Summer School on Stress
June 13-17 2016, Osijek, Croatia

From Hans Selye’s original concept to recent advances

Stress is the salt of life!

PROGRAM and ABSTRACTS
Summer School on Stress
From Hans Selye’s original concept to recent advances

-An interactive educational experience-

June 13 - 17, 2016
Osijek, Croatia

PROGRAM and ABSTRACTS

Josip Juraj Strossmayer University of Osijek
FACULTY OF MEDICINE OSIJEK

Hans Selye Society
School of Medicine,
University of California, Irvine
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 “non-specific 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.)

Local Organizing Committee
Chair: Marija Heffer
Secretary: Marta Balog
Members: Ines Drenjančević, Ljubica Glavaš-Obrovac, Teuta Opačak-Bernardi, Martina Smolić, Ana Stupin, Barbara Viljetić
Summer School on Stress
From Hans Selye’s original concept to recent advances

June 13 - 17, 2016
Osijek, Croatia

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

Hosted by: Faculty of Medicine, J. J. Strossmayer University of Osijek

Accreditation:
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint providership of the University of California, Irvine School of Medicine and the Faculty of Medicine, J. J. Strossmayer University of Osijek. The University of California, Irvine School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation:
The University of California, Irvine School of Medicine designates this live activity for a maximum of 28AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.
Disclosure Information

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These speakers/planners have provided the following disclosures regarding relevant financial relationships:

<table>
<thead>
<tr>
<th>Speaker/Planner Name</th>
<th>Name of Commercial Interest</th>
<th>Nature of Relevant Relationship</th>
<th>Conflict Resolution Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martina Rojnić Kuzman</td>
<td>Janssen Pharmaceutical Companies</td>
<td>Honorarium Recipient</td>
<td>Dr. Kuzman will support her presentation and clinical recommendations with the “best available evidence” from medical literature. And she will refrain from making recommendations regarding products or services.</td>
</tr>
<tr>
<td>Bruno Bonaz</td>
<td>Otsuka MSD Ferring Abbvie</td>
<td>Consultant</td>
<td>Dr. Bonaz will support his presentation and clinical recommendations with the “best available evidence” from medical literature.</td>
</tr>
</tbody>
</table>

The following speakers have indicated they have no relevant financial relationships to disclose:

Ines Bilić-Ćurčić
Goran Ćurić
Ines Drenjančević
Janos Filakovszky
Ludmila Filaretova
Marija Heffer
Aleksandar Klašnja
Martina Lovrić-Bešičić
Daniela Marić
Jasminka Milas-Ahić
Sven Seiwerth
Predrag Sikirić
Martina Smolić
Arpad Somogyi
Sandor Szabo
Jelena Šuran
Yvette Tache
Ante Tvrdeić
Željka Vukšić
Oksana Zayachkivska
Jack Wood
# PROGRAM & ABSTRACTS

Scientific social program overview

**Summer School on Stress: From Hans Selye’s original concept to recent advances**

June 13-17, 2016

*Faculty of Medicine, J. J. Strossmayer University of Osijek, Osijek*

<table>
<thead>
<tr>
<th>Monday, June 13</th>
<th>Tuesday, June 14</th>
<th>Wednesday, June 15</th>
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<tbody>
<tr>
<td><strong>Registration &amp; sign-in:</strong> 8:00 – 9:00</td>
<td><strong>Registration &amp; daily sign-in:</strong> 8:30 – 9:00</td>
<td><strong>Registration &amp; daily sign-in:</strong> 8:30 – 9:00</td>
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<td><strong>Main lectures &amp; discussions:</strong> 9:00 – 16:00</td>
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<td><strong>Main lectures &amp; discussions:</strong> 9:00 – 12:30</td>
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<tr>
<td>Lunch: 12:00 – 13:00</td>
<td>Lunch: 12:00 – 13:00</td>
<td>Lunch: 12:30 – 13:15</td>
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<tr>
<td>Informal reception &amp; social get-together: 16:30 – 18:00 at the Museum of Modern Arts</td>
<td><strong>Free oral communications session:</strong> 14.45-17.00</td>
<td><strong>Free oral communications session:</strong> 13:30 – 20:00 Osijek sightseeing</td>
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<tr>
<th>Thursday, June 16</th>
<th>Friday, June 17</th>
<th>Weekend</th>
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<tbody>
<tr>
<td>Registration &amp; daily sign-in: 8:30 – 9:00</td>
<td>Registration &amp; daily sign-in: 8:30 – 9:00</td>
<td><strong>Free!</strong></td>
</tr>
<tr>
<td><strong>Main lectures &amp; discussions:</strong> 9:00 – 14:45</td>
<td><strong>Main lectures &amp; discussions:</strong> 9:00 – 12:30</td>
<td><strong>Travel in &amp; around Osijek:</strong></td>
</tr>
<tr>
<td>Lunch: 12:00 – 13:00</td>
<td><strong>Adjournment:</strong> 12:30</td>
<td><strong>Baranja, Kopački Rit, Đakovo:</strong></td>
</tr>
<tr>
<td>Poster session: 15:00 – 16:30</td>
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<td><em>All about 30-50 km from Osijek!</em></td>
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### Monday, June 13, 2016

*Rektorat, Trg Svetog Trojstva 3, Aula*

<table>
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<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>8.00 – 9:00</td>
<td><strong>Registration</strong></td>
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</table>
| 9.00–9:10   | Welcome & greetings  
Marija Heffer & Ljubica Glavaš-Obrovac, Local Organizing Committee, Osijek |
| 9:10 – 9:30 | Introduction  
Arpad Somogyi, Brussels/Berlin; Sandor Szabo, Irvine/Los Angeles; Yvette Tache, Los Angeles |
| 9:30 - 10:00| Historic origins of stress concept  
Lejla Vendégh, Bratislava; Katalin Szabo, Budapest; Sandor Szabo, Irvine/Los Angeles |
| 10:00 -10:30| The Hans Selye, the grandmaster of creativity and originality  
Arpad Somogyi, Brussels/Berlin; Sandor Szabo, Irvine/Los Angeles |
| 10:30 – 11:00| Stress is 80-year-old: From distress to eustress  
Sandor Szabo, Irvine/Los Angeles |
| 11:00 – 11:30| Stress at workplace  
Janos Filakovszky, Komarno |
| 11:35 – 12:00| General discussion: Comments, questions, answers |
| 12:00 – 13:00| **Lunch**                                                              |
| 13:00 – 13:30| The neuroendocrine mechanisms of stress  
Yvette Tache, Los Angeles |
| 13:30 – 14:00| Central insulin resistance: From chronic stress to Alzheimer disease  
Marija Heffer, Osijek |
| 14:00 – 14:15| Coffee break                                                          |
| 14:15 – 14:45| Do regulatory agencies (e.g., for food, drugs and the environment) create psychological stress?  
Arpad Somogyi, Brussels/Berlin |
| 14:45 – 15:15| Psychological trauma – past, present, future  
Željka Vukšić, Osijek |
| 15:15 – 16:00| My good & bad experience with stress: Challenges & lessons learned  
Open forum: Short comments & interactive presentations by attendees |
| 16:30 – 18:00| **Informal reception & social get-together at the Museum of Modern Arts Osijek** |
Tuesday, June 14, 2016
[Rektorat, Trg Svetog Trojstva 3, Aula]

Morning & afternoon sessions

Chairs: Jack Wood & Marija Heffer

9:00–9:30  Physiologic & pharmacologic actions of glucocorticoids  
Ludmila Filaretova, St. Petersburg

9:30–10:00  Stress as a precipitating factor of endocrine disorders; Impact of stress on pre-existing endocrine disorders.  
Ines Bilic-Curcic, Osijek

10:00 – 10:15  Coffee break

10:15 – 10:45  Stress & allergic diseases  
Jasminka Milas-Ahić, Osijek

10:45 – 11:15  Novel role of melatonin, a key hormone of brain-gut axis, in health & disease  
Oksana Zayachkivska, Lviv,

11:15-11:45  Effect of BPC-157 on GI ulcers  
Predrag Sikiric, Zagreb

11:45 – 12:00  General discussion: Comments, questions, answers

12:00 – 13:00  Lunch

13:00 – 13:30  Stress & cardiovascular system  
Martina Lovrić Benčić, Zagreb

13:30 – 14:00  Other organ systems involved in biologic stress  
Sven Seiwerth, Zagreb

14:00 – 14:30  Biologic stress in animals & plants  
Jelena Šuran, Zagreb

14:30 – 14:45  Coffee break

14:45 – 17:00  Free oral communications session  
Chairs: Oksana Zayachkivska & Martina Smolić
Wednesday, June 15, 2016
[Rektorat, Trg Svetog Trojstva 3, Lecture room one]

Morning session
Chairs: Ludmila Filaretova & Ljubica Glavaš-Obrovac

9:00 - 9:30  The brain-gut axis: Basic concepts
            Jack Wood, Columbus, Ohio

9:30 – 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 – 10:45  Coffee break

10:45 – 11:15  Endogenous modulators of stress-induced gastric ulcers
               Ludmila Filaretova, St. Petersburg

11:15 – 11:45  Stress, neuropeptides, brain-gut & gut-brain axis
               Klara Gyires, Budapest

11:45 – 12:15  Stress & gastroprotection: Current & future pharmacologic approaches
               Martina Smolić

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

12:30 – 13:30  Lunch

13:30 – 20:00  Osijek sightseeing
Thursday, June 16, 2016
[Rektorat, Trg Svetog Trojstva 3, Lecture room one]

**Morning & afternoon sessions**
*Chairs: Bruno Bonaz & Barbara Viljetić*

9:00 – 9:30  Stress & hypertension-sympathetic link: Cause & consequence  
*Ines Drenjančević, Osijek*

9:30 – 10:00  Stress & neurologic diseases  
*Janos Filakovszky, Komarno*

10:30 – 10:45  Coffee break

10:45 – 11:15  Genetic architecture of stress axis in suicidal behavior  
*Goran Ćurić, Osijek*

11:15 – 11:45  Animal models of stress & anxiety  
*Ante Tvrdeić, Zagreb*

11:45 – 12:00  General discussion: Comments, questions, answers

**12:00 – 13:00  Lunch**

13:00 – 13:30  Stress in chronic fatigue syndrome: Graded exercise therapy in chronic fatigue syndrome  
*Aleksandar Klašnja, Novi Sad*

13:30 – 14:00  Oxidative stress in chronic viral infections  
*Daniela Marić, Novi Sad*

14:00 – 14:30  Vagus nerve stimulation: A non-drug therapy in IBD  
*Bruno Bonaz, Grenoble*

14:30 – 15:00  Stress during early life & its physiological consequences on brown & white fat in later life  
*Oksana Zayachkivska, Lviv*

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

15:15 – 15:30  Coffee break

**15:30 – 16:30  Poster session**
*Chairs: Jack Wood & Teuta Opačak-Bernardi*
Morning session
*Chairs: Arpad Somogyi & Sandor Szabo*

9:00 – 9:30  Stress & mental disorders
*Martina Rojnić Kuzman, Zagreb*

9:30 – 10:00  Management strategies for stress
*Martina Rojnić Kuzman, Zagreb*

10:00–10:30  Stress & life style changes, including body weight control
*Sandor Szabo, Irvine/Los Angeles*

10:30 – 10:45  Coffee break

10:45 –11:15  Stress in our daily lives – transformation of distress into eustress
Open forum with participation of all registered attendees

11:15 –11:45  Putting it all together: Take-home messages
*Arpad Somogyi, Brussels/Berlin; Sandor Szabo, Irvine/Los Angeles*

11:45 –12:15  Final group discussion, feedback & course evaluation

12:30  Adjournment

Free afternoon

**Acknowledgments**

The course directors & organizers want to thank *Dr. Martina Rojnić Kuzman* for collecting & editing the submitted abstracts of free communications. We also express our deep appreciation to *Prof. Gerald Maguire*, chair & *Ms. Ellen Seaback*, executive director of the CME Committee of University of California-Irvine School of Medicine for obtaining accreditation.
Free communications

