St. Petersburg, Vasilievsky island

Solo Sokos Hotel Vasilievsky
11-13, 8th Liniya, Vasilievsky island

Grad Petrov restaurant
5 Universitetskaya emb.

Scan for more info or visit:
www.stresseducation.org

Summer School on Stress

Pavlov Institute of Physiology of the Russian Academy of Sciences
University of California-Irvine, School of Medicine, USA

June 25-28, 2019
St.Petersburg, Russia

PROGRAM & ABSTRACTS

Pavlov Institute of Physiology of the Russian Academy of Sciences

School of Medicine
University of California • Irvine
Discover • Teach • Heal

25 YEARS RFBR

Pavlov Institute of Physiology
of the Russian Academy
of Sciences

SCHOOL OF MEDICINE
UNIVERSITY of CALIFORNIA · IRVINE
Discover · Teach · Heal

25 YEARS RFBR

Acknowledgements

The conference organizers sincerely appreciate
the financial support & the inkind contributions from the following
organizations & foundations:

Contributor
Russian Foundation for Basic Research (grant №19-015-20047)

Sponsors
Merck & Co., Inc.
Vivariy Group of companies
Stelmas (“Vody Zdoroviya” Llc)
Russkiy Kholod OJSC, Tri Pingvina Llc

MERCK

Русский Холодъ

ВОДЫ ЗДОРОВЬЯ

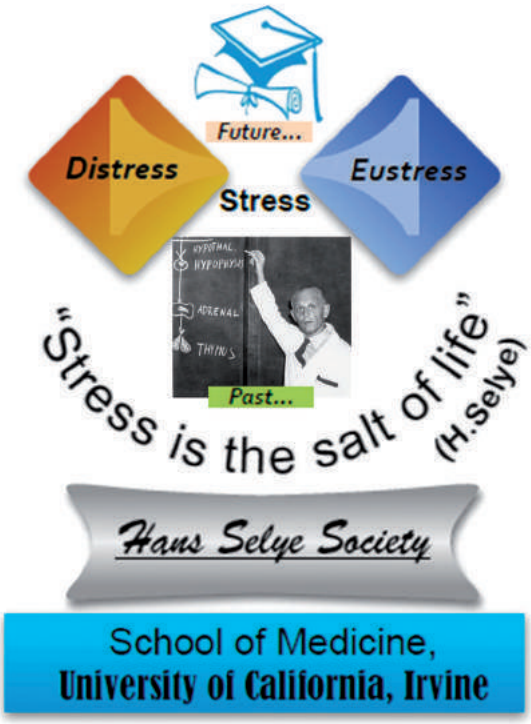
Summer School on Stress

From Hans Selye's original concept to recent advances

An interactive educational experience

June 25-28, 2019

St. Petersburg, Russia



Program

Organized by: Selye International Institute for Advanced Studies & IUPHAR GI Section

Original program accredited by: University of California-Irvine, School of Medicine

Venue:
Pavlov Institute of Physiology of the Russian Academy of Sciences,
6 Makarova emb., St.Petersburg, Russia

OBJECTIVES AND GOALS

The objective of this international conference is to better understand the concept of biologic stress, its manifestations, mechanisms & its pharmacologic ramifications (e.g., the anti-inflammatory & immune-modulating actions of glucocorticoids & the possibility of drug-interventions in severe distress), as well as to learn new avoidance, management & coping strategies. Since the "morphologic triad" of stress, in addition to the adrenal glands, involves mostly the immune system & the gastrointestinal (GI) tract, the focus of this conference is mostly related to these organ systems. The goals are to review these concepts based on the original discoveries & interpretations of stress by Hans Selye who first described biologic stress as a "nonspecific adaptive response" in 1936. Although initially ignored & criticized, but by 1940s & 1950s Selye's initial findings in experimental animals were widely reproduced worldwide both in animal models & humans.

Furthermore, in the subsequent decades the stress concept became so popular that the word "stress" has been often misused & inappropriately implied that even Selye complained that at the end of his life (he died in Montreal in 1982) that "stress became too popular. Thus, our ultimate goal is to correct some of these misconceptions that we could use the original concepts of Selye appropriately, updated by modern molecular mechanistic findings, but devoid of the almost non-critical use of the word & implications of biologic stress.

FORMAT

The format of this conference is a lively forum where experts present & integrate historic & new findings on the meaning, mechanisms, manifestations & consequences of biologic stress, i.e., both distress & eustress.

In addition to round table discussions, the major presentations are complemented by short oral presentations selected from submitted abstracts. A poster session is also organized.

COURSE DIRECTORS

Professors Arpad Somogyi, Sandor Szabo & Yvette Tache
(All former PhD students of Hans Selye, the 'father of biologic stress'. Therefore, the conference should be authentic, free of frequent distortions & over-implications of stress.)

Core Faculty Members

Professors Bruno Bonaz, Ludmila Filaretova, Martina Rojnić Kuzman, Jackie D. Wood,
Arpad Somogyi, Sandor Szabo, Yvette Taché

LOCAL ORGANIZING COMMITTEE

Chair: Prof. Ludmila Filaretova
Secretary: Ekaterina Saveleva
Members: Dr. Elena Rybnikova, Dr. Natalia Yarushkina, Dr. Elena Yakimova, Yury Punin

MAIN TOPICS

The origins of stress concept & the seminal discoveries of Hans Selye
What is stress, what is not
Stress: distress vs. eustress & transtress – similarities in the adrenal glands, big difference in the brain
The neuroendocrine mechanisms of stress; physiologic & pharmacologic actions of glucocorticoids
Effect of stress on immune response & its role in the mechanisms of various diseases
Stress & structural GI diseases, e.g., gastro-duodenal ulcers, IBD (inflammatory bowel diseases)
Stress & functional GI disorders, e.g., motility disorders, IBS (irritable bowel syndrome)
PTSD & organ systems involved in biologic stress
Management strategies for stress: Pharmacologic interventions and/or life style changes
My good & bad experience with stress: Challenges & lessons learned (Short, oral or poster presentations by attendees)
Stress in our daily lives – from distress to eustress: Open forum with participation of all registered attendees

VENUE

After six years of annual conferences in Europe & Japan, the 7th Summer School on Stress is held in St. Petersburg, the former & still beautiful capital of Russia, the site of many museums & historic buildings, including the world-famous Hermitage museum & art gallery. The course directors thank Prof. Ludmila Filaretova, Director of Pavlov Institute of Physiology for hosting this renown and focused international conference on stress and stress-related diseases. The conference is held at the famous Pavlov Institute of Physiology, in very center of St. Petersburg, not far from Hermitage.

The year 2019 is Ivan P. Pavlov`s 170th birthday anniversary

Pavlov Institute of Physiology of the Russian Academy of Sciences was founded in 1925. The first Director of the Institute of Physiology until 1936 was the first Nobel Prize winner in theoretical medicine Academician Ivan P. Pavlov.

The present Director of Pavlov Institute of Physiology is Corresponding Member of RAS Ludmila P. Filaretova.

Pavlov Institute is one of the largest physiological institutions of the country. By continuing traditional studies initiated by Ivan P. Pavlov and taking into account advances in modern physiology, the Institute goes on with development of fundamental and applied studies on mechanisms of the higher nervous activity, function of the sensory and visceral systems, understanding of processes of their regulation and adaptation. The Institute traditionally carries out extensive international cooperation.

The Institute is partly located in St. Petersburg, but its major part is a research campus founded by Ivan Pavlov and located in a village of Koltushi. Pavlovian Koltushi is the first scientific city of Russia and a UNESCO world heritage site.

Contacts:
6 Makarova emb., St.Petersburg
tel. +7 (812) 328-07-01
e-mail: Pavlov.institute@infran.ru

CREDIT DESIGNATION

The University of California, Irvine School of Medicine will provide certificates to those participants who attend all sessions.

DISCLOSURE INFORMATION

UCI OCME requires that the content of CME activities and related materials provide balance, independence, objectivity, and scientific rigor. Planning must be free of the influence or control of a commercial entity, and promote improvements or quality in healthcare. It is the policy of the UCI Office of Continuing Medical Education to insure balance, independence, objectivity, and scientific rigor in all its educational activities. All faculties participating in UCI sponsored CME programs are expected to disclose to the activity participants any real or apparent conflict(s) of interest that may have a direct bearing on the subject matter of the continuing medical education activity. This pertains to relationships with pharmaceutical companies, biomedical device manufacturers, or other corporations whose products or services are related to the activity content. The intent of this policy is identifying potential conflicts of interest so participants can form their own judgments with full disclosure of the facts. It remains for the participants to determine whether the speaker's outside interests reflect a possible bias in either the exposition or the conclusions presented.

PROGRAM

Scientific & social program overview

Monday, June 24	Tuesday, June 25	Wednesday, June 26
Core faculty meeting **18:00 – 19:00**	***Pavlov Apartment Museum*** ***11:00 – 12:00, 12:00 – 13:00,*** ***13:00 – 14:00*** *Registration & daily sign-in:* *13:00 – 15:00* **Opening & Main lectures:** **15:00 – 17:30** ***Group photo: 17:30*** ***Welcome dinner & City bus tour:*** ***18:30 – 21:30***	*Registration & daily sign-in:* *08:30 – 09:00* **Main lectures & discussions:** **09:00 – 17:30** *Lunch: 14:00 – 15:00* **Free communications:** **17:30 – 18:30**
Thursday, June 27	**Friday, June 28**	**Weekend**
Registration & daily sign-in: *08:30 – 09:00* **Main lectures & discussions:** **09:00 – 12:30** **Poster session: 12:30 – 14:00** *Lunch: 14:00 – 15:00* **Free communications** **15:00 – 17:30** **Merck Seminar 17:30–18:10** ***Farewell party & Boat tour*** ***18:30–21:30***	*Registration & daily sign-in:* *08:30 – 09:00* **Main lectures & discussions:** **09:00 – 10:00** **Take-home messages:** **10:00 – 11:30** *Farewell Tea: 11.30 – 12:00* ***Koltushi Tour: Pavlov Scientific City & Museum of Ivan Pavlov*** ***13.00 –19.00***	*Free*

Tuesday, June 25, 2019

Opening & Main lectures

Chairs: **Sandor Szabo & Ludmila Filaretova**

13:00 – 15:00	**Registration**
15.00 –15:10	Welcome & greetings *Pavlov Institute of Physiology, Local Organizing Committee, Ludmila Filaretova, St. Petersburg*
15:10 –15:30	Introduction *Arpad Somogyi, Brussels/Berlin; Sandor Szabo, Irvine/Los Angeles; Yvette Taché, Los Angeles*
15:30 –16:00	Stress is more than 80-year-old: From distress to eustress *Sandor Szabo, Irvine/Los Angeles*
16:00 –16:30	The Hans Selye, the grandmaster of creativity and originality *Arpad Somogyi, Brussels/Berlin*
16:30 –17:00	The neuroendocrine mechanisms of stress *Yvette Tache, Los Angeles; Bruno Bonaz, Grenoble*
17:00 –17:30	Endogenous adaptation of the heart to ischemic stress: Importance in cardioprotective drug development *Péter Ferdinandy, Budapest*
17:30 –17:40	**Group photo**
18:30 – 21:30	**Welcome dinner & City bus tour**

Wednesday, June 26, 2019

Morning session

Chairs: **Jackie D. Wood & Klara Gyires**

09:00 - 09:30	The brain-In-The-Gut *Jackie D. Wood, Columbus, Ohio*
09:30 –10:00	Stress & functional GI disorders: Motility disorders, IBS (irritable bowel syndrome) *Bruno Bonaz, Grenoble; Yvette Tache, Los Angeles*
10:00 – 10:30	Stress & structural GI diseases: Gastro-duodenal ulcers, IBD (inflammatory bowel diseases) *Sandor Szabo, Irvine/Los Angeles; Jack Wood, Columbus, Ohio*
10:30 – 11:00	Endogenous modulators of stress-induced gastric ulcers *Ludmila Filaretova, St. Petersburg*
11:00 – 11:15	*Coffee break*
11:15 – 11:45	Influence of adrenalectomy on protective effects of urocortin I, a CRF-related peptide, against indomethacin-induced enteropathy in rats *Koji Takeuchi, Kyoto*
11:45 – 12:15	Stress, neuropeptides, brain-gut & gut-brain axis *Klara Gyires, Budapest*
12:15 – 12:45	Stress and gut microbiota: impact on liver health and disease *Gyorgy Baffy, Boston*
12:15 –13:00	General discussion: Comments, questions, answers
13:00 – 13:20	*Sponsor presentation (Merck)*: More publication-quality data with less stress: New solutions for sensitive protein detection *Stanislav Kukla, Merck, Prague*
14:00 – 15:00	***Lunch***

Afternoon session

Chairs: **Daniela Ježová & Martina Rojnić Kuzman**

15:00 – 15:30 Evaluation of stress in real-life situations
Daniela Ježová, Bratislava

15:30–16:00 Management strategies for stress
Martina Rojnić Kuzman, Zagreb

16:00 –16:30 Vision and stress
Yury Shelepin, St. Petersburg

16:30 – 17:00 Modern experimental insight and stress paradigm
Konstantin Shelepin, St. Petersburg

17:00 – 17:15 General discussion: Comments, questions, answers

17:15 – 17:30 *Coffee break*

17:30 – 18:30 Free oral communications
Chairs: **Arpad Somogyi & Zsuzsanna Helyes**

Thursday, June 27, 2019

Morning sessions

Chairs: **Koji Takeuchi & Bruno Bonaz**

09:00 – 09:30 Vagus nerve stimulation: A non-drug therapy in IBD
Bruno Bonaz, Grenoble

09:30 –10:00 Spinal cord stimulation as a tool of emotional stress regulation in spinal cord injury patients
Yury Gerasimenko, St. Petersburg

10:00 – 10:30 Chronic stress and pain: interactions and common mechanisms
Zsuzsanna Helyes, Pecs

10:30 –11:00 Stress and molecular mechanisms of nociception: role of NaV1.8 channels
Boris Krylov, St. Petersburg

11:00 –11:15 Coffee break

Special free oral communications

Chairs: **Hyeyoung Kim & Boris Krylov**

11:15 –11:30 Effect of antioxidant nutrients and astaxanthin on *Helicobacter pylori*-induced gastric stress
Hyeyoung Kim, Seoul

11:30 –11:45 Supraspinal control of visceral nociception in inflammatory bowel disease: pathological alterations and their pharmacological targeting
Olga Lyubashina, St. Petersburg

11:45 – 12:00 Stress-induced analgesia: involvement of the HPA axis hormones
Natalia Yarushkina, St. Petersburg

12:00 – 12:15 Influence of perinatal stress on development of adaptive behavior and prenatal effects of antidepressants
Irina Butkevich, St. Petersburg

12:15 – 12:30 General discussion: Comments, questions, answers

12:30 –14:00 **Poster session**
Chairs: **Sandor Szabo & Ludmila Filaretova**

14:00 – 15:00 Lunch

15:00 – 17:30	**Free oral communications** *Chairs*: **Arpad Somogyi & Zsuzsanna Helyes**
17:30 –18:10	**Merck seminar: "Rethink protein detection"** *Chairs:* **Stanislav Kukla**
18:30 – 21:30	**Farewell party & Boat tour**

Friday, June 28, 2019

Morning session

Chairs: ***Arpad Somogyi & Sandor Szabo***

09:00 –09:30 Hypoxia and psycho-emotional stress: Mechanisms of cross-tolerance
Elena Rybnikova, St. Petersburg

Special free oral communications

09:30 –09:45 Different susceptibility to learned helplessness in animals with opposite coping styles: putative role of progesterone
Dmitriy Zhukov, St. Petersburg

09:45 –10:00 The role of melanocortin peptides in the regulation of the stress response
Irina Romanova, St. Petersburg

10:00 –11:00 **Putting it all together: Transformation of distress into eustress. Take-home messages**
Open forum with participation of all registered attendees

11:00 –11:30 Final group discussion, feedback & course evaluation

11:30 – 12:00 *Farewell tea*

13:00 – 19:00 ***Koltushi Tour: Pavlov Scientific City & Museum of Ivan Pavlov***

SPECIAL FREE COMMUNICATIONS

INFLUENCE OF PERINATAL STRESS ON DEVELOPMENT OF ADAPTIVE BEHAVIOR AND PRENATAL EFFECTS OF ANTIDEPRESSANTS

I. Butkevich[1,2], V. Mikhailenko[1], E. Vershinina[1]
[1]I. P. Pavlov Institute of Physiology, Russian Academy of Sciences, Saint Petersburg, Russia [2]Department of Normal Physiology, Saint Petersburg State Pediatric Medical University, Russia

EFFECTS OF ANTIOXIDANT NUTRIENTS AND ASTAXANTHIN ON *HELICOBACTER PYLORI*–INDUCED GASTRIC STRESS

E. Byun, B. Park, H. Lee, S.H. Kim, J.W. Lim, H. Kim
Department of Food and Nutrition, Brain Korea 21 PLUS Project, Research Center for Food, Nutrition & Foodservice Management, College of Human Ecology, Yonsei University, Seoul 03722, Republic of Korea

SUPRASPINAL CONTROL OF VISCERAL NOCICEPTION IN INFLAMMATORY BOWEL DISEASE: PATHOLOGICAL ALTERATIONS AND THEIR PHARMACOLOGICAL TARGETING

O. Lyubashina [1,2], I. Sivachenko [1], I. Busygina [1], S. Panteleev [1,2]
[1] Pavlov Institute of Physiology of the Russian Academy of Sciences, Saint Petersburg, Russia; [2] Valdman Institute of Pharmacology, Pavlov First St. Petersburg State Medical University, Saint Petersburg, Russia

THE ROLE OF MELANOCORTIN PEPTIDES IN THE REGULATION OF THE STRESS RESPONSE

I. Romanova, A. Mikhrina, E. Mikhailova
Sechenov Institute of Evolutionary Physiology and Biochemistry Russian Academy of Scienses, Saint-Petersburg, Russia

STRESS-INDUCED ANALGESIA: INVOLVEMENT OF THE HPA AXIS HORMONES

N.I. Yarushkina
Pavlov Institute of Physiology, Russian Academy of Sciences, St. Petersburg, Russia

DIFFERENT SUSCEPTIBILITY TO LEARNED HELPLESSNESS IN ANIMALS WITH OPPOSITE COPING STYLES: PUTATIVE ROLE OF PROGESTERONE

D.A. Zhukov[1], E.P. Vinogradova[2]
[1] Pavlov Institute of Physiology of the RAS, St-Petersburg, Russia; [2] Biological Faculty, St-Petersburg State University, St-Petersburg, Russia

FREE COMMUNICATIONS

POLYDIPSIA AS A COPING STRATEGY TO SCHEDULE-INDUCED STRESS: HT AND LT SELECTED RAT STRAINS

N. Bortnikov[1], I. Sukhanov[1], M. Semina[1], A.Vaido[2], N. Dyuzhikova[2], I. Belozertseva[1]
[1] Pavlov First Saint Petersburg State Medical University, Valdman Institute of Pharmacology, St. Petersburg, Russia; [2]Pavlov Institute of Physiology of the Russian Academy of Science, St.Petersburg, Russia

STRESS IN ANIMALS: AN ECOLOGICAL VIEW

D. Csabai[1], B. Czeh[1,2]
[1]Neurobiology of Stress Research Group, Szentágothai János Research Centre, University of Pécs, Pécs, Hungary; [2]Instute of Laboratory Medicine, Medical School, University of Pécs, Pécs, Hungary

PROTECTIVE ROLE OF THE SOMATOSTATIN RECEPTOR SUBTYPE 4 IN THE INDOMETHACIN-INDUCED GASTROINTESTINAL MUCOSAL INJURY MODEL

K. Csekő[1,2], V. Kormos[1,2], Á. Horváth[1,2], M. Sudalina[3], I. Natalia[3], D. Zelena[4,5], L. Filaretova[3], Z. Helyes[1,2,6]
[1]Dept. of Pharmacology and Pharmacotherapy, Medical School and Szentágothai Research Centre, University of Pécs, Hungary; [3]Laboratory of Experimental Endocrinology, Pavlov Institute of Physiology, Russian Academy of Sciences, Russia; [4]Dept. of Physiology, University of Pécs, Hungary; [5]Institute of Experimental Medicine, Hungarian Academy of Sciences, Hungary; [6]PharmInVivo Ltd, Pécs, Hungary

PROGNOSTICATION OF ANTISTRESS OPTIONS OF SPELEOCLIMATOTHERAPY

Y.V. Dorokhov, N.P. Gorbatenko, A.V. Karpova
Voronezh N.N. Burdenko State Medical University, Voronezh, Russia

PLANTSUNDER PRESSURE: DO NOT STEP ON THE GRASS!

P. Keringer, A. Garami
Institute for Translational Medicine, Medical School, University of Pecs, Pecs, Hungary

GENERAL ADAPTATION SYNDROME THEORY BY H. SELYE: AGEING PROCESS AND POSSIBILITIES FOR ITS INHIBITION

V. Khavinson
Saint-Petersburg Institute of Bioregulation and Gerontology, St. Petersburg, Russia

ASTAXANTHIN INHIBITS *HELICOBATER PYLORI*-INDUCED EXPRESSION OF INFLAMMATORY MEDIATOR INGASTRIC EPITHELIAL CELLS

S.H. Kim, J.W. Lim, H. Kim
Department of Food and Nutrition, Brain Korea 21 PLUS Project, Research Center for Food, Nutrition & Foodservice Management, College of Human Ecology, Yonsei University, Seoul 03722, Republic of Korea

ANTIOXIDATIVE STRESS IN NORMAL CELLS: GENERAL CONCEPT OR NON-SPECIFIC DRUG ACTION?

