of long-term alcoholization of rats, which received injections of saline as a control. CONCLUSIONS: The data obtained indicate the ability of ginsenosides to exert a corrective effect on the pathophysiological mechanisms observed in the NAc of the rat brain under conditions of prolonged alcoholism. Key words: alcoholization, mRNA, nucleus accumbens.

EFFECT OF OREXIGENIC PEPTIDES ON OVEREATING AND EMOTIONAL RESPONSES INDUCED BY SOCIAL ISOLATION IN RATS, ME Abrosimov, EA Vetlugin, AR Moskalev, AG Pshenichnaya, NR Evdokimova, VA Lebedev, ER Bychkov, AA Lebedev, SS Pyurveev, PD Shabanov, Anichkov Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia

INTRODUCTION: Chronic stress of social isolation is associated with an increased risk of mental illness, such as atypical depression, and is usually accompanied by hyperphagia and weight gain. Social isolation is known to induce changes in neurotransmitter systems. In animals after social isolation, an increase in serotonin and neuropeptide Y levels, a decrease in dopamine, norepinephrine,

neurosteroids, alpha-melanocyte-stimulating hormone, and cocaine and amphetamine-regulated peptide have been shown. However, the exact neural mechanisms that underlie hyperphagia and weight gain caused by social isolation have not yet been elucidated. We have previously shown that the antagonist of orexigenic peptides orexinreduces the conditioned place preference of ethanol. The involvement orexigenicpeptides in non-chemical forms of addiction is assumed. The aim of this work was to analyze the effects of antagonists of orexigenic peptides using antagonist of neuropeptide Y Y1RBMS 193885 on emotional responses and elements of bindge eating in rats caused by rearing in social isolation.
METHODS: The animals were kept with free access to water and food under inverted light conditions (8.00–20.00) at a temperature of 22 ± 2 ° C. The litters of rat pups were removed from their mothers on the 21st day of life. The males were randomly divided into two experimental groups. Rats of one group (n = 37) were placed in individual plastic cages 40 × 30 × 25 cm (social isolation). The rats of the second, control group (n = 42) were kept 6–8 per cage (53 × 32 × 19 cm).We used the tests “open field”, “elevated plus maze”, Porsolt's forced swimming test, “resident intruder” test and method of conditioned eating test in well-fed rats.
RESULTS: The level of depression, negative emotionality and locomotor activity increased in rats reared in isolation. After intranasal administration of BMS 193885 high locomotor activity was maintained, but investigating activity increased in isolated rats. Isolated animals showed an increase in body weight at the 6th week of life. By to the 9th week, the body weight of the isolated rats was significantly higher than in animals reared in the community ($p \leq 0.05$). Intranasal administration of 20 μg BMS193885 for 1 week caused a decrease in feed intake in both groups of animals ($p \leq 0.05$). Isolated rats began to consume the same amount of food as animals reared in the community after administration of 0.9% NaCl solution. At the same time, elements of bindge eating were observed in the study of the conditioned food test in satiated isolated rats, which did not appear after 1 week of intranasal administration of 20 μg of BMS193885. CONCLUSIONS: The data obtained prove that rats reared in isolation can be considered as a potential model for binge eating, the basis for metabolic imbalance caused by individual housing in rodents. These considerations are of particular relevance when evaluating the effectiveness of drugs, diet, or other interventions for metabolic health and depressive disorders. Key words: neuropeptide Y, BMS 193885, orexigenic peptides, emotional behavior, social isolation, overeating.

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