Oral presentations

Why are men more sensitive to chronic stress?
M. Balog
Department of Medical Biology and Genetics, Faculty of Medicine, J. J. Strossmayer University of Osijek, Croatia

Proteomics-based in silico model of acute stress threshold – a pilot project
M. Fenrich
Faculty of Medicine, J. J. Strossmayer University of Osijek, Croatia

The Hans Selye club in Bratislava
B. Gálffy, N. Žiaček, Cs. Eke, M. Csóka, D. Fehér, A. Méhes, S. Pénzes, P. Zsemlye, N. Busnyák
Faculty of Medicine, Comenius University, Bratislava, Slovakia

Psychological stress in sport coaches: a review of concepts, research and practice
A. Imširović
Faculty of Medicine, J. J. Strossmayer University of Osijek, Croatia

“Comfort food” – comfort just for a moment
V. Ivić
Department of Medical Biology and Genetics, Faculty of Medicine, J. J. Strossmayer University of Osijek, Croatia

Short stature as a result of chronic psychosocial stress
A. Katić
Faculty of Medicine, J. J. Strossmayer University of Osijek, Croatia

Can microbes in our gut influence how we deal with stress?
T. Kovačević
Department of Microbiology and Parasitology, Faculty of Medicine, J. J. Strossmayer University of Osijek, Croatia

An alternative to Red bull
L. Kuna, J. Jakab
Department of Integrative Medicine, Faculty of Medicine, J. J. Strossmayer University of Osijek, Croatia

Sleep deprivation really reflects my memory!
I. Lovric
Department of Histology and Embriology, Faculty of Medicine, J. J. Strossmayer University of Osijek, Croatia

Cellular stress is passage to system stress - the good, the bad, the ugly
T. Opačak-Bernardi
Department of Medical Chemistry, Biochemistry and Clinical Chemistry, Faculty of medicine, J.J. Strossmayer University of Osijek, Croatia

The role of prolactin in stress modulation
A. Rončević
Faculty of Medicine, J.J.Strossmayer University of Osijek, Croatia
Stress-related effects in autoimmunity
S. Tokić
University Hospital Osijek, Osijek, Croatia

Adaptive neuronal stress response
B. Viljetić
Department of Medical Chemistry, Biochemistry and Clinical Chemistry, Faculty of Medicine, J. J. Strossmayer University of Osijek, Croatia

Chronic stress effects on rat brain lipidome
M. Zjalić
Department of Biology, Josip Juraj Strossmayer University of Osijek, Croatia

Poster session

The role of transcription factor egr-1 in the pathogenesis of stress-induced gastric ulcers
S.M. Beregovyi1, T.M. Chervinska1, A.S. Drantsina1, G.M. Tolstanova1, S. Szabo2
1Educational and Scientific Centre Institute of Biology, Taras Shevchenko National University of Kyiv, Ukraine
2University of California, Irvine, USA

Celecoxib induced gastrointestinal, liver and brain lesions in rats, counteraction by BPC 157 or L-arginine, aggravation by L-NAME
D. Drmic1, D. Kolenc2, S. Illic1, L. Bauk1, M. Sever1, A. Zenko Sever2, K. Luetic1, J. Suran1, S. Seiwerth2 and P. Sikiric1
1. Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia
2. Department of Pathology, School of Medicine, University of Zagreb, Zagreb, Croatia

Analysing the effect of imidazoline receptor ligands on DSS-induced colitis
A. Fehér, V.E. Tóth, K. Gyires, Z.S. Zádori
Department of Pharmacology and Pharmacotherapy, Semmelweis University, Faculty of Medicine, Nagyvárads tér 4. 1089 Budapest, Hungary

The effect of BPC 157 on ischemic/reperfusion injuries in rat brain
J. Vukojevic1, B. Vrdoljak1, D. Malekinusic1, M. Siroglavic1, G. Aralica2, D. Kolenc2, D. Drmic1, S. Seiwerth2 and P. Sikiric1
1Department of Pharmacology, School of Medicine, University of Zagreb, POB 916, Šalata 11, 10000 Zagreb, Croatia
2Department of Pathology, School of Medicine, University of Zagreb, Šalata 9, 10000 Zagreb, Croatia
Lecture outlines
Stress as a precipitating factor of endocrine disorders and impact of stress on preexisting endocrine disorders

Ines Bilić-Ćurčić, MD, PhD, Department of Pharmacology, Faculty of Medicine, J.J.Strossmayer University Osijek, 31000 Osijek, Croatia
ibcurcic@mefos.hr

Psychological distress has been reported in up to 65% of younger patients with hyperthyroidism and physical stress in many older patients. However, most of the studies are retrospective case-control studies and it is quite difficult to evaluate the effect of a given stressful event in different individuals. Stress may lead to immunologic perturbations and may affect the immune response to TSH receptor through modulation of hormones, neurotransmitters and cytokines. Severe stress may also be a risk factor for diabetes. However, it has been shown that stress in early life may be a risk factor for diabetes, but not in young adults. Furthermore, in females stress can lead to anovulation, amenorrhea and other menstrual irregularities. In males, there can be decreased sperm count, motility and altered morphology. Psychosocial dwarfism is an extreme form of failure to thrive and may be associated with dramatic behavioral abnormalities. Reversal of GH insufficiency within three weeks of removal from hostile environment has been reported. The organic incapability of confronting stress on a genetic basis, and/or the fact of repeated stresses, from exhaustion of the homeostatic mechanisms, could make some groups of patients liable to suffer depressive symptoms associated with a wide range of deleterious consequences in the endocrine system leading to delayed growth. In addition, cortisol favors central fat deposition, a decrease in the adipostatic signal leptin and an increase in the orexogenic signal ghrelin, inducing increased appetite and food intake. This phenomenon contributes to the current epidemic of obesity. Stress may also worsen diabetic control, while poor metabolic control has also been reported in children and adolescents with Type 1 diabetes with stress. Patients with adrenal insufficiency may develop adrenal crisis on exposure to stress. To prevent this, the replacement doses of steroid need to be doubled during the period of stress. Thyroid storm may be precipitated by physical stress. Acute emotional stress can also precipitate thyroid storm.

Rationale:
‘Stress’ may be defined as any situation which tends to disturb the equilibrium between a living organism and its environment. Some of these stressful responses can lead to endocrine disorders like Graves’ disease, gonadal dysfunction, psychosocial dwarfism and obesity. Stress can also alter the clinical status of many preexisting endocrine disorders such as precipitation of adrenal crisis and thyroid storm. As an adaptive response to stress, there is a change in the serum level of various hormones including CRH, cortisol, catecholamines and thyroid hormone. These changes may be required for the fight or flight response of the individual to stress. However, long-term exposure to stress may lead to many deleterious consequences leading to various endocrine disorders or worsening preexisting ones.

Learning objectives:
• Understand the role of stress in preexisting endocrine disorders and in the onset of new ones
• Role of stress in development of hyperthyroidism and diabetes
• Influence of stress on male and female reproductive system
• Influence of stress on delayed growth and obesity
• Impact of stress on diabetes, adrenal insufficiency and thyroid storm
Vagus nerve stimulation: a non-drug therapy in inflammatory bowel disease

Bruno Bonaz, MD, PhD, Professor of Gastroenterology, Clinique Universitaire d’Hépato-Gastroentéologie 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 adrenal axis leading to the release of cortisol by the adrenal glands. 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 b2 adrenergic receptor of splenic lymphocytes that release ACh. Finally ACh inhibits the release of TNFα by spleen macrophages through a-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.

Learning 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

References


Questions
1. What are the components of the anti-inflammatory pathways of the vagus nerve?
2. How the vagus nerve is able to have anti-inflammatory effects
3. What are the diseases that may be a therapeutic target for 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. BBonaz@chu-grenoble.fr

Introduction:
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.

Rationale:
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 noxious 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
References:
Genetic architecture of stress axis in suicidal behavior

Goran Ćurić, MD, PhD, Assistant Professor, Laboratory for DNA analysis of Department of Medical Chemistry, Biochemistry and Clinical Chemistry, Faculty of Medicine, University of Osijek, Croatia
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Rationale:
Etiology of suicide is complex, with contribution of psychiatric, social and environmental factors associated with an individual life path. Many of these factors are also known as stressors. Inadequate stress response is considered as a biological background of suicide behavior. Central neuroendocrine system that regulates the stress response is hypothalamic-pituitary-adrenal (HPA) axis. Therefore, genetic architecture of HPA axis may contribute to development of suicidal behavior. Variation in stress susceptibility and resilience is a reflection of variations in genes of HPA axis and developmental programming of the HPA axis – through epigenetic modification of the genome. It is well-established that exposure to stress, particularly in early life, has both acute and long-term effects on physiology and behavior of an individual. Genetic and epigenetic determinants of the HPA-axis provide a part of a puzzle of suicidal behavior.

Learning objectives:
• To describe types and epidemiology of suicidal behavior
• To identify stressors associated with suicidal behavior
• To recall current state-of-knowledge about the role of genetic variation of HPA axis genes in suicidal behavior
• To name known epigenetic modifications of the HPA axis gene associated with early life stress exposure
Stress and hypertension—sympathetic link of the cause and the consequence

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Rationale:
The control of arterial pressure is a complex interaction of the long- and short-term influences of hormones, local vascular factors, and neural mechanisms. The autonomic nervous system is a major player in modulating cardiovascular functions and in controlling blood pressure values, both at rest and in response to environmental stimuli as documented by many experimental and clinical studies (1). Overactivity of sympathetic arm of autonomic nervous system, as well as blunted responses of parasympathetic arm has an important role in the development of hypertension and related cardiovascular disorders. Development of obesity-related illnesses including hypertension, insulin resistance, metabolic syndrome and renal, cardiac, and vascular impairment is related to the elevated activity of the sympathetic nervous system (2,3). The signs of subclinical organ damage may be found already in young, normotensive, overweight and prehypertensive persons (1,3) and are likely related to disbalance in autonomic control. Stress in several aspects is evident in individuals with hypertension and in those with the metabolic syndrome and may account, at least in part, for the extent and pattern of sympathetic nervous activation (3). Stressful situations present as environmental (job deadline, surrounding noise), psychological (loss of partner, illness) or physiological conditions (strenuous exercise) that activate a cascade of stress hormones that produce well-orchestrated physiological changes. Amygdala starts stress response by sending signals to hypothalamus which activates the sympathetic nervous system by sending signals through the autonomic nerves to the adrenal glands, resulting in increased levels of adrenalin and noradrenalin in the blood. As the initial surge of adrenalin subsides, the hypothalamus activates the second component of the stress response system - the hypothalamus-pituitary gland-adrenal glands (HPA) axis. Activation of HPA axis leads to release of corticotropin-releasing hormone (CRH), which triggers the release of adrenocorticotropic hormone (ACTH) in pituitary gland triggering the release of cortisol from adrenal gland. All of these hormones, as well as sympathetic neural activation have significant cardiometabolic impacts. Acutely, heart and vasculature respond by increasing the heart rate, minute volume and increase of the total peripheral resistance, subsequently increasing the blood pressure. Metabolic changes include increase in plasma glucose levels and subsequent high insulin levels and insulin resistance, renal retention of sodium and water and prolonged vasoconstriction. All of these changes, including the blunted parasympathetic response are causative to chronically increased blood pressure.
The baroreceptor system opposes either increases or decreases in arterial pressure, and the primary purpose of the arterial baroreflex is to keep blood pressure close to a particular set point over a relatively short period of time. The ability of the baroreflex to powerfully buffer acute changes in arterial pressure is well established. Novel studies propose that the sympathetic nervous system and arterial baroreceptor reflex control of renal sympathetic nerve activity may play a role in long-term control of arterial pressure (2).