Ju. Kornienko, I. Smirnova, N. Pugovkina, Ju. Ivanova, A. Shatrova, N. Aksenov, V. Zenin, N. Nikolsky, O. Lyublinskaya
Institute of Cytology, Russian Academy of Sciences; St.Petersburg, Russia

WATER IMMERSION SHORT-TERM STRESS IN TWO RAT STRAINS DIFFERING IN THE NERVOUS SYSTEM EXCITABILITY THRESHOLD

A.S. Levina[1], N.A. Bondarenko[2], N.V. Shiryaeva[1], A.I.Vaido[1], N.A. Dyuzhikova[1]
[1]I.P.Pavlov Institute of physiology RAS, Saint-Petersburg, Russia; [2]RPC OpenScience Ltd, Moscow, Russia

THE EFFECT OF CHRONIC RESTRAINT STRESS ON GLUCOSE ABSORPTION IN THE RAT SMALL INTESTINE

E. V. Savochkina[1], N. M. Grefner[2], A. A. Gruzdkov[1], A. S. Alekseeva[1], Yu. V. Dmitrieva[1], L. V. Gromova[1]
[1]Pavlov Institute of Physiology, RAS; [2] Institute of Cytology, RAS, St. Petersburg, Russia

DYNAMICS OF PHYSIOLOGICAL COMPONENTS OF THE MENTAL STATUS UNDER EXPOSURE STRESS FACTORS IN MEN OF AGE 20–30 WITH DIFFERENT LEVELS OF PHYSICAL TRAINING

I. B. Sivachenko[1,2]
[1]Pavlov Institute of Physiology, Russian Academy of Sciences, St. Petersburg, Russia; [2]Research Institute of Hygiene, Occupational Pathology and Human Ecology, Federal Medical Biological Agency of Russia, St. Petersburg, Russia

ANALYSIS OF EXPRESSION OF PROINFLAMMATORY CYTOKINES IN REGIONS OF RAT HIPPOCAMPUS IN EARLY PERIOD AFTER TRAUMATIC BRAIN INJURY

L.V. Tretyakova, M.N. Volobueva, I.G. Komoltsev, A.A. Kvichansky, A.P. Bolshakov, N.V. Gulyaeva
Institute of Higher Nervous Activity and Neurophysiology of RAS, Moscow, Russia

STRESS AT CELLULAR AND TISSUE LEVEL

V. Vincze, B.Czeh
University of Pécs Medical School, Dept. of Laboratory Medicine, Pécs, Hungary

MOLECULAR FACTORS OF INNATE IMMUNITY IN STRESS REGULATION

I. Yankelevich[1,2], M. Shustov[1], G. Aleshina[2], V. Kokryakov[2]
[1]Saint-Petersburg State Chemical and Pharmaceutical University, Saint-Petersburg, Russia; [2]Federal State Budgetary Research Institution "Institute of Experimental Medicine", St. Petersburg, Russia

STRESS- AND GASTROPROTECTIVE EFFECTS OF HYPOXIC PRE- AND POSTCONDITIONING IN THE RAT ULCEROGENIC COLD-RESTRAINT STRESS MODEL

M.Y. Zenko, O.P. Komkova
Pavlov Institute of Physiology, Russian Academy of Sciences, St. Petersburg, Russia

POSTER PRESENTATIONS

EXPRESSION OF GROWTH FACTORS IN RAT BRAIN FOLLOWING THE DELTA OPIOID RECEPTOR BLOCKADE BY NALTRINDOLE AND EXPOSURE TO HYPOKINESIS

P. Chomanic[1,2], L. Balagova[1], J. Graban[1], D. Jezova[1]

[1]Laboratory of Pharmacological Neuroendocrinology, Institute of Experimental Endocrinology, Biomedical Research Center, Slovak Academy of Sciences; [2]Department of Pharmacology and Toxicology, Faculty of Pharmacy, Comenius University in Bratislava, Slovakia

FACIAL EXPRESSION DURING SOCIALLY EVALUATED COLD PRESSOR TEST IN RELATION TO STRESS PERCEPTION IN HEALTHY MEN

Z. Chuda[1,2], K. Buzgoova[1,2], L. Balagova[1], I. Riecansky[3], D. Jezova[1]

[1]Laboratory of Pharmacological Neuroendocrinology, Institute of Experimental Endocrinology, Biomedical Research Center, Slovak Academy of Sciences; [2]Department of Pharmacology and Toxicology, Faculty of Pharmacy, Comenius University; [3]Department of Behavioral Neuroscience, Institute of Normal and Pathological Physiology, Centre of Experimental Medicine, Slovak Academy of Sciences, Bratislava, Slovakia

CREATION OF THE VIRAL VECTORS FOR THE INHIBITION OF THE SEROTONERGIC NEURONS USING LIGHT SENSITIVE PROTON PUMP

U.S. Drozd, D.A. Lanshakov

Institute of Cytology and Genetics SB RAS, Novosibirsk, Russia

DANIO RERIO AS A NOVEL BEHAVIORAL MODEL FOR ANXIOLYTIC AND ANTIDEPRESSANT DRUGS SCREENING

V.R. Gedzun, E.V. Razumkina, I.S. Sukhanova, A.V. Malyshev, I.I. Doronin, M.L. Lovat, A.R. Kuchumov, G.A. Babkin

Lactocore LLC, Moscow, Russia

STRESS RESPONSE-RELATED MOLECULAR MECHANISMS OF POST-STROKE DEPRESSION AND DEMENTIA

M.Y.Kasatkina[1,2], P.I.Belov[3,4], A.B.Guekht[2], N.V.Gulyaeva[1,2]

[1]Institute of Higher Nervous Activity and Neurophysiology RAS, Moscow, Russia, [2]Moscow Research and Clinical Center for Neuropsychiatry, Moscow, Russia, [3]Moscow City Clinical Hospital after V.M. Buyanova, Moscow, Russia, [4]Pirogov Russian National Research Medical University, Moscow, Russia

CONTRIBUTION OF GLUCOCORTICOIDS TO GASTROPROTECTIVE EFFECT OF REMOTE ISCHEMIC PRECONDITIONING

O.P. Komkova, M.N. Sudalina, L.P. Filaretova

Laboratory of Experimental Endocrinology, Pavlov Institute of Physiology, Russian Academy of Sciences, St. Petersburg, Russia

INDOMETHACIN-INDUCED SMALL INTESTINAL DAMAGE AND BILE ACID ALTERATIONS IN THE RAT

B. Lázár[1], S. B. László[1], B. Hutka[1], Á. Kemény[2], Z. Helyes[2], K. Gyires[1], Z. S. Zádori[1]

[1]Department of Pharmacology and Pharmacotherapy, Faculty of Medicine, Semmelweis University, Nagyvárad tér 4, 1089, Budapest, [2]Department of Pharmacology and Pharmacotherapy, University of Pécs, Szigeti út 12, 7624, Pécs, Hungary

NOVEL HUMANIZED MODEL FOR PHARMACOLOGICAL RESEARCH: GENERATING HUMAN SOMATOSTATIN RECEPTOR 4 (HSSTR4) EXPRESSING TRANGENIC MICE

B. Nemes[1], K. Bölcskei[1,2], T Aczél [1,2], A. A. Alkurdi[1], Y. Abuawwad[1], A. Dinnyés[3], J. Kobolák[3], Z. Sándor[1], E. Pintér[1,2], Zs. Helyes [1,2]

[1]Department of Pharmacology and Pharmacotherapy, University of Pécs Medical School, Hungary; [2]Centre for Neuroscience & Szentágothai Research Centre, University of Pécs, Hungary; [3]BioTalentum Ltd, Gödöllő, Hungary

ASSOCIATION OF CLOCK GENETIC VARIANTION WITH STRESS RESPONSE IN SCHOOLCHILDREN

D. Petrashova, S. Kolomeichuk, R. Mikhaylov

Kola Science Centre, Russian Academy of Science, Apatity, Murmansk region, Russia

THE RISK FACTORS OF THE OF FORMATION OF ACUTE LESIONS OF THE GASTROINTESTINAL TRACT IN HUMAN.

D. Sakhno[1], A. Efimov [2], B. Sigua[2], E. Zakharov [2], A. Grinev[2]

[1]The Yaroslav-the-Wise Novgorod State University, Institute of Medical Education, Veliky Novgorod, Russia; [2]North-Western State Medical University named after I. I. Mechnikov, St.Petersburg, Russia

EFFECTS OF KETAMINE AND STRESS ON THE NEUROTROPHIN RECEPTORS EXPRESSION

E.V. Shaburova[1,2], Lanshakov D. A.[1,2]

[1]Institute of Cytology and Genetics SB RAS, Novosibirsk, Russia; [2]Novosibirsk State University, Novosibirsk, Russia

CRITERIA OF STRESS AND ADAPTATION ACCORDING TO THE DATA FROM ELECTROENCEPHALOGRAPHY AND SUPER SLOW BRAIN ACTIVITY

M.A. Skedina, A.A. Kovaleva

Institute of Biomedical Problems of the Russian Academy of Sciences, Moscow, Russia

THE EFFECTS OF SHORT-TERM AND LONG-TERM ACTION OF DEXAMETHASONE ON CRF-1 AND CRF-2 RECEPTORS IN THE GASTROINTESTINAL TRACT

M. Sudalina

Laboratory of Experimental Endocrinology, Pavlov Institute of Physiology, Russian Academy of Sciences, St. Petersburg, Russia

IMPACT OF FORCED SWIM STRESS ON THE RATS' CAPACITY TO SOLVE THE WATER ESCAPE TASK

M. Tur, I. Belozertseva

Pavlov First Saint Petersburg State Medical University, Valdman Institute of Pharmacology, St. Petersburg, Russia

EFFECT OF HIGH FREQUENSY ELECTROMAGNETIC WAVES ON sod1 AND sod2 GENE EXPRESSION IN THE HONEYBEE BRAIN

T. Zachepilo[1,2], A. Pribyshina[2], D. Khlebaeva[1], N. Lopatina[1], N. Dyuzhikova[1]

[1]Pavlov Institute of Physiology of RAS, [2]Herzen State Pedagogical University of Russia, Russia

***HSP70* GENE EXPRESSION IN THE HONEYBEE BRAIN UNDER THE ACTION OF HIGH FREQUENCY ELECTROMAGNETIC RADIATION**

T. Zachepilo[1,2], A. Pribyshina[2], N. Lopatina[1], N. Dyuzhikova[1]

[1]Pavlov Institute of Physiology of RAS, [2]Herzen State Pedagogical University of Russia, Russia

Lecture outlines

Lecture outlines

Stress and gut microbiota: Impact on liver health and disease

Gyorgy Baffy, MD, PhD, Associate Professor, Department of Medicine, VA Boston Healthcare System and Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

gbaffy@gmail.com

Rationale:
This talk links three seemingly disparate spaces of medical knowledge: (i) non-alcoholic fatty liver disease (NAFLD), (ii) stress and physiological adaptation, and (iii) gut microbiota. Closely linked to obesity and diabetes, NAFLD has become the most common liver disorder. NAFLD is a complex disease with heterogeneous clinical outcomes determined by a combination of genetic and environmental factors. Currently, risk stratification for adverse outcomes (e.g., cirrhosis and liver cancer) gives insufficient guidance for preventing and monitoring progression in NAFLD. Selye's original concept of stress and subsequent formulations of the general adaptation syndrome allow us to view dysfunctional stages of NAFLD as successive adaptation strategies, which we recently revisited from a complex network perspective ('restore', 'explore', 'abandon'). Notably, the success of responding to various perturbations depends on inherited and acquired abilities of living organisms. In this sense, the fact that we host complex microbial communities (the largest of which resides in the gastrointestinal tract) in the form of a super-organism or holobiont has profound implications for the role of stress in NAFLD. Our knowledge about the triangular relationship of the host, gut microbiota and liver disease ('gut-liver axis') is rapidly evolving and includes evidence for the impact of bacterial diversity and metabolites on disease path phenotypes such as leaky gut, impaired mucosal immunity, liver inflammation and sinusoid endothelial dysfunction. Less is known about how stress-related mechanisms apply to this relationship and alter adaptation strategies during the progression of NAFLD. Better identification of inter-kingdom (host-microbial) molecular mechanisms will assist risk prediction and management of NAFLD.

Learning Objectives:
- Describe the natural history of NAFLD and impact on liver-related mortality
- Define 3 stages of physiological adaptation in the multidimensional phase space
- Identify key adaptation strategies (restore, explore, abandon) in NAFLD progression
- Recognize the holobiont as a unit of multicellular hosts and their microbial communities
- Discuss the triangular relationship between host, disease, and microbiota

References
Byrne CD, Targher G. NAFLD: A multisystem disease. *J. Hepatol.*, 2015; 62:S47-64.
Baffy G. Allostasis in nonalcoholic fatty liver disease: Implications for risk assessment. *Dig. Dis. Sci.,* 2013; 58:302-308.
Baffy G, Loscalzo J. Complexity and network dynamics in physiological adaptation: An integrated view. *Physiol. Behav.,* 2014; 131:49-56.
Nicholson JK et al. Host gut microbiota metabolic interactions. *Science,* 2012; 336:1262.
Baffy G. Gut microbiota and tumor of the host: Colliding interests. *Adv. Exp. Med. Biol.,* 2019

Vagus nerve stimulation: A non-drug therapy in inflammatory bowel disease

Bruno Bonaz, MD, PhD, Professor of Gastroenterology, Clinique Universitaire d'Hépato-Gastroentérologie and Grenoble Institute of Neurosciences (GIN), INSERM U1216, CHU Grenoble Alpes and University Grenoble Alpes, Grenoble, France

BBonaz@chu-grenoble.fr

Rationale:
The brain and the digestive tract communicate bidirectionally through the autonomic nervous system composed of the sympathetic and parasympathetic nervous systems. The vagus nerve (VN) is the principal component of the parasympathetic nervous system, containing approximately 80% afferent and 20% efferent fibers. The VN plays multiple key roles in the homeostatic regulation of visceral functions. The VN has an anti-inflammatory role through its afferents activating the hypothalamic-pituitary adrenal axis leading to the release of cortisol by the adrenal glands. More recently, Tracey's group has described the cholinergic anti-inflammatory pathway which is mediated through vagal efferent fibers that synapse onto enteric neurons which release acetylcholine (ACh) at the synaptic junction with macrophages. ACh binds to α-7-nicotinic ACh receptors of those macrophages to inhibit the release of tumor necrosis (TNF)□, a pro-inflammatory cytokine. The same group has described the splenic sympathetic anti-inflammatory pathway where the VN stimulates the splenic sympathetic nerve. Norepinephrine released at the distal end of the splenic nerve links to the β2 adrenergic receptor of splenic lymphocytes that release ACh. Finally, Ach inhibits the release of TNFα by spleen macrophages through α-7-nicotinic ACh receptors. The VN has thus an anti-TNFα effect. We have shown that vagal tone is significantly blunted in inflammatory bowel disease (IBD; Crohn's disease and ulcerative colitis) in relation with negative affect and high TNFα levels. Consequently, low vagal tone has a pro-inflammatory effect and restoring a normal vagal tone would be of interest. VN stimulation (VNS) has been approved in the treatment of drug refractory epilepsy and depression. VNS, either invasive or non-invasive, could be of interest as a non-drug therapy in the management of TNF mediated diseases as represented by IBD. In this context, we have performed a preclinical study in rats showing that VNS is able to improve an experimental model of colitis. In a translational approach, we have performed a pilot study of VNS in patients with active Crohn's disease and shown that VNS is of interest in such patients. These data can be extrapolated to other inflammatory diseases such as rheumatoid arthritis.

Leaning objectives:
- To understand the anti-inflammatory role of the vagus nerve
- To understand how to activate the vagus nerve for an anti-inflammatory effect
- To understand what are the anti-inflammatory implications of vagus nerve stimulation

Stress & functional GI disorders: Motility disorders & IBS (irritable bowel syndrome)

Bruno Bonaz, MD, PhD, Professor of Gastroenterology, Clinique Universitaire d'Hépato-Gastroentérologie, CHU de Grenoble, Grenoble, France

Yvette Taché, PhD, Professor of Medicine, David Geffen School of Medicine, UCLA, USA

ytache@mednet.ucla.edu

Rationale:
The effects of stress on digestive functions have been associated with modifications of visceral sensitivity, local inflammatory response and motility. Convergent evidence indicates that underlying mechanisms of IBS involves dysfunction of the "brain-gut axis. Psychosocial factors and concomitant psychopathologies such as somatization, anxiety and depression are key components in IBS clinical manifestations. Abdominal pain is the main symptom which justifies the patient to refer to a gastroenterologist; altered bowel habits, bloating and discomfort are also associated to pain. Heightened sensitivity to visceral distension, particularly when perceived as noxious, has been described in these patients. Visceral hypersensitivity has underlined the role of visceral (digestive) afferents of the sympathetic and parasympathetic systems, in particular with the role of inflammation/infection, as well as the spinal (spinal hyperexcitability) and supra-spinal treatment of the nociceptive visceral message. More recently, perturbations of descending spinal inhibitory pathways have been evoked in the pathophysiology of IBS. The gastrointestinal sensory motor dysfunction in IBS is consistent with an up-regulation in neural processing between the gut and the brain and functional dysfunction of the sympatho-vagal balance is observed in IBS. There are many arguments for a conceptual model of an increase of the stress response to explain many of the symptoms observed in IBS patients. Major advances have been made in unraveling the biochemical coding of stress with the identification of 41 amino-acids, corticotropin releasing factor (CRF) and other CRF-related peptides urocortins (Ucns) 1, 2, and 3 in the brain and the gut. The CRF receptor 1 (CRF-R1) and CRF-R2 display distinct binding affinity with selectively for) CRF and Ucn 1 (CRF-R1) or Ucns (CRF-R2. The use of selective CRF-R antagonists have enabled to unravel the role of CRF-R1 in the stress-related endocrine (activation of pituitary-adrenal axis), behavioral (anxiety/depression), autonomic nervous system sympathetic system and sacral parasympathetic activation, vagal inhibition), and immune responses. Patients with IBS have been reported to have an increase colonic motor response to CRF consistent with the occurrence of an increased gastrointestinal stress response. Experimental studies using CRF-R1 antagonists also supported the involvement of CRF-R1 in the hypersensitivity to colorectal distension (CRD) and increased in colonic motility induced by intracerebroventricular CRF and in a variety of rodent IBS models namely acute or repeated exposure to water avoidance stress combined with neonatal maternal separation or sets of nociceptive CRD or repeated daily CRD six weeks after the development of colitis, intracolonic infusion of 0.5% acetic acid or a high-anxiety rat strain, the Kyoto. It is actually obvious that stress, i.e. the CRFergic system (either central or peripheral), is a major effector in the pathophysiology of many functional digestive disorders and particularly in IBS Recent studies identified the hippocampus and the central amygdala (CeA) as brain sites of action. CRF microinjected into the CeA induces a hyperalgesic response to CRD and enhances the noradrenaline levels at this site which are blocked by a CRF-R1 antagonist injected into the CeA. Pharmacological interventions targeting the CRFergic system would be of interest in stress-related functional bowel disease. So far non-pharmacologic therapies to reduce the stress component including cognitive behavioral therapy, relaxation therapy, and hypnotherapy, alone or in combination, are reportedly effective for IBS symptoms.

Learning objectives:

- To understand the implications of brain-gut axis in functional bowel disease
- To gain insight to the influence of stress in the manifestations of IBS
- To delineate the role of CRF signalling pathways in stress-related IBS symptoms

Endogenous adaptation of the heart to ischemic stress: Importance in cardioprotective drug development

Péter Ferdinandy, Professor and Director, Department of Pharmacology and Pharmacotherapy, Semmelweis University, Budapest, Hungary; Founder and CEO, Pharmahungary Group, Szeged, Hungary.

peter.ferdinandy@pharmahungary.com

Rationale:
Ischemic heart disease is the leading cause of mortality worldwide; therefore, identification of valid drug targets for cardioprotection is of great importance. The discovery of ischemic conditioning (more than 3 decades ago) triggering endogenous cardioprotective mechanisms that render the heart more resistant to lethal ischemic-reperfusion injury gave much hope to identify cardioprotective drug targets. However, we still do not have cardioprotective drugs on the market. It seems that major cardiovascular co-morbidities such as hyperlipidemia, diabetes, depression and their co-medications as well as risk factors like ageing and sex interfere with cardioprotective mechanisms. Cardiac stress adaptations have been shown to affect global myocardial gene expression profile. Cardiovascular co-morbidities have been also shown to affect global cardiac gene expression profile. Further understanding and the comprehensive analysis of the cardioprotective gene expression by unbiased multiomics approach followed by molecular network analyses may lead to identification of novel molecular targets for cardioprotection. This approach is useful for identification of molecular target for drugs in any other diseases.

Learning objectives:
- Myocardial ischemia-reperfusion injury and endogenous adaptation to it - the clinical problem.
- Known cellular mechanisms of cardioprotection – clinical trials
- Effect of comorbidities and risk factors and their drug treatments on cardioprotection
- Unbiased approach to find molecular drug targets: multi-omics and their evaluation by bioinformatics tools to build molecular networks

References
Hausenloy DJ, Garcia-Dorado D, Bøtker HE et al. Novel targets and future strategies for acute cardioprotection: Position Paper of the European Society of Cardiology Working Group on Cellular Biology of the Heart. *Cardiovasc. Res.*, 2017; 113: 564-585.
Perrino C, Barabási AL, Condorelli G et al. Epigenomic and transcriptomic approaches in the post-genomic era: path to novel targets for diagnosis and therapy of the ischaemic heart? Position Paper of the European Society of Cardiology Working Group on Cellular Biology of the Heart. *Cardiovasc. Res.,* 2017; 113:725-736.
Ferdinandy P, Hausenloy DJ, Heusch G et al. Interaction of risk factors, comorbidities, and comedications with ischemia/reperfusion injury and cardioprotection by preconditioning, post conditioning, and remote conditioning. *Pharmacol. Rev.,* 2014; 66(4): 1142-1174.

