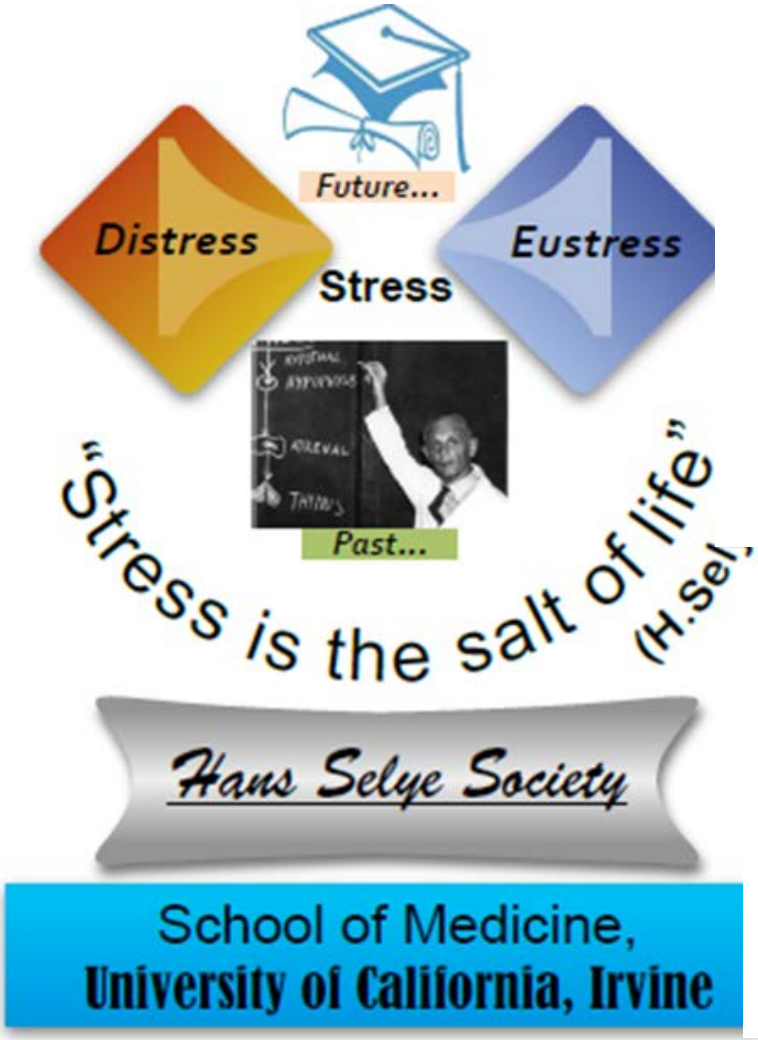
Summer School on Stress

From Hans Selye's original concept to recent advances

An interactive educational experience

June 29 - July 2, 2015

University Hospital Center and
Grenoble Institute of Neurosciences
Grenoble, France



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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, by the 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 Taché*

(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

Chairs: Pr. Bruno Bonaz, Dr Sonia Pellissier, Dr Amandine Rubio
Secretaries: Dr. Valérie Sinniger & Chantal Baumes
Members: Dr Sonia Pellissier, Dr Amandine Rubio

Acknowledgments

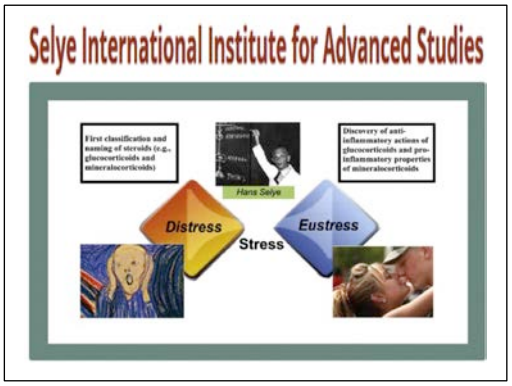
The course directors & organizers want to thank *Prof. Oksana Zayachkivska* for collecting & editing the submitted abstracts of free communications. We also thank Mr. *Viktor Fero* for building & maintaining our website as well as Mr. *Dean Spencer*, MS1 student of the Hans Selye Academic Society of UCI for creating & managing our Facebook page. We also express our deep appreciation to *Prof. Gerald Maguire* and Ms. *Ellen Seaback*, executive director of the CME Committee of University of California-Irvine School of Medicine.