Learning objectives:
• The role of the autonomic nervous system in blood pressure physiological regulation and control
• Physiological and pathophysiological activity of cardiovascular system in response to acute and chronic stress
• Metabolic changes in stress response
• How may sympathetic system be the link between stress and hypertension
• Interaction of sympathetic renal nerves and baroreceptor system in the control of blood pressure

References
Work-related stress, stress at workplace: Transformation of distress into eustress

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Rationale:
Since the seventies research examining the relationship between work stress and well-being has been showing clear links between work-related stress and a variety of physical and mental disorders.
According to latest statistics about 65% of U.S. employees are citing work as a significant source of stress, and cc.35% suffer from chronic work stress leading to cc. $27 billion worth of work days lost to mental health-related absences each year. Similar National Survey in UK reported work related stress accounting to 35% of work related illness and cc 43% of days lost.
Chronic workplace stress in addition to affecting employee health, can have serious repercussions for employers and lead to organizational low performance. The American Institute of Stress estimates that job stress costs U.S. industry more than $300 billion a year in absenteeism, turnover, diminished productivity, and medical, legal and insurance costs.
The reasons cited as primary causes of work related stress are also consistent: over time with workload, lack of managerial support and organizational change. Nixon et al’s (2011) in a meta-analysis demonstrated statistically significant, but modest correlations of stressors (i.e., interpersonal conflict, lack of control, organizational constraints, role ambiguity, role conflict, work hours, and work load) with a composite measure of self-reported physical complaints (i.e., backache, headache, eye strain, sleep disturbance, dizziness, fatigue, appetite loss, and gastrointestinal problems). Although research and reports often aim to construct lists of the “most” and “least” stressors related to work stress, it is not the job but the person-environment fit that matters. The significance of the reported statistics also depends on research methodology.
While stress at work will remain a major challenge to occupational health, our ability to understand and manage that challenge is improving. Breaking the distress cycle through series of individual and organizational level interventions remains on the top of the agenda of all players: the policy makers, the public and profit oriented organizations, too.

Learning objectives:
• Definition of work related stress, review of epidemiology of work related stress: Prevalence, incidence (by industry, by age and gender, by occupational category/job grade, skills, social environment)
• Model of job stress (distress-eustress) and health, causes of workplace stress (stressors)
• Job stress assessment instruments: Stress & well-Being Survey™, Job Satisfaction Survey, Human Factors Inventory (HFI) → Employee Engagement Survey (EES), Coping Questionnaires
• Breaking the distress cycle, leveraging eustress: individual and organizational level Interventions, stress reduction programs for employees- (Increasing ability to cope with stress) and on “Healthy” organization (organizational structure, job content, work time, leadership style, employee benefits, training)
• Review of work related stress-case study examples: Discuss practices leading to employee-workplace-business win-win outcomes: employee training, flexible working time, differentiated-performance related variable pay, workplace practices in establishments, interactive-involving leadership styles

References
www.hse.gov.uk/statistics/sources.htm
Managing the High-Intensity Workplace
Professor John Quelch about his case entitled “Mental Health in the American Workplace.” The Real Cost of Ignoring Mental Health in the Workplace HBR, May, 2016
Reid E, Ramarajan L. Managing the High-Intensity Workplace, HBR June 2016
HSE (Health and Safety Executive), Work-related stress, anxiety and depression statistics in Great Britain 2015
2016 American Psychological Association Center for Organizational Excellence
Stress and neurological diseases

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Rationale:
“Stress is a wear and tear on the body and mind in response to a stressful agent”. Hans Selye called such agents stressors and said they could be physical, physiological, psychological and sociocultural. When stressed positive or negative, acute or chronic manner, can lead to illnesses or disease worsening. The body responds to each type of stress in similar ways, however different people may feel it in differently. For example, some people experience mainly digestive symptoms, while others may have headaches, sleeplessness, depressed mood, anger, and irritability. While stress plays an important role in immunological and cardiovascular diseases, the role of stress in onset, development, and progression of neurological disorders is complex one.
Evidence for connection between stress and selected neurological diseases has been reported, in particular on neuromuscular, neurodegenerative and neuroimmunological diseases. Stress plays significant role in disease susceptibility, progress and actual outcome. Does stress cause or exacerbate related disease process? For decades, studies have implicated the hypothalamic pituitary adrenal (HPA) axis role in variety of progressive neurodegenerative diseases including Parkinson’s disease. According to recent research, stress appears to be related to the onset of Alzheimer’s disease, by triggering a degenerative process in brain and precipitating disruption of neuroendocrine and immune system. The researchers found that nearly three out of four Alzheimer’s patients had experienced severe emotional stress during the two years preceding their diagnosis, compared to just over one in four in the control group. However, for many other neurological diseases the evidence that stress triggers certain mechanisms of pathophysiological importance still needs further research. For the purpose of this review we will focus on Parkinson’s disease, Alzheimer’s disease, Multiple sclerosis, Posttraumatic stress disorder (PTSD), chronic muscular spasm \(\rightarrow\) Back – Head ache.

Learning objectives:
- Review of Stress impact on Neurological disorders
- Neurological Disorders “caused” by stress
- Discuss the evidence of pathophysiological mechanisms HPA axis in selected neurological diseases
- Review of selected neurological disorders impacted by stress: Parkinson’s disease, Alzheimer’s disease, Multiple sclerosis, Posttraumatic stress disorder PTSD, Pseudo Epilepsy, Sleep, Chronic muscular spasm \(\rightarrow\) Back – Head ache,
- Distress-Eustress impact worsening / improving of neurological symptoms e.g. acute stress improves chronic stress worsens cognitive functions

References
Physiological & pharmacological actions of glucocorticoids

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Rationale:
Even though society has always looked upon stress as being a negative phenomenon it’s important to note that by its very nature stress is an adaptive reaction of the body which allows it to resist harmful actions of various kinds of stimuli. It is critically important to change public opinion about stress, which is considered to be “murderer No. 1” in our modern world, against one must fight by all means. Understanding the fact that stress is a source of good health should promote the betterment of one’s health. The activation of hypothalamic-pituitary adrenocortical (HPA) axis is the key hormonal system of stress response. Glucocorticoids released during acute stress-induced activation of the HPA axis help the body overcome negative effects of stress stimuli thanks a wide range of concerted physiological effects. These hormones are absolutely fundamental for human health. For over 60 years synthetic analogues of endogenous human glucocorticoids are used in almost all medical specialties for systemic as well as topical therapy as anti-inflammatory and immunosuppressive drugs. However, from the early trials clinicians were also well aware of the many adverse effects of the hormonal therapy. The adverse, pharmacological, effects of glucocorticoids have been repeatedly confirmed by extended clinical experiences over the past 60 years. Thus, in general glucocorticoid hormones may have dual action: physiological and pathological one. To prevent or decrease a risk of glucocorticoid adverse effects, it is important to understand how their initially physiologic action can be transformed to pathological effect.

Learning objectives
• Historical background.
• The “general adaptation syndrome”: The triad of enlarged adrenal glands, atrophy of lymph nodes and thymus, and gastric erosions/ulcers.
• Activation of hypothalamic-pituitary-adrenocortical axis as main characteristic of stress.
• Classification & naming of steroids.
• Physiologic actions of glucocorticoids (a wide range of physiologic effects with a prime physiologic function i.e. stimulating hepatic gluconeogenesis).
• Anti-inflammatory action of glucocorticoids.
• Synthetic analogues of endogenous human glucocorticoids and their beneficial effects.
• Pharmacological actions of glucocorticoids (adverse effects of glucocorticoid therapy).
• Transformation of initially physiologic action of glucocorticoids to pathological effect.
Endogenous modulators of stress-induced gastric ulcers

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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.

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

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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
Central insulin resistance: From chronic stress to Alzheimer disease

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Rationale:
Stress response is closely linked to relocation of energy resources in time and tissue specific manner. Demanding functional requirements reduce ATP concentration in cell no more than 20% due to fast production and swift transition between various resources (glucose, fat and proteins). While other tissues, particularly muscles, can use any store of energy, blood cells and neurons depend on blood glucose. If blood glucose is too low for demand - body collapses, but if its level is too high it leads toward development of central and peripheral insulin resistance – mechanism which ultimately removes glucose transporters from cell membrane and prevents further import of glucose. Balance between too low and too high glucose is literally 'sweet point' between eustress and distress.

Improper management of stress response finally leads toward development of diabetes and other pathologies connected to metabolic syndrome. Due to the fact that insulin cannot cross brain-blood barrier, it was believed that diabetes is peripheral phenomenon. Everything changed with the finding of insulin synthesis in the brain tissue. Link between type 2 diabetes and Alzheimer’s disease (AD) at the first came from clinical finding that treatment designed for diabetes helped in alleviating symptoms of AD. Using [18F] 2-fluoro-2-deoxy-D-glucose (FDG) - PET is possible to follow brain glucose metabolism and evaluate early changes in parieto-temporal areas of AD patients. Also, animal studies proved changes in brain insulin signalling pathways following stress and gave rationale for use of anti-diabetic drugs in AD treatment.

Learning objectives:
- Available ATP metabolic sources and means of delivery for different tissue under condition of mild and extreme demands.
- Endocrine signals involved in control of metabolic steady-state.
- Cross talk between cellular signalling pathways and development of insulin and leptin resistance under condition of distress.
- Difference between ‘diabetes type 2’ and ‘diabetes type 3’.
- Link between insulin resistance and neurodegeneration.
- Possible risk factors and preventive life style changes designed to improve brain fitness.
- Possible treatment of mild cognitive decline in the light of new findings.
Stress and chronic fatigue syndrome: Graded exercise therapy in chronic fatigue syndrome

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Rationale:
Chronic fatigue syndrome (CFS) is a medically unexplained illness characterized by persistent or relapsing fatigue lasting at least 6 consecutive months that substantially reduces physical activity and is accompanied by 4 or more of the following symptoms: impaired memory or concentration, sore throat, tender lymph nodes, muscle and/or multiple-joint pain, headaches, unrefreshing sleep, and postexertional malaise. Many different potential etiologies for CFS including neurological, endocrine, immunological, genetic, psychiatric and infectious have been investigated. CFS is associated with abnormal immunological response to exertion, reduced ability to recover from exertion, neuroendocrine abnormalities, reduced natural killer cell function, forms of orthostatic intolerance and increased oxidative stress. Acute physical or psychological stress might trigger the onset of CFS. Three-quarters of patients with the disorder have reported an infection, such as a cold, flu-like illness, or infectious mononucleosis, as the trigger. Serious life events, such as the loss of a loved one or a job, and other stressful situations have been found to precipitate the disorder. CFS could be conceptualized as a stress disorder, in which adverse life experiences, stress regulation, and pain-processing mechanisms are highly inter-related. The functional capacity of individuals with CFS varies greatly. Many patients are unable to work with often severely debilitating symptoms that last for several months or years. The most effective therapies for CFS are cognitive behavioral therapy and graded exercise therapy (GET). The theory behind GET is deconditioning. After a period of illness most people take some time to recover and tend to avoid physical activity. The result is that they become physically tired much sooner. Prolonged inactivity can also affect sleep, hormonal rhythms, immune system and mood, making it more difficult to cope with everyday activities. Exercise in CFS patients must be applied gradually and patiently, not to worse patient’s state.