Endogenous modulators of stress-induced gastric ulcers

Ludmila Filaretova, PhD, DSc, Corresponding Member of the Russian Academy of Sciences,
Chief of Laboratory of Experimental Endocrinology, Pavlov Institute of Physiology, Russian Academy of Sciences, St. Petersburg, Russia

filaretovalp@yandex.ru

Rationale:
Various manifestations of pathological changes induced by stress in the gastrointestinal tract (from functional changes to erosions and ulcer damage), are a serious medical problem, which can be solved with results gained from fundamental studies. The findings of fundamental studies suggest that gastric mucosal injury may occur when noxious factors overwhelm an intact mucosal defense or when the mucosal defensive mechanisms are impaired. Stress-related mucosal disease (SRMD) occurs in conditions in which gastric mucosal injury is directly related to impairment in mucosal defense. SRMD was also observed in critically ill patients. Endoscopic studies generally indicate that approximately 75-100% of critically ill patients have gross gastric lesions. The mortality in patients with stress-related bleeding is high. Knowledge regarding gastric mucosal defense mechanisms has led to the development of current and potential future therapies to reduce stress-induced gastric injury. *(Supported RSF 19-15-00430).*

Learning objectives:

- Stress-related mucosal disease
- Gastric cytoprotection/Gastroprotection
- Endogenous modulators of gastroprotection
- Prostaglandins (PGs), nitric oxide (NO), capsaicin-sensitive sensory neurons: concerted regulation of gastroprotection
- Glucocorticoids and gastric ulceration
- Stress-induced activation of the HPA axis as gastroprotective component of stress response & stress-produced glucocorticoids as gastroprotective hormones.
- Compensatory gastroprotective action of glucocorticoids during inhibition PGs, NO production and desensitization of capsaicin-sensitive sensory neurons.
- Gastroprotective action of corticotropin-releasing factor: Involvement of glucocorticoids.
- Biphasic effects of glucocorticoids on the gastric mucosa.
- Transformation of initially gastroprotective action of glucocorticoids to pro-ulcerogenic effect.

References

Filaretova L. Gastroprotective effect of stress preconditioning: Involvement of glucocorticoids. *Current Pharmaceutical Design*, 2017; 23 (27): 3923–3927.

Filaretova L., Bagaeva T. *The realization of the brain-gut interactions with corticotropin-releasing factor and glucocorticoids*. Current Neuropharmacology, 2016; 14 (8): 876-881.

Filaretova L., Bagaeva T., Morozova O. Stress and the stomach: corticotropin-releasing factor may protect the gastric mucosa in stress through involvement of glucocorticoids, *Cell. Mol. Neurobiol*., 2012; 32: 829-836.

Spinal cord stimulation as a tool of emotional stress regulation in SCI patients

Yury Gerasimenko, PhD, DSc, Corresponding Member of the Russian Academy of Sciences, Chief of Laboratory of Movements, Pavlov Institute of Physiology, Russian Academy of Sciences, St. Petersburg, Russia

gerasimenko@infran.ru

Rationale:
Spinal cord injury (SCI) patients suffer negative stress connected with induced immobility. Spinal cord electrical stimulation is an effective way to rehab movements to these patients. The development of acute and posttraumatic stress symptoms after a traumatic event is a typical for SCI patients. Experiments will be described which demonstrate that after complete paralysis the lumbosacral spinal circuitry can be functionally reorganized by repetitive practice of a given motor task, including standing and stepping as well as the recovery of standing and voluntary control and assisted stepping in humans that have been completely paralyzed for more than a year. Other effects that have been observed in paralyzed human subjects have been improved autonomic functions controlling multiple physiological systems. The most surprising observation has been the consistent recovery of voluntary function after complete paralysis of the lower limbs. The potential mechanisms that underlie these widespread changes motor and autonomic functions will be presented. Finally, these results observed after paralysis suggests several neurophysiological phenomena that have not been previously recognize play a central role in the control movement. How these physiological phenomena are related to emotional stress regulation will be discussed.

Learning objectives:

- To understand the effects of spinal neuromodulation for posture and locomotion control
- To understand integrative mechanisms of somatic-visceral interactions
- To clarify the effects of spinal neuromodulation for emotional stress regulation

References

Harkema S, Gerasimenko Y, Hodes J et al. Effect of epidural stimulation of the lumbosacral spinal cord on voluntary movement, standing, and assisted stepping after motor complete paraplegia: a case study. The *Lancet,* 2011; 377 (9781): 1938-1947.

Gerasimenko YP, Lu DC, Modaber M et al. Noninvasive reactivation of motor descending control after paralysis. *J. Neurotrauma,* 2015; 32 (24): 1968-1980.

Gill ML, Grahn PJ, Calvert JS et al. Neuromodulation of lumbosacral spinal networks enables independent stepping after complete paraplegia. *Nat. Med.*, 2018; 24(11): 1677.

Stress, neuropeptides, brain-gut, gut-brain axis

Klara Gyires, MD, PhD, DSc, Professor of Pharmacology, Department of Pharmacology and Pharmacotherapy, Faculty of Medicine, Semmelweis University, Budapest, Hungary

gyires.klara@med.semmelweis-univ.hu

Rationale:
Exposure of the organism to a hostile stimulus results in a series of coordinated reactions that aims to avoid the aversive effect and maintain or restore the homeostasis of the organism. In response to noxious stimuli corticotropin-releasing factor (CRF) is released from the paraventricular nucleus (PVN) resulting in activation of hypothalamic–pituitary–adrenocortical axis and coordination of the endocrine, autonomic, behavioral and immune responses to stress. Several other neuropeptides, released in a coordinated way, each following a determined time course and specific for a determined stressor, are also involved in regulation of the stress response. However, besides the development of adaptive physiological, beneficial reaction, pathological, non-desired somatic and psychic responses can also develop, among others, gastric mucosal damage, erosion, ulceration.

Learning objectives:

- The mechanism of stress-related gastric mucosal lesions.
- Effects of stress-related neuropeptides (such as CRF, SP, N/OFQ, opioids, oxytocin, prolactin) on stress- and other ulcerogenic stimulus-induced mucosal lesions.
- Stress and intestinal mucosal lesions and inflammation.
- Why does stress negatively influence the course of IBD?
- Effect of inflammatory processes in the GI system (particularly in the gut) on brain functions.

References

Monnig AA, Prittie JE. Review of stress-related mucosal disease. *J. Vet. Emerg. Cri. Care (San Antonio)*, 2011; 21: 484-495.

Brzozowski B, Mazur-Bialy A, Pajdo R et al. Mechanisms by which stress affects the experimental and clinical inflammatory bowel disease (IBD). Role of brain-gut axis. *Curr. Neuropharmacol.*, 2016; 14(8): 892-900.

Holzer P, Hassan AM, Jain P et al. Neuroimmune pharmacological approaches. *Curr. Opin. Pharmacol.,* 2015*;* 25: 13-22.

Chronic stress and pain: Interactions and common mechanisms

Zsuzsanna Helyes, Professor, Department of Pharmacology and Pharmacotherapy, Medical School & Szentagothai Research Centre, University of Pecs, Pecs, Hungary.

zsuzsanna.helyes@aok.pte.hu

Rationale:
Clinical and experimental data strongly suggest that chronic psychological distress increases pain sensation (e.g. in arthritis) and can be an etiological factor of several diseases characterized by persistent pain (e.g.: fibromyalgia, chronic regional pain syndrome, irritable bowel syndrome, low back pain; Crettaz et al. 2013). These are among the most common and greatest medical burdens leading to severe disability, reduced life quality and increased mortality.
Abnormalities of the hypothalamic-pituitary-adrenal axis, the sympathetic and the sensory nervous systems are involved in stress-induced pain. The function of peripheral nociceptive fibres is deteriorated, their number is decreased, Transient Receptor Potential ion channels (vanilloid 1 and ankyrin 1: TRPV1, TRPA1) playing a crucial role in nociception are up regulated, their mediator composition including sensory neuropeptides is changed in response to chronic stress. Central sensitization mainly due to neuroinflammation in the common stress- and pain-related brain structures (amygdala, hypothalamus, hippocampus, habenula, piriform, prefrontal and somatosensory cortices) is also an important factor in increasing the intensity and maintaining the pain. Furthermore, chronic pain also results in stress and depression; there are complex, bidirectional interactions between stress/mood regulation and pain systems (Vachon-Presseau 2018). The currently available therapy is often not effective or results in a broad spectrum of unwanted effects upon long-term administration, particularly in patients with co-morbidities. These facts clearly show that it is inevitable to understand the mechanisms of the interactions between these pathways to find interventional strategies and identify new drug targets (Botz et al. 2015).

Learning objectives:

- Chronic psychological distress-induced pain conditions, clinical problems
- Common structures and pathways of stress and pain: connections of stress-related brain areas and the "pain matrix"
- Common mediators and molecular mechanisms of stress and pain, functional abnormalities and interactions
- Therapeutic opportunities and novel approaches to inhibit stress-induced chronic pain

References

Crettaz B, Marziniak M, Willeke P et al. Stress-induced allodynia—evidence of increased pain sensitivity in healthy humans and patients with chronic pain after experimentally induced psychosocial stress. *PLoS One*, 2013; 8(8): e69460.
Botz B, Bölcskei K, Helyes Zs. Challenges to develop novel anti-inflammatory and analgesic drugs. *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.,* 2017; 9(3): 1427.
Vachon-Presseau E. Effects of stress on the corticolimbic system: implications for chronic pain. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* 2018; 87(Pt B): 216.

Evaluation of stress in real-life situations

Daniela Jezova, Professor, Institute of Experimental Endocrinology, Biomedical Research Center, Slovak Academy of Sciences, Bratislava, Slovakia.

daniela.jezova@savba.sk

Rationale:
Most of the stress stimuli occurring in the daily life are mental in origin. Somatic stressors are inducing appropriate neuroendocrine activation also under laboratory settings, allowing evaluation of potential pathophysiological consequences and regulatory mechanisms involved. However, laboratory mental stress tasks result in sympathetic-adrenomedullary activation without clear impact on the hypothalamic-pituitary-adrenocortical (HPA) axis. Exceptions are stress tests involving psychosocial components. Psychosocial stress related to tasks which involve standing and speaking in front of an unknown audience are certainly stressful enough to induce broad neuroendocrine responses including huge activation of the HPA axis (Jezova et al. 2016). Relatively little work has been done on neuroendocrine responses to repeated "naturalistic" stressors. An anticipatory stress response was observed in operating surgeons. The cortisol response depended on the difficulty of the surgery. Surprisingly, the nurses working at an intensive care unit showed increased cortisol concentrations in the morning and not in the evening of the working day compared to a leisure day. Several disease states modify hormonal reactivity and coping with stress. Recently, the measurement of cortisol concentrations in hair is increasingly used, however, mainly without appropriate methodological validation. We have developed a methodology for measurement of cortisol concentrations in human hair (Balagova and Jezova 2018) as an innovative and non-invasive method showing reliable results with low variability. *Supported by APVV-17-0451*.

Learning objectives:
- Differences between laboratory and real-life stressors
- Stress in physicians, nurses, musicians, theatre actors
- Stress response in patients with atopy
- Stress response in patients with multiple sclerosis
- Which mental stressor is the most intensive under laboratory conditions?
- Are stressful jobs accompanied by increased stress hormones?
- Which approaches are used to measure hormonal stress response under real life condition in humans?

References
Balagova L, Jezova D. Importance of methodological details in the measurement of cortisol in human hair. *Endocrine Regulations*, 2018; 52: 134-138.
Jezova D, Hlavacova N, Dicko I et al. Psychosocial stress based on public speech in humans: Is there a real life/laboratory setting cross-adaptation? *Stress*, 2016; 19: 429-33.

Stress and molecular mechanisms of nociception: Role of $Na_V1.8$ channels

Boris Krylov, Professor, Pavlov Institute of Physiology Russian Academy of Sciences, Saint Petersburg, Russian Federation

krylov@infran.ru

Rationale:
Understanding the relationship between stress and pain is necessary to create new approaches to the treatment of both chronic pain and chronic stress. The first steps we have taken in this direction show that the slow sodium channels ($Na_V1.8$) of a sensory neuron are a key molecular structure, the pharmacological modulation of which can help relieve chronic pain. Comenic acid, a specific agonist of the opioid-like receptors, effectively and safely relieves neuropathic pain by decreasing the $Na_V1.8$ channel voltage sensitivity (Krylov et al., 2017). This agent triggers the downstream signaling cascade, the key role in which is played by the Na,K-ATPase/Src complex. After the complex, the signal diverges in tangential and radial directions. It is directed tangentially along neuron membrane towards $Na_V1.8$ channels, decreasing the effective charge of their activation gating device. In the radial direction towards the cell genome, the downstream signalling pathway involving PKC and ERK1/2 is activated. A remarkable feature of comenic acid is the ability to modulate $Na_V1.8$ channels which results in chronic pain relief and at the same time to stimulate neurite growth due to receptor-coupled activation of ERK1/2-dependent signalling pathway. This approach, being absolutely safe (comenic acid as a medicinal substance of a non-opioid analgesic drug has successfully passed the first phase of clinical trials) opens up fundamentally new prospects for the treatment of chronic pain, including pain associated with stress.
The present work was funded by the Russian Foundation for Basic Research, project No. 18-015-00079. The study was financially supported by the Program of Fundamental Scientific Research in State Academies for 2014-2020 (GP-14, section 64).

Learning objective:
- Pain as an important stress factor
- Specific molecular mechanisms causing neuropathic pain
- New approaches to the treatment of chronic pain without the use of opiates

References
Krylov BV, Rogachevskii IV, Shelykh TN et al. New nonopioid analgesics: Understanding molecular mechanisms on the basis of patch-clamp and quantum-chemical studies, Bentham Science Publishers Ltd, Sharjah, U.A.E., 2017. https://doi.org/10.2174/9781608059300117010l.

Hypoxia and psycho-emotional stress: Mechanisms of cross-tolerance

Elena Rybnikova, PhD, DSc, Pavlov Institute of Physiology RAS, St. Petersburg, Russia

RybnikovaEA@infran.ru

Rationale:
Hypoxia and its various types is one of most frequent harmful exposure which can cause severe injury to the organism at multiple levels, including depletion of bioenergetic proceeses, oxidative damage of cells and tissues, loss and dysfunction of brain neurons, as well as impaired adaptive responses, in particular neuroendocrine. To copy with hypoxia, multicellular organism successfully enables both phylogenetically ancient intracellular adaptive reactions and systemic adaptive responses developed as a result of long evolution. Due to this, pro-adaptive potential of the hypoxia-driven mobilization of the organism resources appears to be very high. Mild non-injurious hypoxic episodes can induce formation of hypoxic tolerance, i.e. increase resistance to the lethal forms of hypoxia. The phenomenon is called "hypoxic preconditioning" (HP). Interesting that simultaneously with development of the hypoxic tolerance acute hypoxia in HP mode increases resistance to other injurious factors, including psycho-emotional stresses. HP totally prevents development of post-stress pathology in the animal models. At the molecular level HP induces rapid activation of hypoxia-inducible factor HIF-1 which timely initiates HIF-dependent downstream genome-based and biochemical mechanisms. At the neuroendocrine level, HP modifies stress-reactivity of hypothalamic-pituitary-adrenal axis (HPA), shifting the peak of activation to earlier time and increasing its amplitude. In contrast to HP, adaptation to chronic hypobaric hypoxia in mountains does not prevent development of pathogenetic basis of post-stress disorder in the model of time dependent sensitization in rats although anxiolytic effect of such chronic hypoxia is rather potent.

Learning objectives:

- Mild acute hypoxia might be used as a factor inducing cross-adaptation to psycho-emotional stresses
- Chronic hypoxia only masks the behavioral symptoms but does not increase the stress-resistance.
- Stress-protective effects of acute hypoxia are mediated by modifications of HPA regulation
- Adaptive neuronal reactions to the acute hypoxia are HIF-dependent

References

Rybnikova E, Mironova V, Pivina S et al. Involvement of the hypothalamic-pituitary-adrenal axis in the antidepressant-like effects of mild hypoxic preconditioning in rats. *Psychoneuroendocrinology,* 2007; 32(7): 813-823.

Rybnikova EA, Baranova KA, Gluschenko TS et al. Role of HIF-1 in neuronal mechanisms of adaptation to psychoemotional and hypoxic stress. *Int. J. Physiol. Pathophysiol. Pharmacol.,* 2015; 6(1): 1-11.

Rybnikova EA, Samoilov MO. Current insights into the molecular mechanisms of hypoxic pre- and postconditioning using hypobaric hypoxia. Review. *Front. Neurosci.,* 2015, http://dx.doi.org/10.3389/fnins.2015.00388

Management strategies for stress

Martina Rojnić Kuzman, MD, PhD, Associate Professor, University of Zagreb, School of Medicine and University Hospital Centre Zagreb, Zagreb, Croatia

mrojnic@gmail.com

Rationale:
The aim of stress management in general population as well as among those who suffer from psychiatric disorders is the preservation of health and the prevention of psychiatric symptoms. However, effective stress management should involve a personalized approach. The general stress management techniques incorporate a variety of relaxation techniques, like the autogenic training, meditation, visualization, etc. and are suitable for persons without serious mental disorders. For those suffering from mental disorders effective stress managing strategies incorporates the building up of individual capacities - ego strength and it is provided by mental health specialists such as psychiatrists, psychologists, social workers and occupational therapists. It involves different kinds of individual and group psychotherapy, sociotherapy, occupational therapy. For persons suffering from serious mental disorders stress management can be equalized with the treatment itself, and it comprises pharmacotherapy, building up of ego strengths and sometimes actions directed towards their environment such as family interventions. In this presentation three example of an individualized stress management plan will be presented to complement the lecture.

Learning objectives:

- To describe stress management techniques in general
- To differentiate different levels of stress management
- To obtain an understanding on the individualized approach to stress management

Modern experimental insight and stress paradigm

Konstantin Shelepin, I. P. Pavlov Institute of Physiology, Russian Academy of Sciences, St. Petersburg, Russia; Neuroiconica Assistive Ltd., St. Petersburg, Russia

shelepink@yandex.ru

Gennady Trufanof, MD, PhD, DSc, Professor at FGBU V. A. Almazov National Medical Research Center, St. Petersburg, Russia

Vladimir Fokin, MD, PhD, DSc, Professor, head of the department of FGBU V. A. Almazov National Medical Research Center, St. Petersburg, Russia

Peter Vasil'ev, I. P. Pavlov Institute of Physiology, Russian Academy of Sciences, St. Petersburg, Russia

Andrey Sokolov, FGBU V. A. Almazov National Medical Research Center, St. Petersburg, Russia

Rationale:
The development of neurotechnology's in recent years and the creation of self-contained artificial systems that provide purposeful activity and decision making made it necessary to develop neurophysiological studies of insight. In our study we identify the instant of appearance of insight with the image recognition threshold under conditions of indeterminacy. Insight has three stages: the indeterminacy stage, the stage of insight, and post insight period. Our technology is suitable for neurophysiological (fMRI) studies of insight and simulates the basic properties of insight, namely: the incubation period of unconscious accumulation of information necessary to solve the problem; the actual solution of the problem with a threshold of recognition and conscious decision making; pronounced emotional component. The classical Selye model of stress also decomposed into the following time periods: pre-stress, stress, post-stress. Insight period and stress period can have not only the same but very different time scales. Important is common periodicity, involving the same cortical and subcortical parts. The studies were reviewed and approved by the Ethics Committee of St. Petersburg State University (12.06.2017 No. 02-124).

Learning objectives:

- Definition of insight
- Measuring insight
- Insight visualization in human brain
- Definition of Stress from neurosensory position
- Stress and insight in integrative physiology
-

References

Shelepin KY, Vasilev PP, Trufanov GE et al. Digital visualization of the activity of neural networks of the human brain before, during, and after Insight when images are being recognized. *J. Optical Technol.* 2018; 85(8): 468-475.

Shelepin KY, Pronin SV, Shelepin YE. Recognizing fragmented images and the appearance of "Insight". *J. Optical Technol.* 2015; 82(10): 700-706.

Vision and stress

Yuri Shelepin, Professor**;** I. P. Pavlov Institute of Physiology, Russian Academy of Sciences, St. Petersburg, Russia.

Sergei Pronin, at I. P. Pavlov Institute of Physiology, Russian Academy of Sciences, St. Petersburg, Russia.

Olga Zhukova, PhD, I. P. Pavlov Institute of Physiology, Russian Academy of Sciences, St. Petersburg, Russia.

yshelepin@yandex.ru

Rationale:
The "visual brain" design is based on spatial-temporal properties of environments. Human visual system analyzed physical and semantic characteristics of the visual world in conscious and unconscious way. The properties of the environment are selected by the mechanisms of conscious and unconscious vision. The part of the received information works as a stress trigger, or stressors. The search of the visual stressors, their physical and semantic properties, and the investigation of physiological reaction to tem has outstanding importance. The certain spatial-frequency and temporal characteristics during the conscious and unconscious operation mode permit to predict emotionally positive or emotionally negative influence of the signal any complicity even such as face of friend or foe and the mood of the crowd. The stressors search for many centuries inspired by the artists. The particular interest is investigation of the influence the unconscious semantic important stressors, such as facial expressions of the interlocutors. New methods make it possible to identify unconscious changes in facial expressions. The balance between the positive and negative "stressor" effects of the same semantic factor depends on the initial state of the interlocutors.

Learning objectives:

- Real-life visual stressors markers - "The face emotional stress marker computing".
- Awareness and unconsciousness of the presence and influence of stress factors has been investigated.
- New methods - stress anxiety and tension markers, as the result of accumulation of various stressors in observer mind.
- New methods for analyzing facial expressions to evaluate former stress and experienced emotions.

References

Logunova EV, Shelepin Yu. E. Study of the role of spatial-frequency filtering of images when evaluating the age and interpreting the emotional expression of faces. *J. Opt. Technol.*, 2015; 82 (10): 694-699.
Borachuk (Zhukova) OV, Shelepin YuE, Kharauzov AK et al. Study of the influence of the role of the instruction to the observer in tasks of recognizing emotionally colored patterns. *J. Opt. Technol.*, 2015; 82 (10): 678-684.
Zhukova OV, Shelepin YuE, Shchemeleva OV et al. Influence of verbal and nonverbal signals on an interlocutor's electroencephalogram. *J. Opt. Technol.* 2018; 85(8): 455-462.

Hans Selye, the grandmaster of creativity and originality

Arpad Somogyi, DVM, PhD, Professor, Member of the Board of Directors, International Life Sciences Institute Europe, Brussels, Belgium; Former Head of the Unit Evaluation of Health Risks of the European Commission, Brussels, Member, Gesellschaft für Natur- und Heilkunde, Berlin, Germany; External Member of the Hungarian Academy of Sciences, Budapest, Hungary

arpad_somogyi@yahoo.co.uk

Rationale:
Within an academic event entitled *Summer School on Stress* it is particularly fitting that a stand-alone presentation be specifically devoted to multitalented Hans Selye, *the father of the stress concept*. Beyond his best-known work on stress, he also made a host of highly original discoveries on various other fields of experimental medicine by describing, characterizing, and exploring pluricausal diseases (e.g., various cardiopathies, calcergy, calciphylaxis, thrombohemorrhagic phenomenon, acute conditioned necrosis), anaphylactoid edema and catatoxic as well as syntoxic mechanisms. In addition, he made pivotal contributions to the broad field of endocrinology, especially to the classification of steroids and to our better understanding of their mode of action. He developed surgical technics and experimental animal models suitable for studying the pathogenesis and prevention of human diseases. Selye was an extremely well educated, highly intelligent and disciplined individual, an original and creative scientist, an outstanding teacher, a philosopher, a prolific author, a fabulous communicator, and a gifted organizer successfully establishing, developing and managing a major academic research institution, the word-famous Institute of Experimental Medicine and Surgery of the University of Montreal. There, I have had the great privilege of working under his intellectual leadership for four years. While I have enormously benefited from being exposed to his approach to science in general, the way he devised, conducted and evaluated his experiments and how he arrived at his conclusions. I never ceased to be amazed by his work ethic, his extraordinary efficiency, his brilliant organizational talents and his superb skills of communicating his thoughts in his scientific and popular articles as well as in his oral presentations. Working in Selye's institute was a fulltime occupation characterized by long hours of hard work (seven days a week) in a stimulating and competitive atmosphere, spiced with the joy of success and occasionally overcast by the frustration of failure. But it was an overriding privilege that ultimately resulted in a lifelong memory of an unbelievably rewarding experience. Regrettably, the Institut de Médecine et de Chrirurgie expérimentales that Hans Selye founded and made world famous could not survive its creator.

Learning objectives:
- Reflecting on the creativity and originality of Hans Selye
- Discussing his other talents
- His appreciation by his peers and the public
- His legacy

Stress is more than 80 years old: Distress vs. eustress

Sandor Szabo, MD, PhD, MPH, Professor of Pathology & Pharmacology, School of Medicine, University of California, Irvine, CA, USA; External Member of the Hungarian Academy of Sciences, Budapest, Hungary

sszabo@uci.edu

Rationale:

Exactly 80 yeasr ago, Hans Selye first published his General Adaption Syndrome (GAS), i.e., results on experimental animals in one of the best scientific journals of the world (Nature, 1936). Later on, GAS has become the 'stress response' or 'stress reaction'. He was pleased to know that despite the initial criticism & objections, in the last decades of his life (he died in Montreal in 1982) the stress concept was not only widely accepted & reproduced/identified not only in experimental animals, but also proven to exist in humans & plants. Furthermore, he distinguished physical, chemical, biologic & psychologic stressors (agents which cause stress), & emphasized that only the nonspecific, common neuroendocrine manifestations & consequences should be called "stress". His basic definition of stress didn't much changed over the time: 'nonspecific (neuroendocrine) response of the body to any demand upon it'. His favorite illustration was that in cold we shiver, in heat we sweat (physical stressors) & while insulin lowers blood sugar levels, in large doses insulin also elicits enhanced adrenocortical secretion, with all the consequences of the increased bioavailability of glucocorticoids, - hence, insulin may also be a chemical stressor. Selye went out of his way & vehemently protested that by using one agent, the reaction & results can never be called stress! Yet, even nowadays, we see publications, even in best scientific journals, describing & analyzing "cold stress" or "ether stress" where the detected changes should be also specific, unless compared & found to be similar to other (e.g., chemical or psychologic) stressors… Even in our daily life, instead of just saying 'I am exhausted' or 'tired', we often say 'I am under stress' or 'stressed out'… This is a totally unnecessary over-use & over-implication of "stress"!

To better resolve some of these misconceptions, Selye in his last book on "Stress without distress" (1974) introduced the terms of "distress" & "eustress" (from 'euphoria') as two components of stress reaction. Actually, it was the Swedish social scientist Lenart Levi who described a few years earlier that both unpleasant stressors & positive emotions elicit the same or similar adrenal response. In other words, only our brain cortex & not our adrenal glands may feel the difference between arguments with our spouse, & excitement over love, kiss…

Learning objectives:

- Review of the illustrations of physical, chemical, psychological & social stressors.
- Illustrate the frequent & uncritical implication of "stress" in publications & in our daily life.
- Acknowledge that creativity in arts & sciences my flourish under (moderate) distress, -hence 'stress is often good for us'
- Selye was right from the beginning: "Stress is the salt of life"!
- Challenge to new generation of investigators & scientists: Define the mechanisms & identify the molecular mediators of distress & eustress, hopefully leading to pharmacologic transformation of distress into moderate eustress or to chemical induction of eustress…

References

Selye H. A syndrome produced by diverse nocuous agents. *Nature*, 1936; 138: 32.

Selye H. The significance of the adrenals for the adaptation. *Science*, 1937; 85:247-248.

Szabo S, Tache Y, Somogyi A. The legacy of Hans Selye and the origins of stress research:
A retrospective 75 years after his landmark brief "Letter" to the Editor of Nature. *Stress*, 2012; 15: 472–478.

Somogyi A, Szabo S, Vecsei L. Proceedings of the "Selye Symposium-2013". *Clin. Neurosci*., 2014; 67: 77-139.

Stress & structural GI diseases: Gastro-duodenal ulcers & IBD (inflammatory bowel diseases)

Sandor Szabo, MD, PhD, MPH, AGAF, Professor of Pathology & Pharmacology, School of Medicine, University of California, Irvine, CA, USA, and External Member of the Hungarian Academy of Sciences, Budapest, Hungary
Jack D. Wood, MSc, PhD, AGAF, Professor of Physiology & Cell Biology, College of Medicine, Ohio State University, Columbus, Ohio, USA

Rationale:
Hemorrhagic gastric erosions & ulcers which developed in rats exposed to severe stress were one of three components of the initial 'triad of stress' that Hans Selye first described in 1936. Erosions are superficial mucosal lesions that usually heal spontaneously in 3-4 days after distress, while ulcers are deep lesions that penetrate the muscularis mucosae of the gastrointestinal (GI) tract. The healing of deep ulcers requires an angiogenesis-dependent production of granulation tissue, over which proliferating & migrating epithelial cells complete the healing in about a week – unless the stomach is infected by Helicobacter pylori that markedly delays the healing, hence it requires the elimination of these bacteria by antimicrobial drugs. It's important to note that in rodents (e.g., rats, mice) even the most intensive distress produces only gastric lesions & not duodenal ulcers, for the reproduction of which specific duodenal ulcerogenic chemicals are needed in rodents. In humans, on the other hand, the stress- & drug-induced duodenal ulcers are more frequent than gastric ulcers, at least in most countries of the world. It's almost unbelievable that about 80 years after their description, the cause & pathogenesis of these lesions are still debated. Nevertheless, it is generally agreed that they are triggered by the increased secretion of catecholamines & glucocorticoids during severe stress, where vascular & motility factors play a critical role, with a small, if any, contribution by enhanced gastric acid secretion. IBD refers to ulcerative colitis (UC), which may often lead to colonic cancer, & Crohn's disease (CD) that often involves parts of small intestines, in addition to the colon. Stress & environmental factors play a role in the pathogenesis of UC, while genetic & immunologic elements are more important for the development of CD.

Learning objectives:

- Review of the morphology & pathogenesis of gastroduodenal ulceration as well as the etiologic role of stress & the contributory role of H. pylori.
- Discuss the specific mechanistic elements in the pathogenesis of duodenal ulceration.
- Describe the pathology of UC & CD.
- Explain the association between an environmental stressor & fecal factors in the Cotton Top Tamarin model for UC.
- Translate discoveries in the Cotton Top Tamarin model to human UC.

- Erosions & ulcers: superficial vs. deep lesions. (Rate limiting step of maintained blood flow & importance of "granulation tissue").
- **Gastric ulcers vs. gastritis**: Role of H. pylori
- **Duodenal ulcers**: Most frequent form of "peptic ulcers" & not only due acid excess; role of gastroduodenal dysmotility.
- **IBD (ulcerative colitis & Crohn disease):** Clinically most relevant & challenging; critical role of angiogenesis.

The neuroendocrine mechanisms of stress

Yvette Taché, PhD, Professor of Medicine, David Geffen School of Medicine at UCLA, Director, CURE: Digestive Diseases Research Center - Animal Core; Co-Director, Center for Neurobiology of Stress & Women's Health, VA Greater Los Angeles Healthcare System, Los Angeles, CA 90073, USA

ytache@mednet.ucla.edu

Bruno Bonaz, MD, PhD, Professor of Gastroenterology, Clinique Universitaire d'Hépato-Gastroentérologie and Grenoble Institute of Neurosciences (GIN), INSERM U1216, CHU Grenoble Alpes and University Grenoble Alpes, Grenoble, France

BBonaz@chu-grenoble.fr

Rationale:
Selye pioneered the stress concept that is ingrained in the vocabulary of daily life. This was originally build on experimental observations that divers noxious agents can trigger a similar triad of endocrine (adrenal enlargement), immune (involution of thymus) and gut (ulcer formation) responses as reported in a letter to Nature in 1936. Subsequently, he articulated the underlying mechanisms and hypothesized the existence of a "first mediator" in the hypothalamus able to orchestrate these bodily changes. However, he took two generations to identify this mediator. The Nobel Laureate, Roger Guillemin, a former Selye' s PhD student demonstrated in 1955 the existence of a hypothalamic factor that elicited adrenocorticotropic hormone release from the rat pituitary and named it corticotropin releasing factor (CRF). In 1981, Wylie Vale, a former Guillemin's PhD Student, characterized CRF as 41 amino acid and cloned the receptors. This paves the way to experimental studies establishing that the activation of the CRF signaling pathways in the brain plays a key role in mediating the stress-related neuroendocrine, as well as behavioral, autonomic and visceral responses.

Learning objectives:

- The hypothalamic-pituitary axis (HPA)
- Corticotropin releasing factor (CRF) signaling pathways
- Role of arginine vasopressin and catecholaminergic neurons
- Activation of HPA axis during acute stress
- Chronic hyperactivation of the stress system and HPA axis
- Neuroendocrine effects of the acute or chronic stress response
- Genetic and neonatal influences on HPA axis response to stress

Influence of adrenalectomy on protective effects of urocortin I, a CRF-related peptide, against indomethacin-induced enteropathy in rats

Koji Takeuchi, professor emeritus, Kyoto Pharmaceutical University, Kyoto, Japan

koji01210121@yahoo.co.jp

Rationale:

We examined the influence of adrenalectomy on NSAID-induced small intestinal damage in rats, and investigated the possible involvement of adrenal glucocorticoids in the protective effects of urocortin I, a corticotropin-releasing factor (CRF) agonist. Male SD rats without fasting were administered indomethacins and killed 24 h later in order to examine the hemorrhagic lesions that developed in the small intestine. Urocortin I (20 μg/kg) was given i.v. 10 min before the administration of indomethacin. Bilateral adrenalectomy was performed a week before the experiment. Indomethacin (10 mg/kg) caused multiple hemorrhagic lesions in the small intestine, which were accompanied by increases in intestinal motility, enterobacterial invasion, and iNOS expression. Adrenalectomy markedly increased the ulcerogenic and motility responses caused by indomethacin, with further enhancement in bacterial invasion and iNOS expression; severe lesions occurred at 3 mg/kg, a dose that did not induce any damage in sham-operated rats. Such worsening effects were also observed by the pretreatment with mifepristone (a glucocorticoid receptor antagonist). Urocortin I prevented indomethacin-induced enteropathy, and this effect was completely attenuated by the pretreatment with astressin 2B, a CRF2 receptor antagonist, but not significantly affected by either adrenalectomy or the mifepristone pretreatment. These results suggested that adrenalectomy aggravated the intestinal ulcerogenicresponse to indomethacin, and the intestinal hypermotility response may be a key element in the mechanism for this aggravation. It is assumed that endogenous glucocorticoids play a role in intestinal mucosal defense against indomethacin-induced enteropathy, but do not account for the protective effects of urocortin I, which are mediated by the activation of peripheral CRF2 receptors.

Learning Objectives:

- We investigated the possible involvement of adrenal glucocorticoids in the protective effects of peripherally administered urocortin I against indomethacin-induced enteropathy.
- Corticotropin-releasing factor (CRF), a hypothalamic neuropeptide, is the principal regulator of the hypothalamus-pituitary-adrenal (HPA) axis by triggering the release of adrenocorticotropic hormone from the anterior pituitary gland.
- Indomethacin-induced enteropathy was aggravated in adrenalectomized rats or mifepristone-treated rats, in association with the enhanced intestinal hypermotility response to indomethacin.
- Urocortin I, given peripherally, prevented indomethacin-induced enteropathy mediated by the activation of CRF2R, and this effect was functionally associated with the suppression of intestinal hypermotility caused by indomethacin.
- Urocortin I similarly reduced the severity of indomethacin-induced enteropathy in rats with or without adrenalectomy.
- Endogenous glucocorticoids played a role in intestinal mucosal defense against indomethacin-induced enteropathy but did not account for the protective effects of urocortin I.

References

Martinez V, Wang L, Million M et al. Urocortins and the regulation of gastrointestinal motor function and visceral pain. *Peptides* 2004; 25: 1733-1744

Kubo Y, Kumano A, Kamei K et al. Urocortin prevents indomethacin-induced small intestinal lesions in rats through activation of CRF2 receptors. *Dig. Dis. Sci*., 2010; 55: 1570-1580.

Takeuchi K and Satoh H. NSAID-induced small intestinal damage: Roles of various pathogenic factors. *Digestion* 2015; 91: 218-232.

Takeuchi K, Kumano A, Abe N et al. Involvement of corticotropine- releasing factor and CRF2 receptors

in pathogenesis of ischemia/reperfusion-induced small intestinal lesions in rats. *J. Physiol. Pharmacol*., 2016; 67: 697-707.
Takeuchi K, Abe N and Kumano A. Influence of adrenalectomy on protective effects of urocortin I, a corticotropin-releasing factor, against indomethacin-induced enteropathy in rats. *Curr. Neuropharmacol.,* 2016; 14: 866-875.

The Brain-In-The-Gut

Jackie D. Wood, MSc, PhD, AGAF, Professor Emeritus, Department of Physiology and Cell Biology and Internal Medicine, College of Medicine, The Ohio State University, Columbus, Ohio, USA

Jackie.Wood@osumc.edu

Rationale:

I (J. D. Wood) coined the now universally accepted term, *brain-in-the-gut,* for the enteric nervous system in a review published in the 1981 issue of the *Annual Review of Physiology* [1]. This was in view of discoveries in my laboratory and others that the main physiological processes in the digestive tract are controlled by an independent integrative nervous system with neural circuitry containing about 100 million neurons, all within the walls of the gut. Neuronal electrical behavior and synaptic neurotransmission in the microcircuits of the second brain are essentially the same as in the "big brain". The microcircuits in the second brain contain a library of neural programs (think I-phone, I-pad apps) that determine behavior in specialized states including postprandial, interdigestive, emesis and defense against threatening invasions from the outside. My mantra to medical students over 45 years continues to be; "understanding how a system works normally is prerequisite for determination of what is wrong, making a diagnosis and formulating a rational therapeutic plan". My presentation will explain how the brain-in-the-gut is involved in the pathophysiology of several disorders, such as the irritable bowel syndrome, Hirschsprung Disease, food allergies, enteric infections, constipation, diarrhea, psychogenic stress and opioid drug effects.

[1] Wood JD. Intrinsic neural control of intestinal motility. *Annu Rev Physiol*. 1981; 43:33-51.

Learning objectives:

- Explain the concept of the enteric nervous system as a "brain-in-the-gut."
- Describe the functional significance of enteric secretomotor neurons in pathophysiology of constipation and secretory diarrhea.
- Describe how enteric mast cells "talk" to the brain-in-the-gut and the outcomes.
- Explain the relationship between enteric mast cells, sensory afferents and visceral pain.
- Name five of the "apps" stored in the program library in the brain-in-the-gut.
- Explain enteric immuno-neural communication in food allergy.
- Explain the involvement of enteric immuno-neural communication in psychogenic and physical stress.
- Relate the connection of Pavlovian autonomic conditioning to the-brain-in-the-gut.

Abstracts

POLYDIPSIA AS A COPING STRATEGY TO SCHEDULE-INDUCED STRESS: HT AND LT SELECTED RAT STRAINS

N. Bortnikov[1], I. Sukhanov[1], M. Semina[1], A. Vaido[2], N. Dyuzhikova[2], I. Belozertseva[1]

[1]Pavlov First Saint Petersburg State Medical University, Valdman Institute of Pharmacology, St. Petersburg, Russia; [2]Pavlov Institute of Physiology of the Russian Academy of Science, St. Petersburg, Russia.

bns063@gmail.com

Introduction: The high threshold (HT) and low threshold (LT) strains of rats selected by levels of tibial nerve excitability were developed in Pavlov Institute of Physiology of the RAS. These strains were found to have genetically determined differences in neurochemistry, the properties of the nerve cell membranes *etc*. Unfortunately, scare information is available about the stress reactivity of these animals. One of approaches for modeling chronic stress in rats is interval schedules of food reinforcement. Interval schedules induce different behavioral reactions, one of them aims to get food reinforcement, and others are not related to food seeking behavior. Last ones called adjunctive are thought to be defensive strategy against stress conditions. It is known that adjunctive reactions lead to decrease in corticosterone level. The present study aimed to assess behavioral reaction on interval schedule of reinforcement in HT and LT rats.

Methods: The method was performed in concordance with the protocol described in detail early. Animals were exposed to a fixed interval 60-s (FI-60s) schedule of food pellet presentation in 60-min sessions. They have unlimited access to water during the session and it can be observed adjunctive drinking during the interval. The volume of water consumed by the rats stabilized for 10 sessions under the FI 60 schedule. The recorded parameters were the volume of water consumed by each rat, the duration of the experimental session, the number of licks, the drinking duration, the number of lever presses, the latency to the first lick and the latency to the post-food delivery tray nose - poke. **Results:** The statistical analysis of the animal performance revealed that there was no difference between the strains in the levels of polydipsia, but the LT rats performed significantly more operant responses than the HT (two-way RM ANOVA: $F(1,14)=20.31$, $p<0.001$). Also, the same analyses indicated that the LT started operant responding after the reinforcement delivery earlier than the HT rats ($F(1,14)=13.77$, $p<0.01$). **Conclusion:** Generally, the results of the present study indicated that there are some dramatical differences between the HT and LT strains. The findings may reflect decreased difference in a coping strategy to schedule-induced stress between LT and HT rats. The further experiments (including pharmacological assay) are warranted.

INFLUENCE OF PERINATAL STRESS ON DEVELOPMENT OF ADAPTIVE BEHAVIOR AND PRENATAL EFFECTS OF ANTIDEPRESSANTS

I. Butkevich[1,2], V. Mikhailenko[1], E. Vershinina[1]

[1]I. P. Pavlov Institute of Physiology, Russian Academy of Sciences, Saint Petersburg, Russia [2]Department of Normal Physiology, Saint Petersburg State Pediatric Medical University, Russia.

irinabutkevich@yandex.ru

Introduction: Stress during the perinatal period of development (for instance, prenatal stress or invasive manipulations in newborns, as well as depression during pregnancy) leads to impairment of adaptive behavior. The selective serotonin reuptake inhibitor fluoxetine is used to normalize the behavior in pregnant women. Evidence that stress during critical periods of development can increase adaptation to stress in the future requires clarification. The question of the effect of antidepressants under these conditions has not been studied. **Methods:** We investigated in young rats, born to the dams exposed during pregnancy to stress and antidepressant fluoxetine or 5-HT1A receptor agonist buspirone, the effect of peripheral inflammatory pain in the first two days of life on different types of adaptive behavior in the tests: hot plate, formalin test, elevated plus maze, forced swimming and the Morris water maze. All experimental procedures were approved by the Local Ethics Committee for Animal Experiments of the I. P. Pavlov Institute of Physiology, Russian Academy of Sciences (St. Petersburg, Russia). **Results:** Prenatal stress and neonatal pain impaired all types of behavior under study, fluoxetine and buspirone improved these behaviors. Combination of prenatal stress and neonatal inflammatory pain did not increase the influence of the prenatal stress on behavior in any of the tests used. It is important, combined stressor prevented the harmful effects of prenatal stress on the pain sensitivity and inflammatory pain response, and evoked normalization of behavior in the hot plate test and formalin test. Under these conditions, the effect of fluoxetine and buspirone did not manifest itself, which indicates that fluoxetine and buspirone exert an antinociceptive, antidepressant and anxiolytic effects in individuals only with pronounced pain-like or anxiety-depressive behaviors. **Conclusion:** In summary, our study demonstrates that under certain conditions, stress effects in perinatal age can increase the stress resistance of the organism. The results are discussed in the context of the current hypothesis (match / mismatch stress hypothesis), according to which stress at critical periods of development can program the adaptive behavior to subsequent stress events. Supported by the Russian Foundation for Basic Research (project No. 17-04-00214a).