Learning objectives:
- Review and definition of the chronic fatigue syndrome (CFS)
- Epidemiology, clinical manifestations and etiology of CFS
- Explain the etiologic role of physical or psychological stress as triggers of CFS
- Describe the role of oxidative stress in CFS
- Obtain an understanding of CFS therapy options, as well as the role of graded exercise therapy in chronic fatigue syndrome
Stress and cardiovascular system: The effect of BPC-157

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Acute and chronic changes and adaptation during stressful life events may trigger acute myocardial infarction as a major problem and manifestation of disturbed cardiovascular balance. There are several hypothesized mechanisms by which emotional stress might trigger an acute MI. Increases in blood pressure, heart rate, vascular tone, and platelet aggregability may result from mental stress, but also from other situations which can produce transient pressure surges or vasoconstriction, which disrupts a vulnerable atherosclerotic plaque. If the plaque disruption is large with extensive exposure of collagen and atheromatous core contents to the lumen, this may lead immediately to occlusive thrombosis, with MI or sudden cardiac death. These factors may all be related to abnormalities in autonomic tone and activation of sympathetic nervous system activity, which may enhance platelet aggregation and increase the susceptibility to serious ventricular arrhythmias. There are also other mechanisms of stress that can harm cardiovascular system. A number of experimental observations have raised the possibility that oxidative stress may play a role in the development of myocardial failure. Mechanical stretch of a rat papillary muscle can induce myocyte apoptosis and the generation of reactive oxygen species (ROS). Peroxynitrite, the product of nitric oxide and superoxide anion, can cause myocyte injury and death. This injury can be reversed by the free radical scavenger superoxide dismutase (SOD). Isoprostanes, which are bioactive prostaglandin-like compounds that are formed by free radical-catalyzed peroxidation of arachidonic acid, are potent vasoconstrictors. In the isolated pig heart, cyclooxygenase inhibitors increase the amount of isoprostanes and exacerbate the loss of cardiac function due to ischemia-reperfusion injury. Superoxide anion (O2-•) reduces calcium-activated force of contraction in skinned rat trabeculae. ROS may deplete the myocardium of antioxidants and may contribute to myocyte injury resulting from ischemia-reperfusion and anthracycline cardiotoxicity, and in the transition from hypertrophy to heart failure (HF).

During last 20 years our group of researchers extensively examined BPC-157 in numerous experimental stress models:
• Acute and chronic anthracycline cardiotoxicity
• Its antiarrhythmic effect in acute ischemia, and after MI-induced reperfusion injury in dogs' hearts, in models of ischemia (MI) induced by isoprenaline
• In stress induced by immobilization
• In arrhythmias induced by BaCl2, digoxin, desipramine, verapamil, propranolol, amiodarone, bupivacaine, and in deadly hypokalemia induced by furosemide
• L-NAME and L-arginine experiments in cardiovascular and gastrointestinal systems – where BPC-157 administration clearly interacted with homeostasis of endothelial NO system.
• BPC-157 turned out to be a significant stress modulator and its clearly great potential should be further researched.
Oxidative stress in chronic viral infections

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Rationale:
Prevalence and incidence of chronic viral infection is growing and so is the burden of its complications. These apply especially to HIV, HCV and HPV infections which are all increasing in frequency and numbers. The treatment and prevention of these infections have been improved significantly in the past two decades. On the other hand, new and important questions have been raised. Based on research it has now become clear that these chronic infections have implications that surpass local or systemic infection and their pathophysiologic impact. The systemic effects of these viruses are due to chronic oxidative stress caused by the virus itself but also by the immunologic response to the virus. Oxidative stress has proven influence on systems and organs and is in direct relation to general health and outcome of the infections. Relation between HIV infection and chronic inflammation is now well established and is linked to neurologic, cardiovascular, metabolic and bone disease. HCV infection is now certainly more than a hepatotropic virus. HCV related oxidative stress is linked to carcinogenesis and extrahepatic manifestations. Some HPV types cause infections that are now definitely related to cervical carcinomas.

It's very interesting, but also very important to denote these maybe unexpected relationships between infection and oxidative stress as these have serious implications regarding how we view chronic infections.

Learning objectives:
- To describe the role of oxidative stress in infection
- To distinguish the difference between oxidative stress in chronic and acute infections
- To describe the oxidative stress and its role in HIV infection
- To describe the implications of low level inflammation in HIV infection
- To describe the relationship between HCV infection and hepatocellular carcinoma
- To describe the relationship between HPV infection and cervical carcinoma
Stress and allergic diseases

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Rationale:
Allergy has been defined as the result of immune reaction to specific types of typically protein antigens known as allergens. Atopy, genetically mediated predisposition to produce specific IgE following exposure to allergens, is an essential component of the pathogenesis of allergic disorders. In addition, dysregulation of Th1 and Th2 cytokine balance has an important role in the immunopathology of allergic diseases. Recent studies in the field of psychoneuroimmunology (PNI) have shown multiple links between nervous, endocrine and immune systems and behavior. Chronic psychological stress and allergic disorder have been linked together. Stress is known to activate the hypothalamic-pituitary-adrenal axis through the release of corticotropin-releasing hormone (CRH). CRH secreted under stress stimulates mast cell degranulation through activation of CRH receptor-1 (CRHR-1). Moreover, it has been shown that CRH induces the expression of high-affinity IgE receptor and enhances allergic stimulation of human mast cells. An effect of psychological stress on disease activity in allergic patients is supported by studies that have demonstrated that allergic responses can be modulated by mood and psychological stressors.

Learning objectives:
• Altered immunity in allergic diseases.
• Role of dysregulation of Th1 and Th2 cytokine balance in the immunopathology of allergic diseases.
• Communication between neuroendocrine mediators, nerve fibers and immune cells in allergic diseases.
• Relationship between psychosocial factors and allergic disorders.
• Allergen immunotherapy for upper and lower airway disease.
• Immunomodulatory therapy with anti-IgE represents a major advancement in the field of allergy and immunology.
• Strategies for stress management in comprehensive allergic disease management.
**Stress and psychiatric disorders**

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**Rationale:**
The causes of mental disorders are still largely unknown. However, the mainstream concept of the development of mental disorders incorporates the biopsychosocial approach. New findings offer novel insight on complex interaction of the individual biological make up and the environment starting from the beginning of one’s life, and continuing throughout the life cycle.

In humans, each developmental phase involves the action of the environment (which can be regarded as the stressor) and the adaptive response of the individual.

In adult persons with mental illness the result of such interaction is aberrant – there is usually high environmental stress (poor mother infant relationship, disturbed family dynamics, childhood trauma) as well as primary (genetic, biological vulnerability) or secondary (such as a result of childhood trauma, abusive parenting) high vulnerability to environmental stressors prior to the illness. The mental illness itself then produces a state of prolonged stress response further increasing the vulnerability to stress leading to a vicious cycle. In the majority of mental illness biological or psychological stress precede the development of the mental disorders, and stress markers are observable during the course of illness.

**Learning objectives:**

- To describe the current bio-psycho-social approach to the development of mental illness
- To describe the psychosocial stressor
- To describe the interaction of biological factors and environment in the development of mental disorders
- To present examples of the development of different mental in the context of response to stress: 1. the development of posttraumatic stress disorder – as the model of a predominantly environmentally- induced mental disorder; 2. depression as the model of a disorder resulted from both genetic x environmental factors; 3. schizophrenia – as the model of predominantly genetically- induced mental disorder.
Management strategies for stress

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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
Other organ systems involved in biologic stress

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Rationale:
Stress can be regarded as a local event influencing the whole organism or a general event with consequences also to specific organ systems. Although the brain is generally considered to be the key organ in stress both as target and as regulator of adaptation mechanisms most of other organ system are also involved in stress. Best known are the events and disturbances or diseases considered to be consequences of acute or chronic stress. Much less is known about other organ systems as potential active players in the stress coping response.
In general, we can say that the role of other organ systems, besides the brain and the neuroendocrine transmission system, in the stress induced pathology, but especially in the stress induced adaptation e.g. stress coping response is neither well understood nor investigated with due efforts. Although there are enough data showing in the direction of different organ system being strongly involved in the regulation of adaptation mechanisms, and the capacity of the organism to respond to general stress, we still lack general principles adopting this knowledge.

Learning objectives:
• This lecture is going to give an overview on consequences of acute and stress upon different organ systems, such as GI tract, respiratory system, cardiovascular system, immune system, endocrine system, the locomotor system and the skin. In this, morphological, pathophysiological and clinical aspect will be addressed.
• Stress coping response and involvement of different organ system in its concept will also be outlined.
• The involvement of molecular mechanisms in the reaction of different organ systems to stressors will also be briefly elucidated.
• We will also touch the particular importance of stress-induced pathology of different organ systems to the general population and public health.
• In order to cover all aspects of the problem we will also outline some integrative aspects forming the basis of possible integrative therapeutic approaches.
• It will be interesting to see how complex roles can be assigned to the elements of the GI tract, to the musculoskeletal system or even to the skin. Integrative approaches in their understanding will also be proposed.
• It is obvious that in order to be able to successfully confront the consequences of stress induced pathology we must understand their background and pathogenetic mechanisms. On the other hand, understanding the role of different organ systems in adaptation to stress can help us to support this role, prevent possible treatments which could be in collision with these adaptation processes and create new therapeutic approaches and modalities.
Effect of BPC-157 on GI ulcers

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Rationale:
While huge number of various agents, including many peptides, in particular angiogenic growth factors, stable gastric pentadecapeptide could be a particular one. Namely, the concept holds particular BPC-157 significance for cytoprotection and blood vessels providing that BPC-157 is novel mediator of Robert’s cytoprotection. Namely, unlike standard peptides (also implicated in the healing process), BPC-157 is naturally present and stable in human gastric juice. Thereby, providing a convincing range of the animal models of gastrointestinal ulcers and other GI-tract disturbances evidencing that BPC-157 is thereby effective orally, parenterally and locally, it is quite likely that BPC-157 continuously maintains gastric mucosal integrity like we originally claimed. Along with its cytoprotective background (epithelium and endothelium protection) BPC-157 is very safe, LD1 not achieved, thereby already tested in clinical trials, thus, more than suited for long looking healing generalization, and to implement generalization of Robert’s stomach cytoprotection concept for the other tissue healing, various gastrointestinal ulcers, in particular. As a prove of the concept, it should be the evidence that BPC-157 heals all gastrointestinal tract, including fistulas healing, external and internal, for example, esophagocutaneous, gastrocutaneous, duodenocutaneous, colocutaneous rectovaginal, colovesical, and duodenocolic, providing a convincing evidence for an effective simultaneous healing of different tissues. Finally, the question arises whether Andre Robert for his cytoprotection and adaptive cytoprotection adopted previous Selye’s stress concept and general adaptation concept. And if yes, the next question is whether the likely solution for real implementation of Robert’s cytoprotection and adaptive cytoprotection, like BPC-157 indeed may represent, represents likely solution for implementation of realization of Selye’s stress concept, and his long looking (but newer discovered) integrative factor that would integrate adaptive bodily stress response.

Learning objectives:
• Analysis of Robert’s cytoprotection and adaptive cytoprotection
• Selye’s stress concept and Robert’s cytoprotection/adaptive cytoprotection
• BPC-157 as novel mediator of Robert’s cytoprotection and adaptive cytoprotection
• Cytoprotection as the endothelium protection
• BPC-157 beneficial effects on particular ulcers in GI-tract as cytoprotective effects
• BPC-157 and the endothelium protection as the background of its healing effect
Hans Selye, the grandmaster of creativity and originality

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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 Chirurgie 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
Do regulatory agencies (e.g., for food, drugs and the environment) create psychological stress?

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**Rationale:**
Regulatory systems begun to emerge during the last century and gradually reached their currently high level of sophistication. What have been earlier modest approaches to curb and remedy stressful anomalies in limited areas (e.g., food, drugs and the environment) and only in a few countries, developed into complex global regulatory schemes. The most powerful propelling force of this process was the combination of efforts to protect the health and life as well of the economic interests of the public. Industry and commerce were also highly interested and active players in this process. With the increase of international trade during the second half of the past century the need has arisen for a universally acceptable measure to ascertain both a high level of product safety and fair trading practices in international commerce with a wide range of commodities. *Science* with its proverbial reputation of objectivity has been identified and increasingly implemented in international agreements regulating trade. Regulatory decisions have a direct relevance for each and every citizen. Hence, the ever-increasing interest of the public in safety issues is not surprising. Although, in general terms, it can be justifiably said that, for example, food and drugs are safer today than they ever have been, nevertheless, as shown by the results of various public opinion polls, the vast majority of consumers is concerned about the safety of both their food and medicinal products.