EFFECTS OF ANTIOXIDANT NUTRIENTS AND ASTAXANTHIN ON *HELICOBACTER PYLORI* – INDUCED GASTRIC STRESS

E. Byun, B. Park, H. Lee, S.H. Kim, J.W. Lim, H. Kim

Department of Food and Nutrition, Brain Korea 21 PLUS Project, Research Center for Food, Nutrition & Foodservice Management, College of Human Ecology, Yonsei University, Seoul 03722, Republic of Korea.

kim626@yonsei.ac.kr

Abstract

Introduction: Antioxidant nutrients such as alpha-lipoic acid, lycopene, and astaxanthin have anti-inflammatory activities. Therefore, these nutrients may prevent oxidative stress-mediated gastric injury. *Helicobacter pylori (H. pylori)* infection-induced gastric stress involves inflammation and carcinogenesis. In the mucosa of *H. pylori*-infected patients with gastritis or adenocarcinoma, cell proliferation of gastric epithelial cells increased. One of the toxic factors, which causes gastric injury in *H. pylori*-infected cells, is reactive oxygen species (ROS). ROS are produced by the activated NADPH oxidase in the infected cells. Therefore, supplementation of antioxidant nutrients may prevent the development of *H. pylori*-induced gastric diseases. Wnt/beta-catenin signaling is an important signaling in cell proliferation and a critical upstream regulator of c-myc signaling. As a proto-oncogene, c-myc stimulates the expression of target genes, which play important roles in cell proliferation. Since ROS activates several transcription factors, ROS may directly or indirectly induce hyper-proliferation and oncogene expression. **Methods:** At first, we determined the changes in Wnt/beta-catenin signaling, c-myc expression, as well as hyper-proliferation in *H. pylori*-infected gastric epithelial AGS cells. Since oxidative stress was increased in the infected cells, we determined whether oncogene expression is regulated by oxidant-sensitive transcription factor (NF-κB, AP-1) in the infected cells. Secondly, we determined the effect of antioxidant nutrients including alpha-lipoic acid, lycopene and astaxanthin on *H. pylori*-induced cell proliferation and oncogene expression in gastric epithelial cells. **Results:** We found that *H. pylori* infection increased cell proliferation, expression of beta-catenin and c-myc, and nuclear translocation of beta-catenin in gastric epithelial cells. Oncogene expression is inhibited in the cells transfected with IκBα mutant to suppress NF-κB activation or transfected with dominant negative c-jun to inhibit AP-1 activation. Antioxidant nutrients inhibited NADPH oxidase activity and reduced ROS, resulting in suppression of transcription factors NF-κB and AP-1 in *H. pylori*-infected gastric epithelial cells. These nutrients inhibited oncogene expression and hyper-proliferation of *H. pylori* -infected gastric epithelial cells. **Conclusion:** In conclusion, consumption of foods rich in antioxidant nutrients may prevent *H. pylori*-associated gastric diseases.

EXPRESSION OF GROWTH FACTORS IN RAT BRAIN FOLLOWING THE DELTA OPIOID RECEPTOR BLOCKADE BY NALTRINDOLE AND EXPOSURE TO HYPOKINESIS

P. Chomanic[1,2], L. Balagova[1], J. Graban[1], D. Jezova[1]

[1]Laboratory of Pharmacological Neuroendocrinology, Institute of Experimental Endocrinology, Biomedical Research Center, Slovak Academy of Sciences; [2]Department of Pharmacology and Toxicology, Faculty of Pharmacy, Comenius University in Bratislava, Slovakia.

pa.chomanic@gmail.com

Introduction: Endogenous opioid peptides act via u, kappa and delta opioid receptors. To our knowledge, there are no data on the effects of delta opioid receptor blockade on expression of growth factors. The aim of the present studies was to verify the hypothesis that the blockade of delta opioid receptors by naltrindole potentiates negative effects of mild stressors on the expression of growth factors in rat brain. **Methods:** Forty Wistar male rats were used. Half of the animals was exposed to partial restraint stress (hypokinesis) lasting 48 h. Rats were treated with vehicle (saline) or naltrindole (delta opioid receptor blocker) at a dose of 3 mg/kg (s.c.) three times daily. After decapitation, the adrenal glands and the frontal cortex were removed. **Results:** Exposure of rats to the hypokinesis resulted in an increase of adrenal weight. Expression of brain-derived neurotrophic factor (BDNF) in the frontal cortex was significantly reduced by exposure to hypokinesis. The prolonged stressor used failed to affect the expression of fibroblast growth factor 2 (FGF_2). Treatment with naltrindole induced an increase in the expression of delta opioid receptor type 1. **Conclusion:** Present results indicate that the treatment with naltrindole has no influence on gene expression of growth factors measured. Pharmacological blockade of delta opioid receptor type 1 was associated with a compensatory increase of the expression of these receptors.

The study was supported by APVV-15-0388 and FaF UK/10/2019.

FACIAL EXPRESSION DURING SOCIALLY EVALUATED COLD PRESSOR TEST IN RELATION TO STRESS PERCEPTION IN HEALTHY MEN

Z. Chuda[1,2], K. Buzgoova[1,2], L. Balagova[1], I. Riecansky[3], D. Jezova[1]

[1]Laboratory of Pharmacological Neuroendocrinology, Institute of Experimental Endocrinology, Biomedical Research Center, Slovak Academy of Sciences; [2]Department of Pharmacology and Toxicology, Faculty of Pharmacy, Comenius University; [3]Department of Behavioral Neuroscience, Institute of Normal and Pathological Physiology, Centre of Experimental Medicine, Slovak Academy of Sciences, Bratislava, Slovakia.

zuzana.chuda@savba.sk

Introduction: Non-verbal signs include facial expressions and their changes are essential part of the interpersonal communication. The current knowledge on changes in non-verbal behavior during stress situations is insufficient. The most frequently behavioral patterns associated with laboratory psychosocial stressors are displacement, flight, assertivity and affiliation. Studies investigating non-verbal behavior together with neuroendocrine response to stressors are not available. The aim of the present study was to identify typical non-verbal behavior characteristics in persons with high and low stress perception during socially evaluated cold pressor test (SECPT). **Methods:** Twenty-one healthy men aged 20-37 years with normal BMI were exposed to the combined somatic and psychosocial stress test. Participants immersed their hand into an ice-cold water for 2 min and they were carefully observed by female experimenters. The volunteers were videotaped with camera focused on the face. The facial expressions were analyzed with the ethological coding system for interviews (ECSI) by Troisi (Neurosci Behav Rev 1999). The participants were divided into low (N = 10) and high (N = 11) stress perception group according to a visual analogue scale. Saliva samples for hormone measurement were collected before and after SECPT and it was determined by ELISA. **Results:** The volunteers in the group with high stress perception more frequently exhibited affiliate behavior, such as a smile, a head situated to one side, raised eyebrows for shorter and longer time compared to subjects with low stress perception. The flight behavior (looking away from the interviewer, looking down at feet or floor, closed eyes) correlated with salivary cortisol. This correlation was positive in subjects with high and negative in those with low stress perception. Factorial analysis of behavioral and hormonal parameters revealed different pattern of loading distribution with respect to stress perception. **Conclusion:** The physiological significance of different direction of the relationship between salivary cortisol and flight behavior remains to be elucidated. The affiliation, as a type of pro-social behavior, can be an effective tool in coping with stress potentially resulting in a reduction of harmful effects of stress on health.

The study was supported by APVV-14-0840, VEGA 0022/18 and Comenius University UK/213/2019.

STRESS IN ANIMALS: AN ECOLOGICAL VIEW

D. Csabai[1], B. Czeh[1,2]

[1]Neurobiology of Stress Research Group, Szentágothai János Research Centre, University of Pécs, Pécs, Hungary; [2]Instute of Laboratory Medicine, Medical School, University of Pécs, Pécs, Hungary.

csabaidav@gmail.com

Stress may also be defined as a multimodal nonspecific environmental process which forces the entity to adopt and survive. Although short and occasional negative life events can make the individual habituated for such a stressor, yet chronic, repeated episodes of distress (aka. chronic stress) can cause severe behavioral and physiological changes. Chronic stress-related alterations are well-reported in the case of laboratory animals like rats, mice and even primates and researchers are getting closer to understand these effects in humans. Many studies use well validated models to examine stress, but few reports are about the exact impact of chronic stress in wild- or livestock animals. Furthermore, these factors do not only affect phylogenetically higher classes such as mammals but can also worsen the health of fish or even invertebrate animals. Here we collected numerous examples that chronic stress can affect the well-being of livestock and wild animals. Crowding, thermal fluctuation, food or water deprivation, moving cages and noises are main factors of most chronic stress paradigms, and these variables also make part of the regular day of a farm animal. Predation, low resources, dominant conspecifics and human activity are the perfect homologues for chronic stressors in wildlife conditions, but in some cases these factors can contribute to the regeneration of habitats and populations. Thus, chronic stress could be very harmful and disadvantageous for the individual or species, but it may also be a good factor in larger processes such as recultivation and regeneration of habitats on an ecological scale.

PROTECTIVE ROLE OF THE SOMATOSTATIN RECEPTOR SUBTYPE 4 IN THE INDOMETHACIN-INDUCED GASTROINTESTINAL MUCOSAL INJURY MODEL

K. Csekő[1,2], V. Kormos[1,2], Á. Horváth[1,2], M. Sudalina[3], I. Natalia[3], D. Zelena[4,5], L. Filaretova[3], Z. Helyes[1,2,6]

[1]Dept. of Pharmacology and Pharmacotherapy, Medical School and Szentágothai Research Centre, University of Pécs, Hungary; [3]Laboratory of Experimental Endocrinology, Pavlov Institute of Physiology, Russian Academy of Sciences, Russia; [4]Dept. of Physiology, University of Pécs, Hungary; [5]Institute of Experimental Medicine, Hungarian Academy of Sciences, Hungary; [6]PharmInVivo Ltd, Pécs, Hungary.

csekoe.kata@gmail.com

Introduction: Since gastrointestinal ulceration is still associated with high mortality despite advancements in the endoscopic and pharmacological management, precise understanding of the mucosal defensive and protective mechanisms is important. The neuropeptide somatostatin is present in the endocrine cells and sensory nerves, is analogues were shown to reduce mucosal blood flow, pepsin and gastric acid secretion. Its endocrine functions are mediated by the receptors $sst_{2,3,5}$, and our group discovered that the anti-inflammatory and analgesic actions are exerted via the sst_4 receptor. Sst_4 agonists are preclinically tested as novel drug candidates in these areas. Therefore, we investigated the role of sst_4 in gastrointestinal injury. **Methods:** Sst_4 gene-deleted ($sst_4^{-/-}$) mice and wildtype counterparts ($sst_4^{+/+}$) were treated s.c. with 35 mg/kg indomethacin (IDM) or its vehicle. Macroscopic and microscopic mucosal lesions in the stomach and small intestine were evaluated by the ImageJ program and semiquantitative histopathological scoring after 4 and 48 h, respectively. Small intestinal length, thymus, adrenal glands, spleen weight and plasma glucose levels were measured. Neutrophil myeloperoxidase (MPO) activity and plasma extravasation were measured by bioluminescent/fluorescent *ex vivo* imaging after 24 h. **Results:** Macroscopic lesion area and MPO activity in the gastric mucosa were significantly greater in IDM-treated $sst_4^{-/-}$ mice than in wildtypes 4 h and 24 h after IDM administration, respectively. Similar tendency was observed in the duodenum and jejunum even after 48 h. However, IDM did not induce mucosal plasma extravasation in either group at the 24 h timepoint. Thymus weight was significantly less in $sst_4^{-/-}$ mice than in $sst_4^{+/+}$ ones. Histopathological scores, small intestinal length, adrenal and spleen weight, and plasma glucose level were not altered by the sst_4 deletion. **Conclusion:** These results provide evidence for a protective role of the sst_4 receptor against chemical injury-induced gastrointestinal mucosal damage. This shows the safety of sst_4 agonist drug candidates in the gastrointestinal tract, and even highlights their potential use for gastroprotective indication.

Supported by: GINOP-2.3.2-15-2016-00050 – PEPSYS, GINOP-2.3.2 STAY ALIVE, EFOP-3.6.2-16-2017-00008, ÚNKP-18-3 New National Excellence Program of the Ministry of Human Capacities

PROGNOSTICATION OF ANTISTRESS OPTIONS OF SPELEOCLIMATOTHERAPY

Y.V. Dorokhov, N.P. Gorbatenko, A.V. Karpova

Voronezh N.N. Burdenko State Medical University, Voronezh, Russia.

dorofov@mail.ru

One of the major tasks of this research study was to evaluate corrective options of speleoclimatotherapy (SCT) as a technique to non-medically correct vegetative status and quality of life parameters violated by psycho-emotional stress in medical students. Students-vagotonic revealed activation of the CNS sympathetic region under the SCT course; this was expressed in the increased low-frequency (LF) wave and vago-sympathetic index (LF/HF) parameters. The vegetative nervous system (VNS) parasympathetic activity, on the contrary, decreased; this was expressed in the reduced high frequency (HF) wave parameters. Amplitude mode (AMo) parameters and tension index (TI) demonstrating the VNS sympathetic activity under the SCT course decreased in the subgroup of normotonics. Total power (TP) wave parameters reflecting adaptive body capacities increased. The VNS sympathetic region activity decreased under the SCT course in the subgroup of sympatotonics; this was expressed in the reduced TI, LF/HF parameters reflecting the VNS sympathetic region activity. The VNS parasympathetic region activity increased after the SCT course that was reflected in the increased parameters of the variation range (VR) and HF. Thus, mechanisms of action of the SCT depend on the initial vegetative status of students. In vagotonics the VNS sympathetic activity increases due to activation of the sympato-adrenal system as a result of adaptation to the speleochamber microclimate (a cross-resistance phenomenon). Normotonics and sympatotonics, who are characterized by the excessive activity of the stress-releasing systems, manifested adaptogenic action of speleoclimate related to the increase of their activity; this results in repairing of the vegetative homeostasis. The SCT course did not only decrease vegetative symptoms of psycho-emotional stress, but also improved quality of life in most of parameters. Thus, physical component of the quality of life (PhCQL) and psychic component of the quality of life (PsCQL) increased after the SCT course. Based on the results obtained we have developed ways to predict efficiency of PsCQL and PhCQL correction using SCT method in healthy individuals under psycho-emotional stress (patents №2491017 and №2491880). PrI PsCQL = 115.814 + 0.217773* PhCQL – 1.26127* PsCQL + 0.386342*AMo – 0.0262776*VR – 0.161975*TI + 0.00976516*TP – 0.0147198*VLF – 0.0109342*LF – 0.345006*LFnorm – 1.14238*HFnorm + 1.76347*LF/HF; PrI PhCQL = 22.3464 – 0.552734*PhCQL + 0.087694*PsCQL + 0.450294*AMo + 0.0349638*VR – 0.158153*TI + 0.00168456*TP – 0.00394208*VLF – 0.00340523*LF + 0.123804*LFnorm – 0.01193901*HFnorm + 4.80167*LF/HF, PrI PsCQL is a prognostication index of psychic component of the quality of life, PrI PhCQL is a prognostication index of physical component of the quality of life. Initial parameters of PrI PhCQL≤ 2.03 and PrI PsCQL≤ 4.34 prove futility of SCT method application to correct vegetative and psycho-emotional stress manifestations.

CREATION OF THE VIRAL VECTORS FOR THE INHIBITION OF THE SEROTONERGIC NEURONS USING LIGHT SENSITIVE PROTON PUMP

U.S. Drozd, D.A. Lanshakov

Institute of Cytology and Genetics SB RAS, Novosibirsk, Russia.

drozdnsu@gmail.com

Introduction: Serotonergic neurons play the central role in the pathogenesis and the pharmacotherapy of major depression and anxiety disorders. Available treatments (including selective serotonin reuptake inhibitors) seems to be effective for treatment of depression, but more than two-thirds of depressed patients remain symptomatic after an initial intervention and 20% of these fails to respond to any intervention. The recent development of optogenetic tools has made it possible to design new approaches for the treatment of mental disorders. This research was aimed to create lentiviral vectors for the optogenetic inhibition of the serotonergic neurons using the proton pump archaerhodopsin-3. **Methods:** To attenuate firing specifically in serotonergic neurons vectors expressing the proton pump archaerhodopsin-3 under the control of TPH2 promoter were used. Viral vectors were constructed based on plasmids designed by the N. Nishitani group. Lentiviral particles (LVV) were obtained by transfection of HEK29 cells by the mixture of plasmids for the virus assembly (pPAX2 and pMD2.G) as well as a TPH2-eArchT3.0-eYFP-WPRE plasmid carrying the sequence of the archaerhodopsin-3 (eArchT3.0) and a yellow fluorescent protein (eYFP) or TPH2-Venus-WPRE plasmid that was used as a control. Rats were stereotaxically injected with the virus in the DRN. One week after infection, green light (560 nm) was applied to the DRN for 3 min. Then animals were sacrificed, and the brain was collected, frozen and sectioned. Expression of eArchT3.0-eYFP and c-fos in the TPH-positive neurons was investigated immunohistochemically using confocal microscopy. The number of c-Fos, YFP, and TPH2 expressing neurons were counted. The expression of c-Fos was used as a marker of the neuron's activity. **Results:** One week after LVV injection, the majority of the TPH2 immunoreactive cells expressed eArchT3.0-eYFP that was detectable without immunohistochemical enhancement. Green light illumination for 3 min via optic fiber placed above the DRN decreased c-Fos expression in eYFP- and TPH2-double-positive cells in TPH2:eArchT3.0 injected rats, compared with the TPH2: Venus injected rats. **Conclusion:** Current injection of TPH2: eArchT vectors in the DRN evoke the expression of the proton pump archaerhodopsin-3. Green light illumination of eArchT3.0 induced outward current and suppressed action potential generation that leads to a decreased number of c-Fox expressing serotonergic neurons.

This work was financially supported by the Russian Foundation for Basic Research (project No.18-315-00114).

DANIO RERIO AS A NOVEL BEHAVIORAL MODEL FOR ANXIOLYTIC AND ANTIDEPRESSANT DRUGS SCREENING

V.R. Gedzun, E.V. Razumkina, I.S. Sukhanova, A.V. Malyshev, I.I. Doronin, M.L. Lovat,

A.R. Kuchumov, G.A. Babkin

Lactocore LLC, Moscow, Russia.

vrgedzun@gmail.com

Introduction: Rapid in vivo screening of drugs activity remains to be a challenging task in modern pharmacology. Even if drug effects are predicted in silico and studied in vitro, it is crucial to prove efficacy in behavioral models as early as possible in drug development process, especially in case of psychotropic drugs. Recent studies showed that *Danio rerio* (zebrafish), a relatively new object in preclinical studies, can be very useful as a fast and low-cost drug screening test system. Zebrafish have shown very well determined stress reactions in several behavioral tests, which allows detecting psychotropic activity of novel drug candidates. The aim of this study was to describe activity of standard of care anxiolytic and antidepressant drugs in *Danio rerio* behavioral test system and compare it with psychotropic profiles of known peptides. **Methods:** To assess zebrafish behavior, we used "novel tank" (NT), "dark-light box" (DLB) and "social behavior" models. Fish were intraperitoneally injected with well-known benzodiazepine anxiolytic drug diazepam (doses 1 mg/kg, 5 mg/kg and 10 mg/kg), SSRI fluvoxamine (doses 5 mg/kg and 10 mg/kg) and two peptides tested in zebrafish for the first time – α-casozepine-10 (ACZ-10, GABA-A receptor positive allosteric modulator, dose 0,6 mg/kg) and β-casomorphine-7 (BCM-7, μ-opioid receptor agonist, dose 5 mg/kg). Control fish had intraperitoneal vehicle injections. **Results:** Diazepam showed no significant effect in NT test, but reduced time spent near shoaling zone (1 mg/kg and 5 mg/kg) in "social behavior" test, increased time spent in the light compartment (5 mg/kg) and reduced latency of entering the light compartment (10 mg/kg) in DLB test. Fluvoxamine had no significant effects in DLB or "social behavior" tests, but both doses significantly increased time spent in the upper half of the aquarium, as well as reduced latency of entering it in NT test. Both peptides had no effects in DLB test and reduced time spent near shoaling zone in "social behavior" test, but ACZ-10 also significantly increased time spent near water surface in NT test, while BCM-7 showed additional negative effect on locomotor activity. **Conclusion:** According to literature, shoal cohesion, scototaxis (dark zones preference) and positioning near the bottom of the tank are well-known markers of stress-related behavior in zebrafish. Thus a decrease in these parameters can be used as indicators of drug's psychotropic activity. Results obtained here support this hypothesis: combination of three different tests provides us with expected efficacy and safety data regarding substances with well-known properties. Thus *Danio rerio* behavioral test system can be used as a predictive and translational screening model for both anxiolytic and antidepressant activity of novel drug candidates including peptides.

STRESS RESPONSE-RELATED MOLECULAR MECHANISMS OF POST-STROKE DEPRESSION AND DEMENTIA

M.Y. Kasatkina[1,2], P.I. Belov[3,4], A.B. Guekht[2], N.V. Gulyaeva[1,2]

[1]Institute of Higher Nervous Activity and Neurophysiology RAS, Moscow, Russia, [2]Moscow Research and Clinical Center for Neuropsychiatry, Moscow, Russia, [3]Moscow City Clinical Hospital after V.M. Buyanova, Moscow, Russia, [4]Pirogov Russian National Research Medical University, Moscow, Russia.

m.u.kasatkina@gmail.com

Introduction: According to the World Health Organization reports, stroke is the second leading cause of death and the third leading cause of disability worldwide. Most common delayed consequences of stroke are post-stroke depression and dementia (PSDD) significantly affecting the quality of life. Definite protective measures are needed to prevent such conditions. However, to elaborate protection approaches, it is necessary to understand molecular and cellular mechanisms of PSDD development. Recently, it has been shown that PSDD are associated with distant damage to the hippocampus. We have suggested that damage to the ventral hippocampus initiates emotional disturbances (depression), while damage to the dorsal hippocampus induces cognitive impairments (dementia). We have hypothesized that stress response neuroendocrine system is intimately involved; when a stroke occurs, the hypothalamic-pituitary-adrenal axis (HPAA) is activated and glucocorticoids (cortisol/corticosterone) are secreted. Excessive glucocorticoids occupy hippocampal mineralocorticoid and glucocorticoid receptors triggering neuroinflammation and subsequent neurodegeneration in the hippocampus as well as corrupting the negative feedback of HPAA. The stress-prone personalities have a higher basal cortisol level and thus may be more vulnerable to post-stroke disorders. Thus, neuropsychiatric examination and basal and stress-induced cortisol assays are necessary to assess individual risk of PSDD. Evaluation of pro-inflammatory cytokines may be an additional relevant assay. **Methods:** A protocol of a two-year long study of stroke patients was elaborated. To determine the neuropsychiatric status of patients NIHSS, MOCA, HADS will be used. Blood serum and saliva of patients and control subjects will be used for evaluation of stress-related indices and cytokines in basal conditions and after dosed stress challenge. Basal (pre-stroke) cortisol level we will measure in the hair. **Expected results and conclusion:** We will obtain the data on basal and reactive cortisol, proinflammatory cytokines, ACTH, and alpha-amylase levels in patients during two years after stroke and compare these biochemical parameters with the results of neuropsychological testing, clinical examinations and FMRI. The data will allow proving or disproving the hypothesis about corticoid-dependent mechanisms of remote hippocampal damage and individual stress-reactivity underlying the risk of PSDD development.

PLANTS UNDER PRESSURE: DO NOT STEP ON THE GRASS!