While the great significance of science in regulatory decisions is now universally recognised, despite great progress, unresolved questions and misunderstandings hamper international efforts to mutually recognize and/or harmonise heterogeneous regulatory systems. It should however be remembered that, even provided the optimal outcome of ongoing negotiations (e.g., TTIP), a blueprint for a watertight system running with flawless reliability cannot reasonably be expected to emerge. Rather, inherent in the nature of science and of commerce, the need for a well functioning dispute-settlement mechanism characterized by a high level of competence, fairness and transparency will unabatedly remain.

The question as to whether regulatory measures are *creating* or *alleviating* psychological STRESS is a key issue that will be the central topic of the presentation. The author, from a basic researcher turned into regulator at national and international levels, will, based on his decades-long experience, cite numerous cases that attracted worldwide attention and led to intense debates.

**Learning objectives:**
- Science in relation to public interest
- Science in relation to commercial interest
- Regulation in whose interest?
- Regulation: creating versus alleviating stress
- The issue of fraud in science
Biologic stress: in animals, plants & people

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Rationale:
Throughout evolution, organisms have adapted to environment and stress in various ways. In plants, stress response has broader meaning of reaction to abiotic and biotic stimuli. In animals, as organisms become more complex, stress response implies narrower phenomena as it comprises more sophisticated, interconnected mechanisms in highly specialized tissues. Although there are differences in stress reactions among species, there are some strategies that both plants and animals use in order to overcome stressful events; variability, redundancy and overcompensation. All responses begin with the recognition of stress and continue with removal of a stressor actively by either relocation or avoidance, which can lead to a recovery and adaptation or exhaustion and irreversible damage. At the organism level stress response can lead to stress tolerance and avoidance, while at the population level stress responses can result in appearance of novel traits or extinction.

Learning Objectives:
• Emphasize the role of stress on evolution of living beings
• Describe the differences in stress response among various species: Plants, insects, vertebrates
• Explain the universal concepts of stress-coping strategies
• Obtain an understanding of the role of variability, redundancy, overcompensation and nonlinearity in stress response.
Stress is 80 years old: Distress vs. eustress

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Rationale:
Exactly 80 years 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 changes 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
Stress & structural GI diseases: Gastro-duodenal ulcers & IBD (inflammatory bowel diseases)

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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
The neuroendocrine mechanisms of stress

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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
Animal models of stress and anxiety

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Rationale:
Anxiety disorders and stress related disorders (post-traumatic stress disorder, unipolar depression) are important psychiatric conditions which present significant economic burden for health systems and society worldwide. From the time of Charles Darwin and Hans Selye we know that human beings and animals, mammals especially, express certain emotions (fear, pain, distress) in similar way. Many brain structures involved in limbic regulation of emotion, such as the hippocampus and amygdala, are evolutionarily conserved from rodents to man. Basically, these are the reasons why we use animals (mainly rodents) in research aimed to ethiopathogenesis of anxiety and stress disorders. Besides, animal models of anxiety and stress are very important for identifying efficacious anxiolytic and/or antidepressant drugs in preclinical phase of drug development. In lecture proposed for submission in Stress Summer School, most popular rodent models of stress (environmental, physical, psychosocial, emotional, and perinatal) and anxiety (elevated plus maze, light-dark box, open field, hole-board, conditioned fear, and Vogel test) will be described. Also, experimental protocols (including video presentation of selected experimental protocols) for anxiety testing and stress induction will be presented, reviewed and discussed. Finally, increasing use of zebra fish in the field of stress and anxiety research will be commented.

Learning objectives:
- Classification of animal models of stress and anxiety
- Description of the main rodent stress models
- Review of experimental protocols for stress induction
- Review of experimental protocols for anxiety testing
- Zebra fish as the model for stress and anxiety
Historic origins of the stress concept

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Rationale:
The term "stress" had none of its contemporary connotations before the 1920s. Hans Selye discovered the biological stress response, although he was not the first to use the word stress. Walter Cannon used it in 1926 to refer to external factors that disrupted what he called homeostasis.
Non-specific adaptive responses were described in the medical literature before Selye. Twenty-four centuries previously, a Greek physician, Hippocrates had written that disease was not only pathos (suffering), but also ponos (toil), as the body fought to restore normalcy. Thus, the stress concept may be led back to the Greek conception of ponos.
Selye at the age of 17 as a medical student observed that patients suffering from different diseases often exhibited identical signs and symptoms – “they just looked sick”. This observation may have been the first step in his recognition of stress. Biological stress, as we know now, was first described by him in a single-author short report on ‘A syndrome produced by diverse nocuous agents’ published in the 4th July 1936 issue of 'Nature'. His experiments and results led to recognition of the non-specific general adaption syndrome (GAS), which he later renamed stress and used for the title of his monograph in 1950.
His historic monograph ‘Stress’, followed by ‘Animal Reports of Stress’ (between 1950-1956), as well as his last major book were devoted to his famous concept of stress. Stress in Health and Disease (1976) was his last attempt to deal as a single author with all aspects of this complex subject. We also have to underline that the word stress was not used for several years after his first publications on the subject in 1936.

Learning objectives:
• This presentation will put Selye's seminal discovery in historic perspectives in order to better understand the origins of concept of biological stress.
• Give credits to major personalities who made medical discoveries.
• Although GAS-like adaptive or defensive reactions have described by a few scientists before Selye, we should appreciate that he was the first one to implicate the neural and endocrine system.
• To present the evaluation of causes of diseases: from mythical forces and miasmas to specific causes (like microbes, chemicals, physical agents). Selye was the first to identify that these agents despite their specific action also trigger similar adaptive-defensive reactions in our body that unfortunately may also result in maladaptation and disease.
Psychological trauma – past, present, future

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Rationale:

This article is a review of the literature on intergenerational transmission of psychological trauma to children. A review is about risks, tendency, mechanisms, vulnerability of parents, children and families, resilience and other factors in the transmission of posttraumatic stress psychopathology (war veterans and intergenerational transmission). There are more questions about developmental models and understanding of this problem.

PTSD is now defined as a pathological anxiety that usually occurs after an individual experiences or witnesses severe trauma that constitutes a threat to the physical integrity or life of the individual or of another person. The individual initially responds with intense fear, helplessness, or horror. The person later develops a response to the event that is characterized by persistently reexperiencing the event, with resultant symptoms of numbness, avoidance, and hyperarousal. These symptoms result in clinically significant distress or functional impairment. To meet the full criteria for PTSD, these symptoms should be present for a minimum of 1 month following the initial traumatic event. The events experienced may be natural disasters, violent personal assaults, war, severe automobile accidents, or the diagnosis of a life-threatening condition. For children, a developmentally inappropriate sexual experience may be considered a traumatic event, even though it may not have actually involved violence or physical injury.

Clinical observations and empirical research have shown that the consequences of traumatic events are not limited to the persons immediately exposed to the event, and that they often affect significant others in their environment such as family, friends, and caregivers. Such effects include a variety of posttraumatic manifestations such as headaches, breathing difficulties, intrusive imagery, heightened sense of vulnerability, difficulty trusting others, and emotional numbing. A variety of terms have been used to describe this phenomenon (secondary traumatization, secondary traumatic stress, covictimization, secondary survivor, traumatic countertransference. The risk is greater in families where the veteran father suffers from PTSD. Examining the literature revealed that in most studies, the fathers who were examined had participated in combat and were diagnosed with PTSD. PTSD was far more significant than exposure to combat.

Examining the literature revealed that research has focused on three broad categories (mental distress, family functioning, and self-esteem). The literature also revealed aspects of direct and indirect mechanisms of intergenerational transmission. Research findings indicate that to achieve a comprehensive understanding of the consequences of intergenerational transmission of trauma, it is necessary to adopt a broader perspective, including an examination of factors that mitigate distress, as well as an examination of the positive aspects of the transmission and factors that reduce the possibility of transmitting distress. It is important to study not only the father’s psychological state, but also to explore the contribution of the child, mother and social system at large to intergenerational transmission of trauma.

Learning objective:

• Clinical observations and empirical research have shown that the consequences of traumatic events are not limited to the persons immediately exposed to the event, and that they often affect significant others in their environment such as family, friends, and caregivers.
• Examining the literature revealed that research has focused on three broad categories (mental distress, family functioning, and self-esteem).
• The literature revealed aspects of direct and indirect mechanisms of intergenerational transmission.
• War veterans with PTSD, family members and extrafamilial factors and social context may contribute to intergenerational transmission of PTSD.
The brain-gut axis: Basic concepts - Neurogastroenterology of functional GI disorders: Sensory afferent neurons and anti-enteric neuronal antibodies

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Rationale:
Functional gastrointestinal disorders are those in adults and children in which no abnormal metabolic or physical processes, which can account for the symptoms, can be identified. Nevertheless, “functional” often is shorthand for “we don’t know what is wrong”. The irritable bowel syndrome (IBS) is an example of a significant functional disorder, which affects 10-20 percent of populations worldwide. Predominant symptoms of IBS are abnormal defecation associated with abdominal pain, both of which may be exacerbated by psychogenic stress.

Learning objectives:
• Obtain an understanding of what is a functional GI disorder in terms of the irritable bowel syndrome.
• 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.
• Gain insight into enteric neuropathy as applicable for IBS.
• Discuss autoimmune enteric neuropathy.
• Address the question of whether a valid biomarker for the irritable bowel is likely?
Novel role of melatonin, a key hormone of brain-gut axis, in health & disease

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Rationale:
Virtually all aspects of human physiology (sleep-wake cycles, body temperature, hormone secretion, gastrointestinal secretory and motor activities etc.) are mapped in 24-h circadian rhythm and melatonin is its one major endogenous regulator. Melatonin helps organisms to anticipate periodic changes in the environment, and consequently represent important adaptive mechanisms, allowing the organisms to survive under markedly altered conditions. Melatonin-related biological rhythms play an important role in physiological gastrointestinal and liver functions and adaptation to stress.

Circadian dysfunction is contributing to the incidence of a wide range of clinical pathological conditions including: sleep disorders, inflammation and even carcinogenesis. Disorders of melatonin releasing associated with aging or environmental factors (rotating shift work, often trans-meridian flights) may result in several gastrointestinal and hepatic diseases, such as, alterations in colonic motility, functional dyspepsia, GERD, peptic ulcer disease, non-alcoholic fatty liver disease, as well as metabolic syndrome.

In this context, here are also reports that L-tryptophan, precursor of melatonin, as well as melatonin acts as an esophagoprotective and reducing hyperglycemia agent.

Learning objectives:
Review of historical outline of melatonin synthesis and old and new melatonin functions.
Describe the role melatonin, as a conductor of large "orchestra" signaling pathways related to chronodisruption.
Translate discoveries in present pre-clinical and clinical study in future perspectives of melatonin in health and diseases.
Describe of L-tryptophan and melatonin effects on esophageal mucosa during stress injury.

References
Impact of physical activity, aging, postprandial hyperglycemia and obesity on stress resistance

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Insufficient physical activity associated with the modern sedentary lifestyle is a major contributor to increased risks of incident of lifestyle diseases, which included obesity, cardiovascular diseases (CVD), type 2 diabetes, osteoporosis, cancer, and depression. Despite a 10-20% reduction in CVD mortality since 80-s, lifestyle diseases are global non-infection epidemic trend. Type 2 diabetes is an example of a lifestyle disease related with overloaded sugar and postprandial hyperglycemia, escalating as a world public health problem, and the rapidly rising incidence in young people will certainly be followed by premature coronary and stroke disease. Recently was shown that low stress-resistance is a model of premature senescence, CVD, immunosuppression and oxidative stress. In meantime, physical activity can improve stress-resistance and prevent lifestyle diseases.