P. Keringer, A. Garami

Institute for Translational Medicine, Medical School, University of Pecs, Pecs, Hungary.

patrik.keringer@aok.pte.hu

Stress is a general nonspecific biological response and it plays an important role not only in animals but in plants as well. Intensive research of plant stress has been conducted since the '90s, and this mini-review provides a brief summary about the topic. Plants may be affected by abiotic (e.g., heat stress, drought) and biotic (e.g., parasites, insects, fungi) stressors. In response to the stress, plants have many types of defence mechanisms like slowing down growth rate or dropping the leaves. Stress can cause several lesions in plants: they may respond to stress with change in shape or colour of the leaves. If the stressor is not ceased, plants will not develop further or die. The molecular mechanisms of stress are mostly known in plants. Namely, stress caused by the sunlight: ultraviolet rays trigger oxygen and energy production covering the needs of the organism, but excessive radiation facilitates free radical production causing damage or death of the cells. In the background, several signalling pathways work simultaneously, with molecules, which also have a role in animals (e.g., MAPK – mitogen-activated protein kinase, TOR – target of rapamycin). In response to stress, different hormones (similarly to humans and animals) help the plants to survive such as abscisic acid and auxin that influence plant growth. Understanding plant stress is very important. Because of the global climate change, several environmental stressors (e.g., forest fire, floods, and drought) destroy the flora resulting in acceleration of the climate change that may have severe consequences on human life. Genetically modified organisms (GMO) might be a solution for global warming because they could be resistant to different environmental effects; however, the safety of GMO-s is currently debated by the community. Nevertheless, stress in plants is the best example of nonspecific biologic response.

GENERAL ADAPTATION SYNDROME THEORY BY H. SELYE: AGEING PROCESS AND POSSIBILITIES FOR ITS INHIBITION

V. Khavinson

Saint-Petersburg Institute of Bioregulation and Gerontology, St. Petersburg, Russia.

v.kh.khavinson@infran.ru

Hans Selye described a general adaptation syndrome, which consists of several stages: alarm stage, resistance stage and the exhaustion stage. We suggested improving the resistance stage by using of physiologically active substances isolated from the thymus (Thymalin) and epiphysis (Epithalamin) of calves. The isolated substances were peptides with low molecular weight of up to 5000 Da. In addition, dipeptide Glu-Trp (Thymogen) was isolated and synthesized from peptide preparation Thymalin, and tetrapeptide Ala-Glu-Asp-Gly (Epitalon) was isolated and synthesized from Epithalamin. The implementation of these complex peptide preparations to animals in various experiments restored and boosted the stage of resistance. The 30-years study of the original peptide preparations and their synthetic analogues showed their ability to increase the average life expectancy of various animal species, reduce the incidence of tumor development, and enhance the function of the immune and antioxidant systems. It also increase melatonin concentration, increase the telomere length and the number of cell divisions, regulate gene expression and protein synthesis, as well as normalize many other vital body functions. Since the ageing process is characterized by a decrease in gene expression and corresponding proteins synthesis, it can be considered as a prolonged stage of resistance. Ageing is characterized by a decrease in the function of the immune system, pineal gland (a decrease in the concentration of melatonin in the blood), brain, endocrine and antioxidant systems, reproductive function, etc., and we suggested that administration of our peptides to people in the second half of life might lead to significant increase in life expectancy. Indeed, the use of Thymalin and Epithalamin in the elderly and senile patients allowed to partially restore the functions of the immune and endocrine systems, epiphysis, brain and reproductive system. Complete absence of allergic and other side effects should be noted, both during the administration period and in the long term. Studying the mechanism of action of these peptides, the possibility of molecular interaction between peptides and DNA, which is based on their complementary correspondence, has been established. Each peptide is capable of binding to a specific chemical structure of a specific gene. These results were obtained *in vitro*, i*n vivo*, as well as in human studies. In conclusion, our long-term (1973-2018) study showed that these peptides are able to restore and maintain the functions of the main organs and body systems, both during the resistance stage of the general adaptation syndrome and the aging process.

ASTAXANTHIN INHIBITS *HELICOBATER PYLORI*-INDUCED EXPRESSION OF INFLAMMATORY MEDIATOR IN GASTRIC EPITHELIAL CELLS

S.H. Kim, J.W. Lim, H. Kim

Department of Food and Nutrition, Brain Korea 21 PLUS Project, Research Center for Food, Nutrition & Foodservice Management, College of Human Ecology, Yonsei University, Seoul 03722, Republic of Korea.

cigdoli2@naver.com

Helicobacter pylori (*H. pylori*) induces NADPH oxidase-mediated reactive oxygen species (ROS) production, which leads to inflammatory cytokine production. In several cell lines, mitochondrial ROS produced by dysfunctional mitochondria act as signaling molecule to trigger inflammatory cytokine production. Astaxanthin (ASTX) is a potent anti-inflammatory agent that protects cells from oxidative stress. The present study was designed to determine whether oxidative stress-induced mitochondrial dysfunction is involved in *H. pylori*-induced inflammatory response, and to examine the effect of astaxanthin on *H. pylori*-induced inflammation. Human gastric epithelial cell line AGS was stimulated with NCTC11637 strain of *H. pylori* at bacterium/cell ration of 50:1. Level of ROS was measured by fluorescence assay, and IL-8 level was determined by PCR and ELISA. Mitochondrial membrane potential (MMP) and ATP level were monitored in order to determine mitochondrial dysfunction. DNA binding activity of NF-κB and PPAR-γ was measured by EMSA and protein level of antioxidant enzymes was determined by western blot analysis. In this study, *H. pylori* induced activation of NADPH oxidase and intracellular ROS production, and provoked ROS-mediated mitochondrial dysfunction in AGS cells. *H. pylori* increased level of mitochondrial ROS, eventually leading to NF-κB activation and IL-8 expression in AGS cells. ASTX pretreatment reduced intracellular ROS production, and inhibited *H. pylori*–induced loss of MMP and drop in ATP level. NF-κB activation and IL-8 expression were also decreased. ASTX activated PPAR-γ in *H. pylori*–stimulated AGS cells, and increased protein expression and enzymatic activity of its downstream catalase and SOD. These results suggest that ASTX suppresses IL-8 expression in *H. pylori*–stimulated AGS cells by reducing ROS production and subsequent mitochondrial dysfunction via antioxidant enzymes catalase and SOD.

CONTRIBUTION OF GLUCOCORTICOIDS TO GASTROPROTECTIVE EFFECT OF REMOTE ISCHEMIC PRECONDITIONING

O.P. Komkova, M.N. Sudalina, L.P. Filaretova

Laboratory of Experimental Endocrinology, Pavlov Institute of Physiology, Russian Academy of Sciences, St. Petersburg, Russia.
olkomkova@yandex.ru

Introduction: Remote ischemic preconditioning (RIPC) is one of the most effective non-invasive approaches to attenuate tissue injury caused by severe ischemia-reperfusion (IR). We previously demonstrated that glucocorticoids participate in protective effect of gastric ischemic preconditioning against IR-induced gastric injury. In the present study we investigated whether RIPC may protect the gastric mucosa against IR-induced injury through involvement of glucocorticoids. **Methods:** Anesthetized rats were exposed to prolonged gastric IR (30 min occlusion of celiac artery followed by 3 h of reperfusion) alone or with brief preliminary RIPC (10 min clamping the back-animal paw followed by 30 min reperfusion). The experiments were carried out: 1) in rats pretreated by the inhibitor of glucocorticoid synthesis, metyrapone (30 mg/kg, i.p), and in control animals; 2) in rats pretreated by glucocorticoid receptor antagonist RU-38486 (20 mg/kg, p.o.) and in control animals; 3) adrenalectomized rats without or with corticosterone replacement (4 mg/kg, s.c.) and in sham-operated animals. **Results:** IR induced corticosterone rise and resulted in the gastric injury and inflammation. RIPC significantly reduced the area of erosions and inflammation. Metyrapone or RU-38486 pretreatments had no effect on IR-induced gastric injury by itself but in both cases prevented the gastroprotective effect of RIPC and, moreover, further aggravated the deleterious effect of IR. Adrenalectomy potentiated IR-inflammation and partly attenuated beneficial effect of RIPC only against the gastric inflammation. Corticosterone replacement significantly reduced both erosion and inflammatory areas of gastric mucosa in adrenalectomized rats. **Conclusion:** The results suggest that glucocorticoids contribute to gastroprotective effect of RIPC.

Supported by: grant of Russian Science Foundation (RSF) № 19-15-00430.

ANTIOXIDATIVE STRESS IN NORMAL CELLS: GENERAL CONCEPT OR NON-SPECIFIC DRUG ACTION?

Ju. Kornienko, I. Smirnova, N. Pugovkina, Ju. Ivanova, A. Shatrova, N. Aksenov, V. Zenin, N. Nikolsky, O. Lyublinskaya

Institute of Cytology, Russian Academy of Sciences; St. Petersburg, Russia

o.lyublinskaya@mail.ru

Introduction: Several clinical trials have shown harmful effects of high-dosage antioxidant interventions. Antioxidative stress, defined as an overabundance of antioxidants in an organism that disrupts normal cell/tissue functions, is one of the concepts being discussed in this regard. At the same time, at the level of individual cells, phenomenology and outcomes of an acute antioxidative stress have not been specified yet. In this study, we focused on moving forward in getting this knowledge. **Methods**: Using immunoblotting, immunofluorescence, flow cytometry, and next generation RNA sequencing, we investigated the response of normal human cells (mesenchymal stem cells and fibroblasts) to high doses of different chemical substances with antioxidant activity (Tempol, resveratrol, N-acetyl-L-cysteine, diphenyleneiodonium). In this study we used high, but not cytotoxic antioxidant doses which are widely used in laboratory practice to protect cells from oxidative damage. **Results**: We found that all tested antioxidants blocked cell proliferation, hampered both initiation and progression of DNA synthesis phase and generated DNA strand breaks in cells replicating their DNA. Antioxidant treatments reduced the level and stability of the key molecular regulators of DNA synthesis, such as cyclin A, geminin and Emi1 proteins. Transcriptomic analysis of the mesenchymal stem cells exposed to Tempol and reseveratrol revealed the enrichment of ten pathways common for both antioxidants. Common pathways were related to the following categories: cell cycle, gene expression, chromatin organization, metabolism of proteins, and signal transduction. As a consequence of antioxidant-induced disturbances, the stress-induced premature senescence program was activated in cells underwent high-dose antioxidant treatments. **Conclusions**: In cultivated normal human cells, high doses of synthetic antioxidants induce an acute stress that damages proliferating cells and causes preliminary cell senescence. We hypothesize that the disturbances of redox-dependent DNA synthesis regulation, as well as protein metabolism can be considered as a potential driving force for this effect. We believe that it is important to take antioxidant-induced cell damage into account while developing a strategy of antioxidant administration in clinical practice.

Research is supported by the RSF Grant №19-14-00108.

MORE PUBLICATION-QUALITY DATA WITH LESS STRESS: NEW SOLUTIONS FOR SENSITIVE PROTEIN DETECTION BY MERCK

S. Kukla

Merck, Prague, Czech Republic

stanislav.kukla@merckgroup.com

Protein profiling technologies have become indispensable tools that are being used in all stages of research, including basic biomedical research dealing with established cell lines, emerging translational research and pre-clinical screening using various animal models and, finally, also in diagnostics where patient samples such as liquid biopsies or tissues are used. One of the hallmarks of current protein biomarker research is achieving higher sensitivity which can lead to identification of new potential biomarkers and elucidation of their role not only on the system, but also on the molecular level. In short, detecting the previously undetectable. This lecture will be an introduction to two innovative, antibody-based technologies for protein detection that can be applied in multiple stages of biomedical research and that have the power and sensitivity to provide completely new and unprecedented insights into complex disease biology, drug efficacy and drug safety and into mechanisms how cells and complete systems react to various external stimuli, including e.g. stress conditions. The first technique that will be discussed during this speech is Duolink® PLA which is based on the principles of proximity ligation assay (PLA) using a pair of target specific antibodies in combination with a massive signal amplification achieved by rolling circle amplification of an artificially inserted ssDNA. Duolink® PLA is a powerful and versatile tool for performing *in situ* analysis of antibody targets at their endogenous levels. Using this unique technology, you can detect, localize and quantify even proteins with low levels of expression and study protein-protein interactions and large complexes without the need to do any genetic modifications or overexpressions. The activation status of specific proteins or signaling pathways can be assessed in established cell lines as well as tissue sections and patient biopsies or xenografts. Duolink® PLA utilizes fluorescent detection and can be used with fluorescent microscopy or flow cytometry read-out. The second technique that will be briefly introduced during the talk combines a traditional and familiar immunoassay workflow and assay anatomy (such as for ELISA) with patented single molecule counting (SMC™) technology and enables the detection of low-abundance biomarkers in body fluids with unparalleled sensitivity and accuracy, capturing concentrations down to the femtogram/mL levels. You will learn about the principles how ultra-sensitivity in this emerging immunoassay technique has been achieved by combining improved sample preparation steps together with cutting-edge laser technology and special algorithms for signal analysis. Counting of individual fluorophore molecules in solution improves signal-to-noise ratios and can lower the limits of detection by two or three orders of magnitude when compared e.g. to classical ELISA, opening completely new horizons in protein biomarker research not only in cancer, but mainly in immunology and neuroscience. Discovery depends on detection. And when your research requires detection of the previously undetectable, this is the lecture to attend.

INDOMETHACIN-INDUCED SMALL INTESTINAL DAMAGE AND BILE ACID ALTERATIONS IN THE RAT

B. Lázár[1], S. B. László[1], B. Hutka[1], Á. Kemény[2], Z. Helyes[2], K. Gyires[1], Z. S. Zádori[1]

[1]Department of Pharmacology and Pharmacotherapy, Faculty of Medicine, Semmelweis University, Nagyvárad tér 4, 1089, Budapest; [2]Department of Pharmacology and Pharmacotherapy, University of Pécs, Szigeti út 12, 7624, Pécs, Hungary

lazar.bernadette@med.semmelweis-univ.hu

Introduction: The non-steroidal anti-inflammatory drugs (NSAIDs), which are among the most commonly used medications, besides damaging the gastric and duodenal mucosa can also cause small intestinal ulceration. The pathomechanism of this enteropathy is complex involving several factors, like inhibition of cyclooxygenase (COX) enzymes, reduced mucosal epithelial integrity, enterohepatic recirculation of the compounds, as well as the cytotoxicity of luminal bacteria and bile. NSAIDs enhance the cytotoxicity of bile, at least partly by individual BAs. In this study, we aimed to analyze the time course of the mucosal damage and BA alterations induced by indomethacin, a non-selective COX inhibitor, in the rat. **Methods:** Male Wistar rats (180-200 g) were treated with indomethacin (20 mg/kg, per os) or with its vehicle (1% hydroxyethylcellulose). After 24, 48 and 72 hours all rats were anaesthetized by inhalation of CO_2, their distal small intestines were examined macroscopically, and the tissue levels of pro- and anti-inflammatory cytokines were analyzed. The luminal concentration of different BAs in the jejunum was measured by mass spectrometry. **Results:** The jejunal levels of inflammatory cytokines showed similar upregulation at all time-points, while the severity of macroscopic alterations (reduction of animal weight and intestine length) increased by time. In parallel, the intestinal levels of several hydrophilic BAs (α- and β- muricholic, ursodeoxycholic acids) were decreased, whereas the hydrophobic deoxycholic acid was elevated. The changes in BA levels showed distinct time-related patterns. The amount of ursodeoxycholic acid correlated negatively with the inflammatory markers. Indomethacin significantly increased the proportion of conjugated BAs at all time-points. **Conclusion:** We have demonstrated that indomethacin altered substantially the levels of numerous BAs, in parallel with the mucosal damage. The decreased proportion of hydrophilic BAs may contribute to the pathogenesis of enteropathy. The elevation of conjugated BAs may be due to changes in the microbiota composition, but further studies are needed to confirm it.

The research was supported by NKFI FK 124878, STIA-KF-17.

WATER IMMERSION SHORT-TERM STRESS IN TWO RAT STRAINS DIFFERING IN THE NERVOUS SYSTEM EXCITABILITY THRESHOLD

A.S. Levina[1], N.A. Bondarenko[2], N.V. Shiryaeva[1], A.I. Vaido[1], N.A. Dyuzhikova[1]

[1]I.P. Pavlov Institute of physiology RAS, Saint-Petersburg, Russia; [2]RPC OpenScience Ltd, Moscow, Russia.

anna.avia@gmail.com

Introduction: Rats are known to be natural swimmers, which allows to use them in laboratory research in swimming and diving tasks. Nevertheless, it's being disputed whether water immersion, swimming and diving are stressful for rodents. It's also interesting if the constitutive features of the animal's nervous system – inborn strain traits in particular – affect it. Thus, the aim of the present study was to evaluate the behavior of two rat strains differing in the nervous system excitability threshold in the «Extrapolation escape task», where animals had to solve an escape task by diving in a potentially stressful situation of immersion into water. **Methods:** We used adult male rats from two rat strains differing in the nervous system excitability threshold as an object: HT strain («high threshold», 76th selected generation) had low excitability level; LT strain («low threshold», 66th selected generation) had high excitability level. The two strains were selected in the end of 1970-s and are since then maintained in the laboratory of higher nervous activity genetics (I.P. Pavlov Institute of physiology RAS, Saint-Petersburg, Russia). The strains are known to display several physiological characteristics bound up with excitability level and related to stress. The «Extrapolation escape task» apparatus (OpenScience, Russia) includes a water tank and a transparent narrow vertical cylinder fixed inside the tank and immersed to water with its bottom edge. The rat is placed to water inside the cylinder and can escape from it only by diving under its bottom edge. Then, after a dive, the rat is immediately removed from water. The procedure is repeated in two hours to check out the acquisition of the escape skill. **Results:** We found an inter-strain difference in the swimming and diving behaviors in the «Extrapolation escape task». LT rats successfully solved the escape task in both trials, finding a way to escape fast, while HT rats tried to jump or climb to the upper edge of the cylinder in the beginning of each trial before finding a way to dive. As the cylinder was tall and its walls were smooth climbing didn't permit rats to escape from it. However, the ineffective jumping behavior in HT rats significantly increased from first to second trial, making it much less likely for HT rats to solve the escape task. As the jumping strategy in this model usually correlates with anxiety, the probable causes of this inter-strain behavioral difference are different sensitivity of two rat strains to water immersion or particularly diving as a stressor, or their different short-term stress response dynamics resulting from their strain characteristics including different anxiety levels. **Conclusion:** We assume that the behavioral difference in the strategies of two rat strains in the «Extrapolation escape task» results from their different reaction to short-term water immersion stress and is related to their nervous system excitability level.

The reported study was funded by RFBR according to the research project № 18-34-01024.

SUPRASPINAL CONTROL OF VISCERAL NOCICEPTION IN INFLAMMATORY BOWEL DISEASE: PATHOLOGICAL ALTERATIONS AND THEIR PHARMACOLOGICAL TARGETING

O. Lyubashina [1,2], I. Sivachenko [1], I. Busygina [1], S. Panteleev [1,2]

[1] Pavlov Institute of Physiology of the Russian Academy of Sciences, Saint Petersburg, Russia; [2] Valdman Institute of Pharmacology, Pavlov First St. Petersburg State Medical University, St. Petersburg, Russia.

lyubashinaoa@infran.ru

Introduction: Recurrent abdominal pain is the most distressful symptom of inflammatory bowel disease (IBD), which disturbs patients even during remission. There is growing body of evidence, suggesting that a dysfunction of supraspinal, in particular serotonergic, control of visceral nociception plays a role in the development of chronic pain state in IBD. However, the precise neurophysiological mechanisms underlying such control as well as alterations in them occurring under intestinal pathology remain poorly investigated, hampering the development of effective IBD pain management. **Aims:** The objectives of this study were to determine changes in neuronal activity of the visceral pain-related supraspinal sites after the induction of colonic inflammation and to examine possible options for their pharmacological modulation. **Methods:** Experiments were performed in two groups of urethane-anesthetized adult male Wistar rats – healthy control or with trinitrobenzenesulfonic acid-induced experimental colitis. All procedures were approved by the Local Animal Care and Use Committee. For inducing abdominal pain, the mechanical distension of the colorectum (CRD) by inflating a rubber balloon to a pressure of 80 mmHg was applied. The neuronal activity of studied supraspinal structures was extracellularly recorded by stereotaxically lowered tungsten microelectrodes. In separate experimental series, the background and CRD-evoked discharges of the recorded neurons were estimated before and after intravenous injections of serotonin 5-HT1A receptor agonist buspirone (1-3 mg/kg), 5-HT3-antagonist granisetron (1-2 mg/kg), 5-HT4-mimetic BIMU8 (1-2 mg/kg) or saline. **Results:** In viscerosensory nuclei of the caudal medulla and in the midbrain central gray (MCG) of both healthy control and colitic rats, the neurons responding to noxious CRD in a specific mode were revealed. In the presence of colitis, an enhancement of CRD-evoked activation of these neurons was observed in the medullary structures as well as in the MCG. Intestinal inflammation was also associated with increased excitatory and decreased inhibitory action of the MCG on visceral pain transmission at the caudal medullary level. The augmented excitability of the medullary and MCG visceral nociceptive neurons in colitis could be substantially suppressed with a systemic administration of 5-HT3-blocker granisetron, whereas 5-HT1A-agonist buspirone and 5-HT4-mimetic BIMU8, which are known to initiate inhibitory serotonergic processes, were ineffective under these conditions. **Conclusion:** These findings indicate that intestinal inflammation is associated with the enhanced excitatory control of visceral nociception within the caudal medulla and midbrain central gray, which appeared to be serotonin 5-HT3 receptor-dependent. The supraspinal alterations revealed can be responsible for persistence of visceral hypersensitivity and be a potential target in the treatment of IBD-related chronic abdominal pain.

This work was supported by the Russian Foundation for Basic Research (grant number 18-015-00055) and by the Program of Fundamental Scientific Research of State Academies for 2013-2020 (GP-14, section 64).