References
Bloomer RJ, Lee SR. Women experience lower postprandial oxidative stress compared to men. SpringerPlus, 2013; 2(1), 553.
Abstracts of free communications
WHY ARE MEN MORE SENSITIVE TO CHRONIC STRESS?

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Introduction: You are in a store and all of a sudden a man enters and announces that he plans to rob the store. He says that he will kill you and everyone present if you don’t cooperate with him. What do you do? The answer depends from person to person and it is highly gender-dependent. Men will either try to run away immediately or fight the robber. Women will most likely try to talk themselves out of this situation. According to scientists there is a distinct response in men and women – stress will provoke “fight or flight” reaction in men and women will try to “tend and befriend”. This is an example of acute stress which is short however it causes strong reaction. It leads to a conclusion that men will pull themselves through dangerous stressful event easier than women. Chronic stress is of a much longer period and disrupts homeostasis which puts a burden on entire body and leads to a variety of diseases. Homeostasis is regulated by a complex endocrine processes engaging the hypothalamic-pituitary-adrenal axis (HPA) and sympathetic autonomic system. If stress is long and strong enough, the action of HPA is unsuppressed. It results in prolonged elevation of cortisol, induced production of energy, vasoconstriction, lipolysis, proteolysis, immunosuppression, and suppression of reproductive function to save energy and retain overall homeostasis. Busy, working mothers have proven – women manage stressors better than men.

Methods: Review articles in the PubMed database have been used for the purpose of writing this abstract and key words “gender”, “acute stress”, “chronic stress” were taken in count while enquiring the topic.

Results: In couple of studies stress research in female rats showed no impairment in object recognition upon stress, while males were not so successful. Impairments in object recognition demonstrate a disruption in prefrontal cortex, part of the brain responsible for working memory, attention, decision-making and other executive processes. Chronic stress caused prefrontal degeneration in male rats, but had no effect in females. The answer of women protection from chronic stress lies in estrogen. When estrogen signaling was activated in males, negative effects of chronic stress were blocked. In female rats estrogen was protective even after ovariectomy which is explained by estrogen production in various tissues (brain, adrenal glands, liver, subcutaneous fat tissue…).

Conclusion: Males cope better with acute stress and women are less susceptible to chronic stress until the period of menopause. Estrogen replacement therapy offers a good strategy for postmenopausal women affected by chronic stress. Since males would have strong hormonal side effects from estrogen treatment a novel compound similar to estrogen that lacks these side effects could be engineered and used for stress-related issues in males. Dear men, I am sorry, but it seems there is still no effective way for you to cope better with stress.

THE ROLE OF TRANSCRIPTION FACTOR EGR-1 IN THE PATHOGENESIS OF STRESS-INDUCED GASTRIC ULCERS

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Introduction: Despite the fact that different factors are involved in gastroduodenal ulcer development, the role of Egr-1 is poorly understood. So, the aim of this study was to investigate mechanisms of erosive and ulcerative lesions development in the stomach involving redox-sensitive transcription factor Egr-1. Methods: Gastric ulcers were induced in male rats by immobilization stress combined with water-immersion (IMO-WI). Serum cortisone levels and gastric mucosal oxygen partial pressure were measured by chemiluminescence method and Hypoxyprobe-1™ kit. Expression of proteins was determined by Western blot analysis and RT-PCR. For inhibition of Erk-1/2 MAP kinase was used selective inhibitor PD98059. Results: We found that the redox-sensitive transcription factors Egr-1 and Sp-1 enter into competitive interactions in the early stages of stress-induced gastric lesions in rats. Stress-induced ulcers caused upregulation of protein VEGF and bFGF. Development of erosive and ulcerative lesions in the stomach during stress action was accompanied by a decrease in the partial pressure of oxygen in the cells of the gastric mucosa, and
increased level of HIF-1α and reduction of protein SH-groups. In the early stages of stress-induced gastric lesions increased concentrations of the stress hormone cortisone in serum was associated with activation of Erk1/2 MAP-kinase pathway and did not affect p38. Inhibition of Erk1/2 by the selective inhibitor PD98059 lead to more aggressive lesions of the stomach accompanied by a reduction in Egr-1, and accordingly, pro-angiogenic factors VEGF and bFGF.

**Conclusions:** The redox sensitive transcription factor Egr-1 is a leading transcription factors in the pathogenesis of stress-induced gastric lesions. This factor is activated by hypoxia and launches gastroprotective mechanisms through Erk1/2-dependent mechanisms.

**CELECOXIB INDUCED GASTROINTESTINAL, LIVER AND BRAIN LESIONS IN RATS, COUNTERACTION BY BPC 157 OR L-ARGININE, AGGRAVATION BY L-NAMED.**

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**Introduction:** Non-selective NSAIDs induce gastrointestinal, liver and brain-toxicity in rats while celecoxib, COX-2 inhibitor, is considered less toxic. We used stable gastric pentadecapeptide BPC 157 to counteract/reveal celecoxib induced toxicity and NO-system involvement. **Methods:** Celecoxib (1g/kg bw ip), was combined with BPC 157 (known to inhibit these lesions, 10µg, 10ng/kg ip) and L-arginine (100mg/kg ip) therapy, as well as NOS-blockade (L-NAME) (5mg/kg ip) given alone and/or combined immediately after celecoxib. Gastrointestinal, liver, and brain lesions and liver enzymes serum values in rats were assessed at 24 hours and 48 hours thereafter. **Results:** High dose celecoxib administration, also through NO-system dysfunction, leaded to gastric, liver, brain lesions and increased liver enzymes serum values. The L-NAME-aggravation of the lesions was with gastric lesions, while in liver and brain lesions there was mitigation of L-arginine beneficial effect. L-arginine counteracted gastric, liver and brain lesions. These provide the NO-system mechanism(s), both NO-system agonization (L-arginine) and NO-system-antagonization (L-NAME), on the whole behind all of these COX-phenomena. An even more complete antagonization was with BPC 157 (at both 24 hours and 48 hours period). Beneficial effect was evident in all increasingly negative circumstances of celecoxib and L-NAME application and in all BPC 157-groups (L-arginine+BPC 157; L-NAME+BPC 157; L-NAME+L-arginine+BPC 157). Thereby, these findings evidenced that BPC 157 may equally counteract both COX-2 inhibition (celecoxib-noxious effect on all lesions counteracted) and additional NOS-blockade (celecoxib+L-NAME-noxious effect also equally counteracted). **Conclusion:** BPC 157 or L-arginine alleviate gastrointestinal, liver and brain lesions, readdressing NSAIDs’ post-surgery application and NO-system involvement.

**ANALYSING THE EFFECT OF IMIDAZOLINE RECEPTOR LIGANDS ON DSS-INDUCED COLITIS**

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**Introduction.** Both imidazoline receptors (IRs) and their putative endogenous ligands (such as agmatine) have been identified throughout the gastrointestinal (GI) tract, but it is still a matter of debate, whether they have any role in the modulation of GI functions. In the last years it was raised that IRs might be related to sphingosine 1-phosphate (S1P) receptors, which are promising targets in the treatment of inflammatory bowel diseases (IBDs). Hence, in the present study we aimed to analyse the effect of different IR ligands on the development of dextran sulfate sodium (DSS)-induced colitis in mice. **Methods.** The experiments were carried out in female C57BL/6 mice. DSS (2,5 %) was added to the drinking water for 7 days. IR ligands were injected in different doses intraperitoneally, once or twice daily. **Results.** 1. DSS induced a moderate-to-severe inflammatory reaction in the colon, which was accompanied by bloody diarrhea, weight loss and colon shrinkage. 2. None of the tested IR ligands (moxonidine, rilmenidine, AGN 192403, agmatine, harmane) altered the DSS-induced inflammation significantly. **Conclusions.** Our results indicate that IR ligands do not have a major impact on the development of DSS-induced colitis. However, further studies with
other colitis models are required to completely rule out the role of IRs in the pathomechanism of IBDs. This work was supported by the Austrian-Hungarian Action Foundation (88ou2 project) and by the Hungarian Scientific Research Fund (OTKA PD 109602).

PROTEOMIC-BASED IN SILICO MODEL OF ACUTE STRESS THRESHOLD – A PILOT PROJECT
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Stress is a primitive and nonspecific bodily reaction to polimodal stimulation. A unimodal stimulus alone cannot trigger the stress response, but few stimuli of different modality applied together should regularly result in stress activation. During the metazoan evolution, multicellular organisms have developed the ectoderm, an outermost cellular layer through which the interaction with the environment is carried out, and even its later evolotional derivatives have maintained exactly the same function. Stress is also ectodermally-based and represents a form of interaction with the environment that is highly conserved among species. For that reason, we hypothesize that signaling pathways, activated by polimodal stimulation, share the same highly conserved proteins that are conditioning the threshold for stress reaction in various species. Identification of common nodes in cross-talk between stress-implicated signaling molecules could give us insight about mechanisms underlying the stress threshold on the cellular level. In order to test our hypothesis, we built the signaling pathways networks of ectodermal tissue in C. elegans, Drosophila melanogaster, Mus musculus and Homo sapiens, using the Cytoscape, a software for biomolecular interaction networks analysis. Proteomics data was obtained from the Cytoscape Public Database, Protein Atlas and Human Proteome Map. We corrected the data for homologous proteins, in order to reduce the networks’ redundancy. Network analysis revealed edge convergence towards a group of nodes implicated in Mitogene-Activated Kinase (MAPK) signaling in cases where many pathways were activated at the same time. This convergence was non evident when each pathway was active alone, suggesting the polistimulation dependence. The most interacting proteins, regardless of the species, under such conditions were MEKK, ASK, MLK and TAK (corrected for homology). Preliminary results might suggest that under conditions of hyper- and polistimulation, cellular signaling becomes less specifically directed and MAPK pathways are being amplified. Since MAPK signaling mediates DNA-repair, apoptosis, heat shock protein upregulation, cell cycle arrest etc., all of which may be useful in stress, it could be suggested that MAPK amplification may represent a cellular hallmark of the stress threshold trespassing. However, no definite conclusions are to be drawn, because results of in silico experiments are yet to be confirmed or rejected in vivo.

THE HANS SELYE CLUB IN BRATISLAVA
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Hans Selye Club was founded in Bratislava soon after the change of regime in March 1990 by the Hungarian students of the Faculty of Medicine of Comenius University led by János Filakovszky. This is the first organization on the birthplace of Professor Selye, which adopted his name after the agreement of his widow. Since the foundation of the club its members have always attached importance to foster Prof. Selye’s inheritance. In 1991, thanks to the initiative of the Hans Selye Club, a commemorative tablet was unveiled in Komárno combined with an inspiring ceremony in honor of Professor Selye. The commemorative tablet marks his residence in the town from 1907 to 1929. At present, the Hans Selye Club is the biggest Hungarian professional students’ organization in Bratislava with eighty active members. The club is a kind of social base that enables its members to keep in touch with each other and it supports our professional development. Scientific medical discussions, organized twice in every semester in Bratislava, are a faithful representation of that. Among our guests have already been: geneticist Endre Czeizel, transplantologist Filip Danninger, angiosurgeon Ferenc Žernovický, epileptologist-pharmaceutical research scientist János Filakovszky, molecular biologist Csaba Bödör, toxicologist Gábor Zacher and also Prof Arpad Somogyi, Prof Sandor Szabo. Besides fostering communal life our club attaches great importance to devotion to science and permanent progress. Our
members can have a possibility to do practice during the summer season at the best hospitals in Budapest such as St. Imre Teaching Hospital, Honvéd Hospital or Heim Pál Children's Hospital. The Teddy Bear Program, based on the Scandinavian model, according to which we visit nursery schools and provide professional and playful activities to children, is also very popular. In the future, we are going to gain an opportunity to get to know the world of international scientific conferences much better. Last year we were pleased that a club member participated in the annual scientific meeting of HMAA in Sarasota. This possibility was supported by the Zoltan Gombos Fund. Furthermore, we are extremely proud of being invited every year to an annually organized Summer School on Stress by Prof. Sándor Szabó. The Hans Selye Club has had three hundred members so far and since it was founded it has been a proper place for cultivating an acquaintance and nursing relations between experienced doctors and medical students. In the future, we would like to maintain our successful projects as well. We believe that we will become proficient and gifted doctors if we do not lose the relationship with our patients as well as with each other and we ensure our gradual development. Our mutual aim is to establish a Selye alumni, where we could utilize professional and human relations between medical students and specialists.

**PSYCHOLOGICAL STRESS IN SPORTS COACHES: A REVIEW OF CONCEPTS, RESEARCH, AND PRACTICE**

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**Introduction:** Stress is present in everyday life of every individual. Types of stressors we are influenced depend on our personal lives – the type of our jobs, environment that we live in and so on. Some professions are more stressful others. In sport, almost everybody is talking or writing about athletes, their success and failure, training, injuries and their everyday life. There are many studies of stress in sport focused on athletes. But, what about their coaches? Sport coaches work in the environment that imposes many pressures on them. **Methods:** Review article found in PubMed database (key words “stress”, “sport”, “coaches”) was used to investigate this topic. **Results:** The literature on stress in sport coaches is less confusing than in athletes. The term stress should be used to represent the overall process including stressors (environmental stimuli encountered by an individual; refer to events, situations or conditions), strains (an individual’s negative psychological, physical and behavioral responses to stressors), appraisals, and coping responses. Psychological impact of these demands will be shown via critical review of the literature pertaining to stress in sport coaches and how stress effect their lives. This review is separated into three main sections: conceptual and definitional issues, theoretical and empirical issues, and implications for applied practice. The review shows which stressors are mostly present in the lives of coaches, coaches’ appraisals of and responses to these demands, and the impact that has on their personal well-being, job performance, relationship with athletes and everyday life. Review also describes the influence of various personal and situational characteristics of sport coaches and their attitudes about stimuli they are struggling with in everyday life. It is also discussed how people close to coaches help them to beat or reduce the stress. **Conclusion:** It is very important that the potential health and performance costs of psychological stress to sports coaches are significant and that all environment influences, either good or bad, can change quality of coaching and consequently results in athletes trained by these coaches. Stress in coaches is an ongoing problem that needs to be monitored because of the dynamic nature of stress.

**“COMFORT FOOD” – COMFORT JUST FOR A MOMENT**

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**Introduction:** Overeating seems to be a major problem nowadays and it brings along consequences as obesity, diabetes type II, cardiovascular disorder as well as cognitive disorders. Stress has considerable impact on feeding behavior. Most of individuals will increase food intake during chronic stress episodes. The common feature of the overeaten food during these episodes is high palatability and it is highly caloric. It is often called “comfort food”. The
rewarding sensation caused by this kind of food overcomes feeling of distress and discomfort and presents the current explanation of overeating-during-stress phenomenon. **Methods:** Original scientific articles and review articles from the PubMed database have been used as a source of information for investigation of this topic and key words "obesity" and "stress" were taken in count. **Results:** Many studies have confirmed that consumption of highly palatable food attenuate stress response. However, the mechanism underlying the explanation is unclear. Limited data is available on brain networks which are controlling food craving behavior during stress and consequently diminishing stress caused discomfort. The main player in stress-response system, hypothalamus-pituitary-adrenal gland (HPA) axis, and amygdala – the emotional brain, are connected with this type of behavior. Suspected metabolic signal to inhibit the stress system comes directly from fat depots. The possible mechanism starts from elevated levels of glucocorticoids (GC). Stressors trigger secretion of GCs what in turn causes increase of corticotropin-releasing factor (CRF) mRNA in the central nucleus of amygdala. CRF will enable activation of brain pathways involved in management of body's chronic stress response. Furthermore, elevated GCs promote rewarding or compulsive activities such as eating palatable food. Finally, increased GCs act to build up abdominal energy stores. **Conclusion:** Therefore, under conditions of chronic stress the brain got the signal to seek high-energy food. If the individual successfully found it the stress and stress-related uncomfortable feelings attenuated. Also, increased abdominal fat provides signals to inhibit further energy intake. Particularly, the expression of CRF in hypothalamic region that regulates adrenocorticotropin attenuates. So, it may be that people eat "comfort food" in an attempt to reduce the activity in the chronic stress-response network with accompanying anxiety. These attempts work well for individuals for short periods of time. However, the use of these foods throughout lifetime results in abdominal obesity which is strongly associated with life-threatening disorders.

**SHORT STATURE AS A RESULT OF CHRONIC PSYCHOSOCIAL STRESS**
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**Introduction:** Various hormones are influence by chronic stress. Those changes result in many pathological effects on endocrine system like hyperthyroidism, diabetes mellitus, gonadal dysfunction and psychosocial dwarfism or short stature. Psychosocial short stature in children is a growth failure without any organic etiology, associated with chronic psychosocial stress. It is presented as failure to thrive, which is low rate of increase in the weight; children are lacking in weight and height in comparison to their peers. If removed from the source of stress, some of the children show spontaneous “catch-up” growth without additional treatment. **Methods:** In this study researchers measured growth-hormone dynamics in the hospital group. Standard behavioural measures were also collected. Group was compared to the children of short-normal stature. **Results:** Growth-hormone insufficiency was found. Subgroup of the participants shown characteristic behavioural, hyperphagia and polydipsia. That subgroup showed that when removed from source of stress, growth-hormone insufficiency is resolved, unlike non-hyperphagic subgroup. **Conclusion:** Psychosocial short stature, in which growth hormone insufficiency is present, is a result of chronic stress exposure. Along with short stature, in some individuals hyperphagia and polydipsia are presented. Within that syndrome, if patients are removed from source of stress, growth-hormone insufficiency is resolved.

**CAN MICROBES IN OUR GUT INFLUENCE HOW WE DEAL WITH STRESS?**
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Microbes are everywhere. The moment we enter the world, microbes colonize our bodies. The human microbiota consists of the 10-100 trillion symbiotic microbial cells harbored by each person, primarily all the bacteria in the gut together posses 100 times more genes than the human genome. They exist in harmony with their hosts and interaction between the bacteria and host is mutually beneficial with the bacteria involved in energy regulation, gut barrier function, protection from pathogens, and immune system function amongst others, while the host provides...
the nutrients and environment in which the bacteria can thrive. Recently a hypothesis of gastrointestinal microbiota as a key regulator of centrally mediated events including stress and neuroinflammation was developed. Stress is a dynamic condition in which homeostasis of an organism is disturbed or threatened. The coordination of stress defensive response is governed by a pathway of the hypothalamic-pituitary-adrenal (HPA) axis. Stressful stimulus increases glucocorticoid level in systemic circulation. It primes the body for „fight or flight“ response. Different types of psychological stress can alter the composition of gastrointestinal microbiota. The number of experiments have been trying to interrogate the role of the microbiota in stress behaviour, including different conditions and models: prebiotic and probiotic intervention, antibiotic administration, faecal transplantation and the use of germ-free and specific pathogen free animals. Studies have shown that animals raised in a sterile environment from birth (germfree) exhibit an exaggerated HPA axis activity with elevated ACTH and corticosterone levels in response to a mild novel arena which normalized after colonization with commensal bacteria from control mice. Also, data suggest that the relationship between gut microbiota and stress and anxiety-related phenotype may be subject to temporal, sex, strain and species dependent factors. Experiments in which antibiotic interventions were used to diminish stable core bacteria showed that antibiotic administration was able to prevent stress-mediated changes in behaviour. Studies have also investigated the effect of probiotic intervention and those rats who had been given different probiotics normalized the behavioural phenotype - in most studies probiotics reduced the stress-induced increase in corticosterone. In one study the effect that was abolished with vagotomy, suggested that a functional neural relay from gut to brain is necessary for governing stress response. In a clinical setting, using cortisol as an index of stress response, different probiotics and prebiotic were effective in boosting the subjects resilience to stress and improved emotional responses in healthy subjects. So, we can conclude that studies, so far, suggest that resilience to stress and dysfunction of stress may be dependent on the diversity and complexity of gastrointestinal microbiota and possibly have role in protection against the development of stress related disease. Although, the question remains; how is the microbiota of the gut modulating physiological response at a central level? A number of mechanisms have been suggested, however the precise mechanism or mechanisms of action are, as yet, unresolved.

AN ALTERNATIVE TO RED BULL
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Stress and fatigue. How to fight them? Meditation. Yoga. Positive attitude. Having proper amount of „me time“. Sure you'll figure out the way to fit all of this along with work, kids and responsibilities in one single basket called life. But if you're like most of the people, you end up asking yourself who are those people reaching for yoga mats and home-cooked organic meals when you only feel like reaching for a cup of coffee and some sugary snack. The thing is, caffeine and sugar don't do anything but turning your day in a rollercoaster of highs and lows. Lifestyle changes are for sure the key to reducing stress, in the long run. Fortunately, there is something to help us while we struggle to build better habits. Adaptogens, special herbs that help your body adapt to stress and resist fatigue in a non-specific way, increasing your overall resistance against physical, chemical and biological stressors. They've been used in Chinese and Indian Ayurvedic medicine for centuries. Till our time studies have found evidence to support facts about positive benefits of adaptogens and their safety in long-term use. Adaptogens can calm you down and boost your energy at the same time. By supporting adrenal function, they counteract the adverse effects of stress. They enable the body's cells to access more energy, help them eliminate toxic byproducts of the metabolic process and help the body to utilize oxygen more efficiently. Unfortunately, in Western medicine the concept of adaptogens is still controversial. The idea that one herb can have a broad range of physical and mental health benefits is a bit unbelievable. But if we think this through, we'll come to conclusion that there are many health problems related to stress, including depression, heart attacks, hypertension and increased susceptibility to infection. However, simply taking an adaptogenic supplement doesn't make you live longer. They are more of an ingredient for “taking your health to the next level” long term.
SLEEP DEPRIVATION REALLY REFLECTS MY MEMORY!
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Once upon a time, when I was a young student, trying to catch up with all the medical material that I was confronted to, day wasn’t long enough for all my obligations, and wakefulness was the only acceptable solution in sight for me. My sleeping period lasted 6, 5, 4 (sometimes even less!) hours per night, depending on how many papers, books or materials was needed to read and memorize. As a rule, a day after staying awake almost all night, my head was like an empty balloon and awful feeling of not having control on my work and personality was pervading me. And pieces of information that yesterday were so simple and easy to memorize, the other day were not memorable. Is it possible that these were the early symptoms of Alzheimer disease? Alzheimer disease, commonly presented among elderly people, is known as a disease that burdens Aβ amyloid in multiple regions of brain, predominantly frontal regions and precuneus. The truth is that I have million times during my life felt the potential symptoms of Alzheimer disease: Oh I can’t remember it! Interesting is that these symptoms intensified after chronic sleep deprivation (4 hours per night during certain period of time). Disturbed sleep is in association with cognitive deficit. Sleep fragmentation and disturbances in older adults are associated with incident Alzheimer disease and the rate of cognitive decline. Poor sleep quality was associated with reduced volume within the right superior frontal cortex and an increased rate of atrophy within widespread frontal, temporal, and parietal regions. Beneficial effect of sleep on memory consolidation is widely accepted in population, but the association between sleep disturbances and Alzheimer disease remained unclear: the question was to which extend is deposition of Aβ amyloid connected to sleep disturbances, duration and its quality. Aβ levels correlate with wakefulness. MRI of brain after chronic insomnia and wakefulness showed decreased gray matter volume of brain and FDG PET showed reduced glucose metabolism in regions of brain that burden Aβ amyloid. Chronic sleep deprivation, as well as orexin injection (peptide that encourages wakefulness) during longer period of time, predisposes people for Alzheimer disease development. On the other hand, people with sleep deprivation, insomnia and delayed falling asleep also accumulate Aβ amyloid in cerebrospinal liquor and multiple parts of brain sensitive to AD. Research showed that sleep-wake cycle and orexin may play a role in the pathogenesis of AD. To sum up, individuals who sleep regularly 8 hours per night without disturbances are supposed to function, learn and remember satisfactorily. So, people, never forget to take your time during night for it. There is no exam more important then it. Except from being tired and indisposed, you would be a potential candidate for Alzheimer disease development.