NOVEL HUMANIZED MODEL FOR PHARMACOLOGICAL RESEARCH: GENERATING HUMAN SOMATOSTATIN RECEPTOR 4 (HSSTR4) EXPRESSING TRANGENIC MICE

B. Nemes[1], K. Bölcskei[1,2], T Aczél[1,2], A. A. Alkurdi[1], Y. Abuawwad[1], A. Dinnyés[3], J. Kobolák[3], Z. Sándor[1], E. Pintér[1,2], Zs. Helyes[1,2]

[1]Department of Pharmacology and Pharmacotherapy, University of Pécs Medical School, Hungary; [2]Centre for Neuroscience & Szentágothai Research Centre, University of Pécs, Hungary; [3]BioTalentum Ltd, Gödöllő, Hungary.

balazs.nemes@aok.pte.hu

Introduction: We discovered that the somatostatin 4 receptor (sst_4) mediates analgesic, anti-depressant and anti-inflammatory functions of somatostatin without endocrine actions. This proposed new drug developmental perspectives and small molecule sst_4 agonists are currently tested. Sst_4 was shown to be present in pain and mood-related brain regions of the mouse, but its expression and function in humans is not known. **Methods**: We constructed a PiggyBac transposon vector containing human chromosomal fragment with the SSTR4 gene that also expresses the Luciferase-tdTomato reporter fusion protein. P2A self-cleaving site ensures that the human sst_4 is expressed separately from the reporter fusion protein not affecting the function. We did transgenesis in SSTR4-deficient mice and one transgenic female was obtained which had offsprings. This first-generation mother had several copies of the randomly inserted transgene. We bred mice carrying one copy of the transgene. With ligation-mediated PCR, we located 3 copies on chromosome 3, 10 and X, and there are 2 lines with yet unknown locations of their transgenes. **Results**: In vivo imaging showed Luciferase luminescence in the brain with the strongest signal in the bulbus olfactorius, but tdTomato was not detectable either in vivo or on histological sections. In the elevated plus maze sst_4 mice spend less time in the open arms showing greater anxiety compared to wild types, but insertion of the human SSTR4 gene reversed this anxious phenotype providing evidence for its functionality. **Conclusion**: The results are promising, the human transgenes are proved to be expressed, the human receptor is showed to be functional. After further testing, this novel humanized model can be very useful for detecting pathology-related expression changes and the effect of our novel sst_4 agonists.

Acknowledgements for support**:** Richter Gedeon Talentum Foundation; KTIA_NAP_13-2-2014-0022, KTIA_NAP_13-1-2013-0001; GINOP-2.3.2-15-2016-00050, EFOP-362-16-2017-00008; 20765-3/2018/FEKUTSTRAT

ASSOCIATION OF CLOCK GENETIC VARIANTION WITH STRESS RESPONSE IN SCHOOLCHILDREN

D. Petrashova, S. Kolomeichuk, R. Mikhaylov

Kola Science Centre, Russian Academy of Science, Apatity, Murmansk region, Russia

dinapetrashova@mail.ru

Introduction: The population living in Far North prone to complex changes in the body, so-called "polar tension" syndrome, the most important manifestations of which are mental stress, desynchrony and sleep disorders. Extreme light fluctuations (polar day and polar night) undoubtedly affect the quality and duration of sleep, and the individual response to this effect is determined by individual psycho-physiological features and ability to spatio-temporal organization (chronotype). The identification of sleep problems among schoolchildren living in the High North is especially important for the effective prevention of sleep disorders and improvement in the performance of this group of the population. It is known that, in people in an emotional state, the sensitivity of the genome to genotoxic effects is greatly increased. The response to stress and stressful situations is individual and depends on the degree of genetic predisposition. Objective: to evaluate the frequency of cytogenetic disorders in schoolchildren with different chronotypes. **Methods:** 77 schoolchildren aged 15-17 were surveyed. Each subject signed an informed consent to the study. Testing conducted: SAN, Spielberg-Hanin test, PSQI and Horne-Ostberg chronotype test. Buccal epithelium sampling and preparation was carried out according to standard methods. DNA was isolated from 200 µl of children's saliva using the DiaGene genomic DNA extraction kit (Dia_M Russia). A section of the CLOCK, ACE and PER3 genes was amplified by the polymerase chain reaction. The significance of differences in the frequencies of alleles and genotypes in the groups was assessed using the $\chi 2$ test. The significance level was considered to be $p < 0.05$. **Results:** According to PSQI testing, most of the children had an intermediate chronotype (53% of boys, 60% of girls). In boys, the average level of situational anxiety was more pronounced (67%), while in girls the level of average and high level of anxiety was the same (43%). The average values of the frequency of cells with micronuclei in the studied groups did not differ significantly and did not exceed the values for the average population norm of 2-4%. When analyzing the frequency of occurrence of cytogenetic abnormalities in buccal epithelial cells with different chronotypes according to the MEQ-SA questionnaire, no significant differences were found. Significant differences in the frequency of occurrence of cells with karyorrhexis were identified for children with moderately evening and intermediate, moderately evening and definitely morning chronotypes; and in terms of the frequency of occurrence with karyopicnosis, for moderately evening and definitely morning, intermediate and definitely morning chronotypes. The analysis of the occurrence of cytogenetic disorders in different variants of polymorphic genes (*ACE, PER3, CLOCK*) was carried out. It was shown that with the variant of the ACE gene ID, the frequency of occurrence of cells with protrusions was significantly higher than with the variant DD. The frequency of occurrence of cells with micronuclei and chromatin condensation is significantly higher in 4/4 carriers of the *PER3* gene relative to heterozygotes. **Conclusion:** It has been shown that with the CC variant of the *CLOCK* gene, the frequency of occurrence of cells with micronuclei and karyopynosis is significantly higher.

THE ROLE OF MELANOCORTIN PEPTIDES IN THE REGULATION OF THE STRESS RESPONSE

I. Romanova, A. Mikhrina, E. Mikhailova

Sechenov Institute of Evolutionary Physiology and Biochemistry Russian Academy of Scienses,
St. Petersburg, Russia.

irinaromanova@mail.ru

Introduction: In the brain the neurons of the arcuate hypothalamic nucleus (ARC) is express a proopiomelanocortin (POMC) from which melanocortin peptides are formed (α-, β- and γ-MSH). Their action in the brain is realized through melanocortin receptors 3 and 4 (MCR3/4). In the neurons of the ARC is also expressed agouti-gene related peptide (AgRp), which is an endogenous antagonist of MCR3/4. The establishment of morpho functional interrelations of the melanocortin system with monoaminergic neurons (dopamine-, norepinephrine-, serotonergic), which are known to be involved in the stress response, is an important physiological problem, which contributes to understanding the integrative interactions of various neurochemical systems of the brain during stress. **Methods:** For the study a single (ABC- method), double fluorescence immunostaining, light and confocal microscopy, Western blotting, high performance liquid chromatography (HPLC), and behavioral analysis («open field» test) were used. **Results:** We showed the expression of MCR3 and 4 in the dopaminergic neurons of the midbrain, norepinephrine neurons of the locus coeruleus, serotoninergic neurons of the raphe nucleus. In experiments in vitro on brain slices and in vivo (stereotaxic injection of peptides to the midbrain and locus coeruleus), we showed an inhibitory effect of active fragments of AgRp (25-51 and 83-132) on the activity of tyrosine hydroxylase, an enzyme of the biosynthesis of dopamine and nnorepinephrine, as well as a decrease in dopamine and norepinephrine in the striatum. It was established that the rats, divided in the «open field» test into active and passive, difference in the level of AgRp, which negatively correlated with the level of tyrosine hydroxylase activity. An increase in the level of AgRp in passive rats was revealed, which corresponded to a lower level of tyrosine hydroxylase compared with that in active rats. **Conclusion:** The obtained results demonstrate the morpho functional interrelations between the melanocortin and monoaminergic systems of the brain and the role of the melanocortin peptides in the adaptive reactions of organism under stress.

This work was supported by FANO (№. AAAA-A18-118012290427-7).

THE RISK FACTORS OF THE OF FORMATION OF ACUTE LESIONS OF THE GASTROINTESTINAL TRACT IN HUMAN.

D. Sakhno[1], A. Efimov [2], B. Sigua[2], E. Zakharov [2], A. Grinev[2]

[1]The Yaroslav-the-Wise Novgorod State University, Institute of Medical Education, Veliky Novgorod, Russia; [2]North-Western State Medical University named after I. I. Mechnikov, St. Petersburg, Russia.

denis_sahno@mail.ru

Introduction: The task in the study was to establish risk factors for the formation of acute gastrointestinal ulcers in patients with a surgical profile based on a retrospective analysis of the clinical material, considering a primary and concomitant pathology and their complications. **Materials and methods:** The analysis of the clinical material from St. Elizabeth Hospital of St. Petersburg, collected during the period from 2010 to 2016, was performed. The data was mainly collected from patients hospitalized in surgical departments with suspected acute surgical pathology, as well as in patients with trauma. 284 clinical observations of discharged patients and 54 deceased patients were analyzed. **Results:** The results of the analysis show that, peptic ulcers of the upper gastrointestinal tract predominated in these patients. Ulcers had a predominantly complicated course: mainly bleeding, rarely perforation. It has been revealed that the predisposing factors of development of acute ulcer pathology, risk factors, include the presence of concomitant cardiovascular pathology, the use of non-steroidal anti-inflammatory drugs, intoxication, age over 75 years, and ulcers in the anamnesis. In the case of surgical treatment, less traumatic organ-sparing operations prevailed, such as suturing a bleeding vessel (51.4%) and closure of perforation (31.5%) when analyzed a conservative treatment tactics. The overwhelming number of patients (99.2%) with acute ulcers of the upper gastrointestinal tract received antisecretory therapy (H2-histamine blockers and or proton pump inhibitors). However, only 68.5% of patients received proton pump inhibitors. Among patients with acute ulcers of the upper gastrointestinal tract, complicated by bleeding, proton pump inhibitors also received only 69.2%. All patients with complicated ulcers of the lower gastrointestinal tract (small and large intestine) received antibiotic therapy. Correction of dysbiosis was not carried out. Among the patients who died, acute ulcers were complicated in all cases and were localized mainly in the stomach and duodenum. Bleeding prevailed in 68.5% cases. Perforations were observed in 31.5% of cases. In patients who have died due to the severity of their condition, it is extremely difficult to clearly identify the predisposing factor. In this case, the obvious risk factor is the old age of patients (men and women). Pneumonia, bleeding, acute cardiovascular insufficiency, pulmonary thromboembolism (PE) and intoxication dominated the causes of death. **Conclusion:** The results of the analysis indicate that the ulcerative pathology of the gastrointestinal tract remains a serious problem requiring the continuation of intensive basic research.

THE EFFECT OF CHRONIC RESTRAINT STRESS ON GLUCOSE ABSORPTION IN THE RAT SMALL INTESTINE

E. V. Savochkina[1], N. M. Grefner[2], A. A. Gruzdkov[1], A. S. Alekseeva[1], Yu. V. Dmitrieva[1], L. V. Gromova[1]

[1]Pavlov Institute of Physiology, RAS; [2] Institute of Cytology, RAS, St. Petersburg, Russia.

savochkinaev@infran.ru

Introduction: Stress has a significant effect on energy metabolism, including glucose absorption in the small intestine. An important step of glucose absorption is its transfer through the apical membrane of the enterocytes. Two glucose transporters are involved in this process: the Na^+-dependent transporter (SGLT1), and the transporter by facilitated diffusion (GLUT2). However, a response of the glucose absorption system in the small intestine to stress (acute or chronic), both in the nature of the reaction, and in the relative involvement of the SGLT1 and GLUT2 in this response, is not clear enough. The evaluation in experiments on rats the effect of chronic restraint stress, caused by moderate immobilization of the animals (at lowed or room temperature), on the glucose absorption from the small intestine, as well on the content of glucose transporters SGLT1 and GLUT2 in the apical membrane of the enterocytes. **Methods:** Rats (Wistar, males) were daily subjected to moderate immobilization for three hours at room (+20–22 °C) or lowed (+5–6 °C) temperatures. After 3, 10 and 16 days of the experiment the glucose absorption in the small intestine was evaluated on the rate of free consumption of glucose solution (200 g/ l) by previously fasted animals. In addition, some animals after their decapitation were sampled tissue from the jejunum to determine the content of SGLT1 and GLUT2 in the enterocytes of the apical membrane using immunohistochemistry and confocal microscopy. **Results:** Chronic immobilization of the rats for 3 days at a temperature of +20–22 °C caused an increase of glucose absorption in the small intestine in 8% ($P < 0.05$) compared with the control (in the absence of immobilization). This increase was accompanied by an increase in the content of the SGLT1 and by a tendency to an increase in the content of the GLUT2 in the apical membrane of enterocytes in the jejunum. Normalization of these indicators was observed 10 and 16 days after the start of the stress. At a temperature of +5–6 °C glucose absorption increased by 28% ($P < 0.05$) after 3 days of chronic stress and remained at this level after 10 and 16 days of the stress. At the same time, the content of the SGLT1 increased and there was a tendency to increase of the content of the GLUT2 in the apical membrane of enterocytes in the jejunum. **Conclusion:** On rats, as an experimental model, it was shown that chronic restraint stress increased glucose absorption in the small intestine. This increase was mainly due to an increase in the content of the SGLT1 in the enterocyte apical membrane. Lowering the ambient temperature enhanced the response of the glucose absorption system and the glucose transporters SGLT1 and GLUT2 in the apical membrane of the enterocytes of the small intestine to the chronic restraint stress.

This work was supported by the Program for Fundamental scientific research of state academies for 2013–2020 (GP - 14, section 64).

EFFECTS OF KETAMINE AND STRESS ON THE NEUROTROPHIN RECEPTORS EXPRESSION

E.V. Shaburova[1,2], **Lanshakov D. A.**[1,2]

[1]Institute of Cytology and Genetics SB RAS, Novosibirsk, Russia; [2]Novosibirsk State University, Novosibirsk, Russia.

sliza.nsk@gmail.com

Introduction: Ketamine, an NMDA receptor antagonist, exhibits a rapid antidepressant activity and involved in structural and synaptic plasticity, but the precise mechanisms of these effects remain unknown. There are many pieces of evidence suggesting neurotrophins and their receptors such as Trk and p75NTR involvement in ketamine effects. Members of Vps10p family of sorting receptors SorCS1, SorCS2 and SorCS3 are also engaged in neurotrophin effects. In the present study, we investigated whether ketamine and stress affect mRNA expression of *bdnf* and neurotrophin receptors *sorcs1-3, p75, trkb* and *trkc* in the different brain areas, associated with depression. **Methods:** Adult male Wistar rats were treated with ketamine (15 mg/kg body weight, i.p.) or saline. Two hours later, half of the animals of each group were subjected to the stress exposure (tail suspension test) for 6 minutes. One hour after, samples of the tissue from different brain area (prefrontal cortex, midbrain and stem) of stressed and unexposed to stress rats of both groups were harvested for measurement of mRNA level by real-time RT-PCR. Statistical differences were determined by two-way ANOVA followed by Fisher's least significant difference *post hoc* analysis. **Results:** In the prefrontal cortex, ketamine and stress both suppressed the expression of SorCS3 mRNA without summing of these effects. However, the levels of SorCS1 and p75 mRNA in the midbrain significantly decreased only after combined ketamine administration and tail suspension test, comparative to saline control. No significant effect neither ketamine nor stress on the SorCS2, TrkB and TrkC expression was observed. The level of BDNF mRNA significantly increases after ketamine treatment in the cortex regardless to stress, unlike in the brainstem, where only stress exposure without ketamine induces BDNF expression. **Conclusion:** Pretreatment with ketamine and acute stress both caused changes in neurotrophin receptors and BDNF gene expression in examined brain areas. These findings surmise that SorCS1, SorCS3 and p75 receptors implicated in the ketamine-induced neuroplasticity and antidepressant activity.

DYNAMICS OF PHYSIOLOGICAL COMPONENTS OF THE MENTAL STATUS UNDER EXPOSURE STRESS FACTORS IN MEN OF AGE 20–30 WITH DIFFERENT LEVELS OF PHYSICAL TRAINING

I.B. Sivachenko[1,2]

[1]Pavlov Institute of Physiology, Russian Academy of Sciences, St. Petersburg, Russia; [2]Research Institute of Hygiene, Occupational Pathology and Human Ecology, Federal Medical Biological Agency of Russia, St. Petersburg, Russia.

avans_d@mail.ru

Introduction: Living conditions in modern society require that young people are capable to adapt to a variety of stress factors. Exposure of young people to stress factors is steadily growing and this decreases the adaptive capacity. It is shown a high physical training level favors optimization of the functional status in difficult and extreme situations. However, some scientific ideas about how exposure to stress factors affects the functional status of people with different levels of physical training are still having to be understood in more concrete terms. The purpose of the work was to study dynamics of the physiological components of the functional status under the influence of stress factors in men 20–30 years old with different levels of physical training. **Methods:** The simulated situation implied solution of a complicated task for cognitive performance (Gorbov–Schulte dual-task method) under the conditions of compressed time frame, interferences, and motivational significance. Continuous, consecutive registration of functional status indicators was carried on a Medikom Egoscop instrument. **Results and conclusion:** It is shown that systematically physically trained persons have a higher adaptive potential of the cardiovascular system to stress factors than professional athletes and persons who do not do fitness and sports. Among the three groups, untrained persons showed a non-optimal control of heart rate and electrical activity of the skin on exposure to stress factors.

CRITERIA OF STRESS AND ADAPTATION ACCORDING TO THE DATA FROM ELECTROENCEPHALOGRAPHY AND SUPER SLOW BRAIN ACTIVITY

M.A. Skedina, A.A. Kovaleva

Institute of Biomedical Problems of the Russian Academy of Sciences, Moscow, Russia.

skedina07@rambler.ru

Introduction: The search for reliable prognostic criteria and methods for evaluating patterns of higher nervous activity is relevant for predicting the reliability of human behavior in extreme situations. The change in the functional activity (FA) of the brain is accompanied by the shift in cerebral energy metabolism, which reflects such an indicator as the level of constant potential (LCP). Its main source is the hemato-encephalic barrier and vascular potentials of cerebral origin, which are closely related to the acidity of the blood. Because of this, LCP is associated with a complex of clinical, biochemical, and immunological parameters characterizing the body's energy inputs and the functional state of its adaptive systems. **Methods:** To assess current FA of the brain, we used the method of synchronous recording of classical electroencephalogram (EEG) and LCP. Recording was made within 10 minutes with eyes closed in the state of calm wakefulness. The indicators were recorded from the surface of the scalp in 7 unipolar leads. The leads used correspond to the standard EEG leads of the international 10-20 system. The EEG evaluated indicators of the alpha rhythm, presence of amplitude asymmetry, spectral, frequency and amplitude characteristics. To analyze the statistical differences of averaged over all leads value of the LCP record (-100; +100 mV) were divided into segments of 20 sec, which were averaged then over time. Before examination, the rapid assessment of the level of the CNS activation was performed – the test “simple visual-motor reaction”. This method has been used: on autotraining –14 people, within electro- and audiovisual stimulation to restore psychological state of patients after stress (28 patients), in the study with 520-day isolation – the “Mars-500” project, within studies in extreme environmental conditions – the project “Climate”, conducted in IBMP. **Results:** The development of a stress reaction begins with the shift of alpha activity anteriorly, an increase in its frequency within 1-2 Hz with decrease in the index and increase in disorganization, accompanied by increase in LCP over the entire surface of the brain. The prevalence of alpha activity in the right hemisphere (more 50%) accompanied by decrease of LCP in the same hemisphere indicates the most pronounced stress reaction and reaching the limit of the level of adaptive capacity. Absence: the shift of alpha activity in the right hemisphere, increase in rhythm frequency by more than 1 Hz and pronounced interhemispheric asymmetry in the LCP distribution topography, allowed to predict high level of adaptation capabilities among respondents and low probability of depletion of adaptation reserves according to neuro-functional correlates. Development of the state of fatigue is accompanied by decrease in the dominant frequency of theta activity, increase in the power of alpha activity, and a slight decrease in the average value of LCP. **Conclusion:** The joint registration of LCP and EEG is one of the objective methods for assessing the peculiarities of the neurophysiological state of a person and can be used in people of extreme professions to predict the reliability of a person under extreme conditions.

THE EFFECTS OF SHORT-TERM AND LONG-TERM ACTION OF DEXAMETHASONE ON CRF-1 AND CRF-2 RECEPTORS IN THE GASTROINTESTINAL TRACT

M. Sudalina

Laboratory of Experimental Endocrinology, Pavlov Institute of Physiology, Russian Academy of Sciences, St. Petersburg, Russia.

sudalina@infran.ru

Introduction: It has been shown previously in our laboratory that the single injection of dexamethasone at the same dose (1 mg/kg) may attenuate or aggravate indomethacin-induced gastric erosions depending on the time of the hormonal action: attenuate in 1 h and aggravate in 24 h after dexamethasone injection. However, dexamethasone did not aggravate indomethacin-induced small intestine lesions. It's well known that dexamethasone inhibits the HPA axis, leads to a decrease of corticosterone level and an increase of CRF production. However, the involvement of the CRF-1 and CRF-2 signaling pathways in the transformation of gastroprotective effect of dexamethasone to proulcerogenic action remains unknown. The aim of this study was to evaluate the effects of short-term (1h) and long-term (24 h) action of dexamethasone on CRF-1 and CRF-2 receptors in the gastric and intestinal mucosa. **Methods:** The expression of CRF-1 and CRF-2 receptors was detected in the gastric corpus and small intestine (ileum) of rat by a immunohistochemical staining technique using CRF-1 (Thermo Fisher Scientific, 1:50) and CRF-2 (Abcam, 1:100) receptor antibodies in 1 h and 24 h after dexamethasone administration. The results of the staining were assessed by a morphometric study of microscopic images in five fields of view using the Image J software. A relative stained area was estimated (a ratio of stained area to selected area, %). For statistical data analysis we used the one-way ANOVA followed by post hoc Student-Neuman-Keuls criteria. **Results:** In the stomach a short-term dexamethasone action (1 h) led to a decrease of CRF-1 receptors expression, but not CRF-2 one. A long-term dexamethasone action (24 h) provoked an increase of CRF-2 receptors level extended throughout the entire fundus glands of gastric mucosa. In the small intestine a short-term effect of dexamethasone led to an increase of CRF-2 receptors expression, while a long-term dexamethasone action provoked a decrease of CRF-1 receptors in the intestinal mucosa. **Conclusion:** An inhibition of the HPA with dexamethasone leads to a decrease of CRF-1 and an increase in CRF-2 peripheral receptors, regardless of the duration of dexamethasone action. The short-term and long-term dexamethasone action induces an opposite effect on CRF-1 and CRF-2 in the gastric and intestinal mucosa. Thus, the changes of peripheral CRF receptors caused by dexamethasone suggest their involvement in the transformation of the gastroprotective effect of glucocorticoids into ulcerogenic one.