CELLULAR STRESS IS PASSAGE TO SYSTEM STRESS - THE GOOD, THE BAD, THE UGLY
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The study of mechanisms of adaptation to stressful and extreme environments provides the basis for addressing health problems and using the healing capacity of the adaptive response to stress. Systemic stress response is a cumulative effect of a large number of factors activating their respective signaling cascades. It prepares us to react and allows us to adapt to stressors. All this comes from a huge collaboration network of cells each sensing and responding in different ways to the stressful stimuli. At the cellular level the cellular stress response is a defense reaction to a strain on macromolecules. Such strain commonly results in damage to proteins, DNA, or other essential macromolecules. The cellular stress response assesses and counteracts stress-induced damage, and depending on the duration of stress, temporarily increases tolerance of such damage, and removes terminally damaged cells. Mechanism involved in these processes vary from reducing ROS levels by altering NAD/NADH ratio to involving cytoprotective proteins like heat shock proteins during periods of stress. There is a difference between short term stress response and adaptation to long term stress through homeostasis. Chronic stress damage is the result of the inability to adapt to long-term exposure to stressor. On the cellular level this failure to adapt results in cell death which, depending on how it happens, leads to further stress and damage. This is why cellular stress response is an important part of the overall stress system. The fact that we are constantly under the influence of some kind of stressor can also be used. The more it is known
about how cells correct the damage after exposure to stress leads to new approaches in treating disorders that arise from damaged cellular macromolecules. Being able to activate cell death in response to stress can and is successfully used to treat tumors. The more we know about stress, we are closer to using our innate responses to it for our benefit, than letting it damage. The more we know, the more our enemy becomes our ally. It’s all a matter of perspective.

THE ROLE OF PROLACTIN IN STRESS MODULATION
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Introduction: Prolactin (PRL) produces a wide variety of physiological effects on human body. Some of those are well studied and understood e.g. PRL’s significant role in lactation, angiogenesis etc. However, PRL acts as neuropeptide as well crossing the blood-brain barrier and affecting many brain areas. In addition, it has an intriguing modulating role on stress response. To be more specific, PRL inhibits hypothalamic-pituitary-adrenal (HPA) axis. Stressors activate the HPA axis, which in turn triggers the release of corticotrophin releasing hormone (CRH) from paraventricular nucleus (PVN). CRH consequently affects pituitary gland to release adrenocorticotrophin (ACTH) which, as a result, stimulates adrenal glands to release glucocorticoids. However, stress exposure also stimulates PRL secretion. Methods: Scientific database PubMed was used in order to explore this topic with key words ‘prolactin’ and ‘stress’ mostly taken in count. Results: Most recent studies suggest that PRL, in fact, inhibits HPA axis reactivity, probably via reduction of neural inputs to the PVN. There are many putative mechanisms of action (ion channels, signaling pathway modulation etc.) but PRL stimulation of CRH transcription is interpreted as the most likely. Conclusion: To conclude, PRL stimulation of CRH transcription is probably the mechanism of PRL action on HPA axis, but further studies are needed to understand stress modulation itself and the role of PRL in depressive-like states.

STRESS-RELATED EFFECTS IN AUTOIMMUNITY
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The loss of self-tolerance is the hallmark defect in autoimmunity which renders immune cells unable to distinguish between self and non-self molecules. As a result, immune cells are deployed against endogenous molecules in the body causing tissue damage and ultimately profound disability of versatile organ systems. Physical and physiological stress have been implicated in the aetiology of multiple autoimmune disorders through several mechanisms including alterations in cytokine production, T helper (Th) cell subsets and regulatory function of T lymphocytes. The major players involved in stress-related modulation of immune response are hormones of the adrenal (cortisol, catecholamines) and gonadal glands (estrogens, androgens, progesterone), products of the hypothalamic-pituitary-adrenal (HPA) and the hypothalamic-pituitary-gonadal (HPG) neuroendocrine circuits, which are activated in the presence of an inflammatory stress. Increases in cortisol and catecholamines are associated with a shift in the Th1 (INF-γ, TNF-a) towards Th2 (IL-4, IL-10, TGF-b) cytokine signature that reduces the likelihood of persistent cell-mediated (Th1) up-regulation and thus, activation of autoreactive lymphocytes. Failure of adequate stress response, reflected by low serum levels of cortisol, increases secretion of proinflammatory cytokines, and raises the state of cell-mediated responsiveness that may influence onset and/or exacerbation of autoimmune disorders. Such scenario is often observed during sustained exposure to stress, i.e. chronic stress, when HPA response axis is exhausted and accompanied by decrease in adrenal glucocorticoid release. Conversely, acute stressors, such as interpersonal conflicts, are associated with increased cortisol secretion which acts as natural immunosuppressor. Thus, nature and severity of stress events can influence secretion of stress related hormones and promote afflicting or protective immune responses. However, in the presence of abnormal immunity against self-antigens, stress exhibit adverse effects and may represent a significant contributing factor in development of autoimmunity. Interaction between neuroendocrine immune system, sex-specific variations and vitamin D endocrine system, are all focus of ongoing extensive research that might in the future offer promising treatment strategies for most prevalent autoimmune disorders; thyroid autoimmune diseases, insulin dependent diabetes and rheumatoid arthritis.
ADAPTIVE NEURONAL STRESS RESPONSE

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Introduction: Epidemiological studies on human population showed that diets rich in fruit and vegetable are associated with reduced risk of several major diseases including neurodegenerative diseases such as Alzheimer and Parkinson disease. Plants contain chemicals that can be either toxic in higher doses or can induce beneficial effect on the cell or organism in low doses and that process is called hormesis. At subtoxic doses phytochemicals can activate adaptive cellular stress-response pathways in different cells including neurons. According to that, neurohormesis is a response to a moderate level of stress that enhances the ability of the nervous system to resist more severe stress that might be lethal or cause dysfunction or disease. Such adaptive neuronal stress results in the activation of stress-responsive transcription factors and upregulation of a range of cellular stress-resistance proteins.

Methods: PubMed was used as a main scientific database to search for the appropriate literature in order to prepare this lecture. What is happening on molecular level when stress-response pathways are activated to strengthen neuronal networks and enhance plasticity will be the focus of the lecture. Results: Neurohormetic phytochemicals such as sulforaphane from broccoli, curcumin from Curcuma longa, allicin from garlic and resveratrol from red vine and grapes might protect neurons against injury and disease by stimulating the production of antioxidant enzymes, neurotrophic factors, protein chaperons and other proteins that will help cells to withstand stress. Physical and mental exercise are also showed to be neuroprotective and especially important for successful brain ageing resulting in synthesis of neurotrophins, synaptic plasticity and neurogenesis. This concept of hormetic action of chemicals can be traced to the 16th century when Paracelsus was writing how all things are poison and only the dose permits something not to be poisonous.

Conclusion: The implications of neurohormetic phytochemicals in protection from neurodegenerative diseases are far-reaching with emphasis on dose-response studies to establish the dose range in which hormesis pathways are activated.

THE EFFECT OF BPC 157 ON ISCHEMIC/REPERFUSION INJURIES IN RAT BRAIN

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Introduction: Ischemic/reperfusion injuries are elementary pathophysiological findings in stroke, thereby making it the third most common cause of death in the modern world and the first cause of long-term disability. Pentadecapeptide BPC 157, has already been proven to have an effect on vessel integrity, it is a mediator of Robert’s cytoprotection and interacts with the NO system, all of which, make it a promising agent when it comes to cerebral ischemic/reperfusion injuries. Methods: In this experiment, ischemic/reperfusion injuries are induced using bilateral carotid artery occlusion (BCAO). The effect of BPC 157 on ischemic/reperfusion injuries was investigated in male Wistar Albino rats. After an occlusion of 20 min, the rats were randomly divided into groups. The treated group received BPC 157 (10μg/kg, 10ng/kg, I.P.) right after surgery, while the control group received saline (1ml, I.P.) immediately after surgery. After a reperfusion period of 24 or 72 hours, the neurological assessment was performed and samples were gathered for further examination. Neurological assessment was conducted using the Morrison water maze test (MWMT) and beam walk test (BWT). Results: In the MWMT the control animals had far greater memory loss and spatial orientation loss, while the BPC 157 treated group had almost no loss in the MWMT. The control group lost 10.3 seconds, while the BPC 157 treated group gained 1 second in comparison to the training results. In the BWT, we also observed substantial differences between the control and treated group, where the control group walked far worse and scored 1, while the BPC 157 treated group walked much better and scored 4. The pathology findings concurred with the results obtained in the neurological assessment. Conclusion: Pentadecapeptide BPC 157 showed that it counteracts ischemic/reperfusion injuries, saving the rats from memory and orientation loss, as well as maintaining their motor capabilities. The results we present here are promising and prove that BPC 157 has
potential as a neuroprotective agent in cerebral ischemic/reperfusion injuries, although further investigations should be conducted to further confirm the full effects of BPC 157.

**CHRONIC STRESS EFFECTS ON RAT BRAIN LIPIDOME**

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**Introduction:** Prolonged exposure to chronic stress affects brain structure and physiological function. Animals exposed to chronic stress have shown changes in prefrontal cortex, amygdala and hippocampus paired with impact on memory and learning. Response to stress is characterized acutely by activation of sympathetic nervous system and chronically by activation of hypothalamic-pituitary-adrenal axis. Finally all culminates by release of glucocorticoids (CORT). CORT have high affinity for mineralocorticoid receptors and only when CORT is high like in chronic stress, it binds to glucocorticoid receptor. Binding of CORT to glucocorticoid receptor may be the main cause of degenerative effects in chronic stress. CORT can modulate activity of several enzymes key to lipid metabolism. First is phospholipase A2 (PLA2) an enzyme that cleaves membrane phospholipids. Second enzyme is diacylglycerol (DG) lipase alpha which modulates DG levels in stress sensitive brain regions. **Methods:** 2 months old Wistar rats were used in experiment and divided in three groups. First group served as negative control with no treatment, second group was chronically stressed, and third was a vehicle control group with subcutaneously injected synthetic CORT. Animals were kept in 12:12 hours light dark cycle. Experiment of chronic unpredictable stress (CUS) was conducted in duration of 4 weeks. Serum was collected for measuring CORT levels. Homogenates of brain were used for lipids analysis with high performance liquid chromatography - mass spectrometry. Expression of sphingomyelinase (SM) genes was determined with qRT-PCR. **Results:** Levels of CORT in serum was raised 58% in CUS animals compared to control group. Prefrontal cortex (PFC) was mostly affected by CUS. Sphingolipid metabolism was affected with decreased levels of ether phosphatidylcholine and phosphatidylethanolamine and increase in ceramide levels. Rats in stressed group showed an increase in 38 carbon lipid levels, and decrease in 36 carbon lipid levels. In hippocampus and PFC high amounts of phospholipids conjugated with arachidonic acid 20:4 (AA). Statistical analysis established correlation between serum CORT levels and brain lipid species. There were no observable changes in sphingomyelinase gene expression. **Conclusion:** Positive correlation with CORT and AA – containing phospholipids was established. Phospholipids with AA have deleterious effects on hippocampus and PFC, similar levels of expression were found in depressive rat model. Because no changes in expression of SM genes were observed, and change in lipid profile occurred, high CORT levels may affect activity of SM, PLA2 enzymes directly. Further investigation is needed for potential development of therapeutics for stress related disorders targeting mentioned enzymes.