Supported by grant of Russian Science Foundation (RSF) N 19-15-00430

ANALYSIS OF EXPRESSION OF PROINFLAMMATORY CYTOKINES IN REGIONS OF RAT HIPPOCAMPUS IN EARLY PERIOD AFTER TRAUMATIC BRAIN INJURY

L.V. Tretyakova, M.N. Volobueva, I.G. Komoltsev, A.A. Kvichansky, A.P. Bolshakov, N.V. Gulyaeva

Institute of Higher Nervous Activity and Neurophysiology of RAS, Moscow, Russia.

kind.dr.lee@gmail.com

Introduction: Traumatic brain injury (TBI) is the leading cause of disability in young people around the world. Affective disorders, memory impairment and dementia are common secondary disorders in patients with TBI. Similar data were obtained in the experimental models of TBI in animals. Severe stress and neuroinflammation, which is one of its components, are considered as important elements of the pathogenesis of hippocampal dysfunction after TBI, and the dorsal (DH) and ventral (VH) parts of the hippocampus have different sensitivity to damage. Here, we studied the development of the neuroinflammation after TBI in DH and VH. **Methods:** We used the lateral hydrodynamic impact model as a model of traumatic brain injury in rats. The rats at 1, 3, 7, and 14 days after TBI were decapitated; the samples of DH and VH were isolated from the ipsi- and contralateral hemispheres relative to the site of impact and frozen in liquid nitrogen. Total RNA from the samples was used to study the expression of pro-inflammatory cytokines Il1b, Il6, and Tnf. **Results:** We showed that the expression of Il1b mRNA after TBI in DH and VH of both hemispheres increased compared with the sham operated animals (SO) from the first day after TBI and in the ipsilateral hemisphere on day 1 it was significantly higher than in the contralateral one. In ipsilateral DH and VH and in contralateral DH, it remained elevated compared to SO animals until the 7th day after TBI. In addition, by day 14, the expression of Il1b mRNA in all samples of experimental and SO animals was higher than in the intact animals. The expression of Il6 mRNA increased in ipsilateral DH and VH and in contralateral DH on the first day compared to SO animals, but the later returned to the control level, except for ipsilateral DH, where the secondary increase in the expression was observed on day 7 after TBI. Tnf mRNA expression increased in ipsilateral DH and VH and in contralateral DH on the first day compared to SO animals, after which it returned to the level of SO animals on the 3rd day in the contralateral hemisphere and by the 14th day in the ipsilateral hemisphere. However, in the ipsilateral VH of SO rats, the expression of Tnf mRNA significantly increased on the 14th day compared with intact animals. **Conclusion:** Thus, we showed the presence of a fading wave of neuroinflammatory activity in the rat hippocampal regions after TBI. DH and VH of the ipsilateral hemisphere showed a similar reaction to TBI, whereas in the contralateral hemisphere DH responded stronger than VH.

IMPACT OF FORCED SWIM STRESS ON THE RATS' CAPACITY TO SOLVE THE WATER ESCAPE TASK

M. Tur, I. Belozertseva

Pavlov First Saint Petersburg State Medical University, Valdman Institute of Pharmacology, St. Petersburg, Russia.

vol4onok_07@mail.ru

Introduction: The Water Escape Test (WET) is used to assess the cognitive abilities of animals in acute stress conditions. The WET allows to analyze individual differences in the style of problem solving, training and skill retention. The present study was aimed to indicate the impact of the forced-swimming experience (FSE) on the WET performance (IACUC protocol # 100_IP1_1218/21_300). **Methods:** Male Wistar rats were kept in groups of 4 animals in TIV cages with free access to food and water. The rats were randomly assigned into six experimental groups: Control group (Gr_C; n=12): no FSE; Group 1 (Gr_1, n=7): WET was performed 1 day after FSE; Group 2 (Gr_3, n=8): WET was performed 3 days after FSE; Group 3 (Gr_5, n=8): WET was performed 5 days after FSE; Group 4 (Gr_7, n=8): WET was performed 7 days after FSE; Group 5 (Gr_14, n=7): WET was performed 14 days after FSE. The glass cylinders (d=20 cm; h=40 cm, water - 24 °C, depth - 30 cm) were used for FSE. The animals were placed into the cylinders for 15 minutes. WET was performed in the water (24°C) tank (d=35 cm, h=38.5 cm) with a transparent tube in the centre (d=10 cm, h=22.5 cm, immersing - 2.5 cm). The tank was supplemented by vertical stairs (11.5 cm x 38.5 cm). The tube could be escaped with diving, the pool - by stairs. The rats were placed into the tube (for up to 3 min) for three times (Trials 1-3) with intervals of 15 min. The behaviour was videotaped for subsequent quantitative analysis with "Ethograph" software (RITEC, Russia). The latencies of diving were analyzed with Kaplan-Meier Survival Analysis followed Holm-Sidak test. **Results:** in the first trial the latencies of diving of rats from all experimental groups were longer than in control animals (Log-Rank test – 47,93; *df*=5; *P*<0,001), which have dived in 20 sec. Not all rats from experimental groups solved the WET task. Also, the duration of FSE-WET intervals (1-14 days) failed to affect rats' problem solving ability. Three trials, moreover, were not enough to get skill of diving in rats with FSE. There were no significant differences in latencies of diving between trials. **Conclusion:** The results of the present study state that FSE has long lasting effect (at least for the 14 days) on the rats' behavior (problem solving and skill training) in WET. This suggests that immobility due to forced swimming is more "learned helplessness" rather an energy-saving behavior strategy. The combination of FSE and WET can be used to evaluate the effects of potential antidepressants and increase the validity of WET as the model of cognitive dysfunctions induced by affective states.

STRESS AT CELLULAR AND TISSUE LEVEL

V. Vincze, B.Czeh

University of Pécs Medical School, Dept. of Laboratory Medicine, Pécs, Hungary.

veronika.vincze@gmail.com

The effect of stress is inevitable in our daily life, and harmful substances influence the functioning of our body, such as drugs, alcohol, smoking, ionizing and UV radiation, chemicals, unhealthy diet, improper physical activity and many more. Hans Selye initially described stress (Nature 1936) at the whole-body level in rats, by grossly visible changes in the adrenals, thymolymphatic system and gastrointestinal tract. Even his last definition (1974) of stress as the "nonspecific response of the body to any demand made upon it" refers to the entire body. Yet, based on the advancements of cellular and molecular biology, we now know that there are nonspecific, common responses in the cell and in extracellular space, that are usually designated as oxidative stress or oxidative tissue damage. This is mostly the result of the action of free radicals and the imbalance of prooxidants and antioxidants in cells and in the extracellular space. Stressors can be physical, chemical psychologic/social and they usually represent the non-specific aspects of any chemical reaction. Stressors at cell/tissue level stress can be osmotic, due to changes in pH, metabolic, or consequence of reactive free radicals. Free radicals, including hydroxyl radical, which is the most reactive among free radicals, may cause lipid peroxidation, structural alterations in DNA, dysregulation of cell growth and cell death through apoptotic and necrotic mechanisms. Free radicals may also play role in the development of cancer. Metabolic stress is a hypermetabolic, catabolic response reaction to injury or disease. The main reasons can be acute phase protein changes, hormonal changes, or increased gluconeogenesis. Endoplasmic reticulum (ER) stress is another highly important process, as unfolded or misfolded proteins can pass the check points of the ER system and lead to loss of function or gain of toxic phenotypes that may play a role in the pathogenesis of Alzheimer and Parkinson's disease, diabetes and other human diseases. Furthermore, ER plays an important role in the defense mechanisms of cells by generating heat shock proteins, thus contributing to an increased glutathione synthesis, and leading finally to the survival of the cells. Fortunately, there are several protective mechanisms such as antioxidant scavenging enzymes, exogenous and endogenous antioxidants, cellular compartmentation and repair mechanisms. Glutathione is one of the most important antioxidants in the life of our cells, inhibiting the damage to the cells and constantly renewing itself through its cycle, thus preventing accelerated aging or cancer. Furthermore, cellular stress may also be protective as free radicals contribute to the elimination of pathogens by the help of phagolysosomes. In summary, medical research of the last about 80 years reveled that stress is relevant not only at the organ or body level, but also in cellular damaging or protective reactions.

MOLECULAR FACTORS OF INNATE IMMUNITY IN STRESS REGULATION

I. Yankelevich[1,2], M. Shustov[1], G. Aleshina[2], V. Kokryakov[2]

[1]Saint-Petersburg State Chemical and Pharmaceutical University, Saint-Petersburg, Russia; [2]Federal State Budgetary Research Institution "Institute of Experimental Medicine", St. Petersburg, Russia.

irina.yankelevich@pharminnotech.com

Introduction: We investigate the role of molecular factors of innate immunity – antimicrobial proteins and peptides in regulation of stress reactions. We studied how preventive administration of antimicrobial peptide – rat neutrophil defensin - 3 (RatNP-3) and antimicrobial protein – human lactoferrin (LF) effect on reactions induced by application of acute stress. **Methods:** All experiments were carried out on male Wistar rats. The model of acute stress we used was – swimming in cold (1°-4°C) water in 2 min. Blood and spleen of experimental animals was collected in 30 min and 3 h after acute stress administration. Plasma corticosterone levels were evaluated by IFA kit for corticosterone (DRG). The intensity of cytokines (IL-1β, IL-10, IL-4, IL-6) and TLR4 mRNA expression in rat splenocytes has been evaluated using real-time RT-PCR. Human lactoferrin from milk was administered intraperitoneal in 5 min prior the stress application in a dose 200 μg/kg weight and RatNP-3 in a dose 100 μg/kg weight. As nonspecific antigen control, we used ovalbumin (OA) in a dose 200 μg/kg weight. Rat defensin was isolated from exudate neutrophils by using set of methods, including the extraction in an acidic medium, fractionation by ultrafiltration and reversed-phase high-performance liquid chromatography. Human lactoferrin was obtained from human milk using degreasing, casein precipitation and ion exchange chromatography. **Results:** As a result of the work it was shown, that preventive administration of both – LF and RatNP-3 reduced stress-induced increasing of concentration of corticosterone. It has been also demonstrated that the administration of RatNP-3 defensin and human lactoferrin modulates the redistribution of blood leukocytes and the level of pro- and anti-inflammatory cytokine (IL-1β, IL-10, IL-4, IL-6) gene expression in rat spleen cells. We have also demonstrated that stress induce changes in expression of pattern recognition receptor – toll like receptor -4 in a spleen of experimental animals, and human LF and defensin RNP-3 modulate this reaction. **Conclusion:** These results suggest that antimicrobial proteins and peptides could be involved in the regulation of defense mechanisms during the development of the stress response and maintain homeostasis. The mechanisms of action of these molecules are not clear yet.

STRESS-INDUCED ANALGESIA: INVOLVEMENT OF THE HPA AXIS HORMONES

N.I. Yarushkina

Pavlov Institute of Physiology, Russian Academy of Sciences, St. Petersburg, Russia
yarni60@mail.ru

Stress exerts bidirectional modulatory effects on pain, either reducing pain sensitivity (hypoalgesia) or exacerbating it (hyperalgesia), depending on stressor nature, its intensity and duration. Acute stress, in contrast to chronic stress, triggers a variety of neuronal and hormonal reactions to protect the body, maintain homeostasis and enhance survival. One of an adaptive consequence of acute stress is a temporary suppression of pain perception in animals and humans, termed stress-induced analgesia (SIA) whereas chronic stress, as rule, results in hyperalgesia. SIA is provided by opioid as well as non-opioid mechanisms. SIA is mediated by the activation of descending inhibitory pathways to the spinal cord. Supraspinal structures such as the prefrontal and cingulate cortex, amygdala, periaqueductal grey matter (PAGM), locus coeruleus and rostral ventromedial medulla are contributed to pain inhibiting system and SIA. PAGM is one of key elements that are essential for development of SIA. PAGM stimulation results in both analgesia and the hypothalamic-pituitary-adrenocortical (HPA) axis activation. Corticotropin-releasing factor (CRF), a major mediator of stress response, activates the HPA axis (it stimulates the ACTH/ β endorphin) and is involved in somatic pain regulation. CRF action is mediated by CRF receptors of subtype 1 and 2 (CRF-R1 and CRF-R2). The HPA axis activation is provided through CRF-R1; CRF-R2 is also involved in the control of its functional activity. Both CRF-R1 and CRF-R2 participate in somatic pain regulation and are expressed within PAGM. Based on these data, it may be hypothesized that one of mechanisms of SIA may be related to CRF and mediated through CRF receptors as well as glucocorticoid or/and opioid dependent mechanisms. This suggestion is supported by a few lines of evidences. Our experimental data showed that blockade of stress-induced corticosterone rise eliminated SIA, but restoration of corticosterone production resulted in an appearance of SIA. CRF as well as glucocorticoid administration, mimicking the HPA axis activation, caused analgesic effect. Pretreatment with CRF-R1 and CRF-R2 antagonists, glucocorticoid or opioid antagonists (NBI 27914, astressin 2β, RU 38486 or naltrexone, respectively) attenuated peripheral or central (intra PAGM) CRF-induced analgesia. Data obtained suggest that CRF-induced analgesia may be provided by glucocorticoid as well as opioid dependent mechanisms and mediated by through CRF-R1 and CRF-R2, and glucocorticoid and opioid receptors including CRF-R2 and opioid receptors within PAGM. Thus, involvement of the HPA axis hormones CRF and glucocorticoids is important in a development of SIA in animals.

Supported by grant of Russian Science Foundation (RSF) № 19-15-00430.

EFFECT OF HIGH FREQUENSY ELECTROMAGNETIC WAVES ON *sod1* AND *sod2* GENE EXPRESSION IN THE HONEYBEE BRAIN

T. Zachepilo[1,2], A. Pribyshina[2], D. Khlebaeva[1], N. Lopatina[1], N. Dyuzhikova[1]

[1]Pavlov Institute of Physiology of RAS, [2]Herzen State Pedagogical University of Russia, St. Petesburg, Russia.

khlebaevad@infran.ru

Introduction: Superoxide dismutase (SOD) is an enzyme that alternately catalyzes the dismutation of the superoxide (O^{2-}) radical into either ordinary molecular oxygen (O_2) or hydrogen peroxide (H_2O_2). Superoxide is produced as a by-product of oxygen metabolism and, if not regulated, causes many types of cell damage. Thus, SOD is an important antioxidant defense in nearly all living cells exposed to oxygen. There are three major families of superoxide dismutase, depending on the protein fold and the metal cofactor: the Cu/Zn type, the Fe and the Mn types and the Ni type. SOD is a marker of oxidative stress. We suggested that prolonged Wi-Fi exposure may increase the level of free radicals and affect *sod1* and *sod2* gene expression. **Methods:** Gene expression of *sod1* (eukaryotic cytosol enzyme) and *sod2* (mitochondrial enzyme) in the honeybee (*Apis melifera*) brain (24h Wi-Fi exposition in Faradey cage, control – 24h Faradey cage (isolation from external electromagnetic fields) and intact honeybees) was studied. After the end of the experiment, all honeybees were frozen at -20°C. Total RNA was extracted (phenol-chloroform method). Reversed transcription, PCR (Evrogen) and gel-electrophoresis were conducted. **Results:** It was shown that the *sod1* expression in all groups did not differ. In contrast, *sod2* expression in intact honeybees was absent. **Conclusion:** Thus, reduction and growth of high frequency electromagnetic fields causes an increase in *sod2* expression (mitochondrial gene). Perhaps, mitochondria are hypersensitive to high frequency electromagnetic waves.

HSP70 GENE EXPRESSION IN THE HONEYBEE BRAIN UNDER THE ACTION OF HIGH FREQUENCY ELECTROMAGNETIC RADIATION

T. Zachepilo[1,2], A. Pribyshina[2], N. Lopatina[1], N. Dyuzhikova[1]

[1]Pavlov Institute of Physiology of RAS, [2]Herzen State Pedagogical University of Russia, St. Petesburg, Russia.

zachepilo_t@infran.ru

Introduction: Now there is a high level of electromagnetic pollution, which can be a stressor. Earlier, we found that EMR impairs unconditioned-reflex food excitability and short-term memory in the honeybee after being irradiated by a WiFi router for 24 hours. The molecular mechanisms of this phenomenon are unknown. In this work, we examine whether cellular stress is observed in a bee's brain. **Methods:** So, we researched the expression of the heat shock protein gene *hsp70* (a universal stress response sensor) in the honeybee brain. Three groups of honeybees were studied: 24h Wi-Fi exposition in Faradey cage, control – 24h Faradey cage (isolation from external electromagnetic fields) and intact honeybees. After the end of the experiment, all honeybees were frozen at -20°C. Total RNA was extracted (phenol-chloroform method). Reversed transcription, PCR (Evrogen) and gel-electrophoresis were conducted. **Results:** There were no differences between the control groups. In the experimental group, the action Wi-Fi exposition led to a decrease in the expression of *hsp70*. **Conclusion:** Probably, a decrease in the expression of *hsp70* can lead to disturbances in the proper folding of neuronal proteins and thus affect the memory and training of honeybees.

STRESS- AND GASTROPROTECTIVE EFFECTS OF HYPOXIC PRE- AND POSTCONDITIONING IN THE RAT ULCEROGENIC COLD-RESTRAINT STRESS MODEL

M.Y. Zenko, O.P. Komkova

Pavlov Institute of Physiology, Russian Academy of Sciences, St. Petersburg, Russia

zenkomichail@mail.ru

Introduction: Pre- and postconditioning with moderate hypobaric hypoxia (360 mmHg, 2 hours, 3 sessions spaced at 24 h) are new effective treatment methods in the rat models of stress-related disorders. The mechanisms of hypoxic pre/postconditioning are not well understood, remaining an actual problem for modern research. The aim of present study was to analyze the gastro-and stress-protective effects of the hypoxic pre- and postconditioning in the rat ulcerogenic cold-restraint stress model. **Methods:** The experiments were performed on Wistar male rats from the resources of the CCU «Pavlov Institute bio-collection» with a body weight of 200–250 g. The rat ulcerogenic «cold-restraint stress» model applied in these experiments comprised of 1-day starvation of animals in cages with a lattice bottom following by 3-hour restraining in the cold (6-10 °C). An exposure to hypobaric hypoxia sessions was carried out as described above before ulcerogenic stress (the preconditioning group), or after (the postconditioning group). The «open field» and «elevated plus maze» tests were used to monitor the behavioral response. Rats were decapitated on the 3rd or 6th day, respectively; the brain tissue was extracted for immunohistochemical analysis, the stomachs - to calculate the average gastric erosion area. Changes in the number of GR-immunopositive (glucocorticoid receptors) cells in the hippocampus and the fronto-parietal neocortex were assessed quantitatively. **Results:** It was found that the ulcerogenic stress resulted in the formation of gastric erosions, and hypoxic preconditioning considerably reduced their area. Animals of the ulcerogenic stress group showed significantly less horizontal activity in the «open field» test, but not in the "elevated plus maze" test, that reflects increased anxiety level. Preconditioning effectively corrected these behavioral abnormalities since the animals of this group did not differ from the control in these tests on day 3. On day 6, both of these tests did not reveal abnormalities in the behavior of all groups. **Conclusion:** The fact apparently indicates a fragility of behavioral consequences in this model. The level of GR expression in the hippocampus and the neocortex did not change neither during ulcerogenesis nor in the pre- or postconditioning groups. In contrast, the ulcerogenic stress modified stress-reactivity as judged by altered corticosterone response to test stress, implying the involvement of the hypothalamic-pituitary-adrenal axis in the pathogenesis of cold-restraint stress ulcerogenesis.

This work was supported by the grant № 19-015-00336 from Russian Foundation of Basic Research.

DIFFERENT SUSCEPTIBILITY TO LEARNED HELPLESSNESS IN ANIMALS WITH OPPOSITE COPING STYLES: PUTATIVE ROLE OF PROGESTERONE

D.A. Zhukov[1], E.P. Vinogradova[2]

[1] Pavlov Institute of Physiology of the RAS, St-Petersburg, Russia; [2] Biological Faculty, St. Petersburg State University, St. Petersburg, Russia.

dazhukov0@gmail.com

Two opposite coping styles are described for many biological species: active and passive. Being exposed to stress they demonstrate opposite behaviors — "fight or flight" and "freeze". Animals with active coping style are susceptible to learned helplessness following uncontrollable inescapable stressors of various types from pain to social defeat and forced restraint. These animals and their subsequent behavioral and physiological reactions represent a model of depressive-like state. In contrast, animals predisposed to passive coping under aversive stimulation are resistant to learned helplessness. Of course, these passive subjects do demonstrate many changes after uncontrollable aversive situation; for example, they become more anxious, but they are not depressive-like. Their behavioral pattern remains unchanged, and their physiological reactions remain integrated. So they represent a model of high anxiety but not a model of depression and coping failure. The state developed following uncontrollable stress in those passive animals is very close to a "learned inactivity". Therefore, interpretation of a state of behavioral non-response developed following exposures to uncontrollable stress as a learned helplessness or as a learned inactivation depends on coping style of animal.

We would like to focus on putative role of progesterone in two coping styles. The changes of anxiety and progesterone levels in blood plasma during estrous cycle were studied in rats genetically selected for high (KHA) and low (KLA) acquisition of active avoidance. Anxiety levels were measured by the time spent in open arms of the elevated plus maze. Plasma progesterone levels were determined by radioimmunoassay. KLA rats have no significant changes in anxiety during estrous cycle. KHA rats showed significant variation of anxiety during estrus cycle: high in diestrus, and low in proestrus. KHA rats showed an anxiety level in diestrus significantly higher than KLA rats. In KLA rats progesterone levels were higher than the KHA rats, during both diestrus and proestrus. Plasma progesterone during estrus cycle in two rats' strains corresponded to anxiety levels and susceptibility to learned helplessness.

Notes