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

June 29-July 2, 2015

Grenoble, France

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

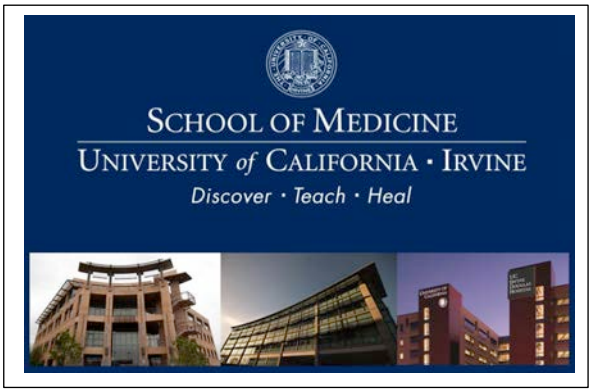


GI Gastrointestinal Section
IUPHAR
International Union of Basic and Clinical Pharmacology

Hosted by: University Hospital Center, Clinique Universitaire d'hépato-gastroentérologie and Grenoble Institute of Neurosciences (Inserm U836 and Université Joseph Fourier)

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 providership of the University of California - Irvine School of Medicine which is accredited by the ACCME to provide continuing medical education for physicians, other healthcare providers & students.

Credit designation:
Full-time conference participants who sign the daily attendance sheet will be eligible to receive 'Certificate of attendance' of the University of California, Irvine School of Medicine.



Disclosure information

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

Speaker/ Planner Name	Name of Commercial Interest	Nature of Relevant Relationship	Conflict Resolution Method
None			

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

Bruno Bonaz
Thierry Bougerol
Stefan Brunnhuber
Frédéric Canini
Cécile Dantzer
Ludmila Filaretova
Sonia Pellissier
Martina Rojnic Kuzman
Amandine Rubio
Predrag Sikiric
Arpad Somogyi
Sandor Szabo
Yvette Taché
Vassilia Theodorou
Jackie Wood
Oksana Zayachkivska

PROGRAM & ABSTRACTS

Scientific & social program overview

June 29-July 2, 2015

Grenoble University Hospital Center and Grenoble Institute of Neurosciences

Monday, June 29	**Tuesday, June 30**
Registration & sign-in: 8:30 – 9:00 **Main lectures & discussions: 9:00 – 12:00** *Lunch:12:00 – 14:00* **Main lectures & discussions: 14:00-17:30** ***Informal reception & social get-together 17:30-19:00***	*Registration & sign-in: 8:50* **Main lectures: 9:00 – 11:25** **Free oral communications session: 11:30-12:30** *Lunch:12:30 – 13:30* **Main lectures & discussions: 13:30-17:30**
Wednesday, July 1	**Thursday, July 2**
Registration & sign-in: 8:20 **Main lectures & discussions: 8:30 – 12:00** *Lunch:12:00 – 13:00* **Main lectures & discussions: 13:00 – 15:45** **Poster presentations: 15:45 -16:45** ***17:00 Sight-seeing tour and dinner***	*Registration & sign-in: 8:50* **Main lectures & discussions: 9:00 – 12:00** ***12:00 End of the Summer School***

Monday, June 29, 2015

Grenoble Institute of Neuroscience
(Amphi Serge Kampf)

8.30 – 9:00 **Reception and registration (*Hall*)**

Morning session

CHAIRS: YVETTE TACHÉ, ARPAD SOMOGYI & SANDOR SZABO

9.00 – 9:15 Welcome & introduction
Bruno Bonaz, Grenoble
Arpad Somogyi, Brussels/Berlin; Sandor Szabo, Irvine/Los Angeles;
Yvette Taché, Los Angeles

9:20 – 9:50 Historic origins of stress concept
Sandor Szabo, Irvine/Los Angeles; Katalin Szabo, Budapest

9:50 - 10:05 **Coffee break**

10:10 - 10:40 The seminal discoveries of Hans Selye
Arpad Somogyi, Brussels/Berlin; Sandor Szabo, Irvine/Los Angeles

10:45 - 11:15 What is stress, what is not: Distress vs. eustress
Sandor Szabo, Irvine/Los Angeles

11:20 - 11:50 General discussion: Comments, questions, answers

12:00 – 14:00 **Lunch *at the restaurant "Le St Pierre"***

Afternoon session

CHAIRS: LUDMILA FILARETOVA & BRUNO BONAZ

14:00 - 14:45 The neuroendocrine mechanisms of stress
. *Yvette Tache, Los Angeles*

14:45 - 15:30 The brain-gut axis: Basic concepts
Jackie Wood, Columbus, Ohio

15:30 - 15:45 **Coffee break**

15:45 - 16:30 The brain-gut axis: Stress & disease implications
Bruno Bonaz, Grenoble

16:30 - 17:30 My good & bad experience with stress: Challenges & lessons learned
Open forum: Short comments & interactive presentations by attendees

17:30 - 19:00 **Informal reception & social get-together**
Local Wine and cheese Tasting (4th floor Grenoble Institute of Neurosciences)

Tuesday, June 30, 2015

Grenoble Institute of Neuroscience
(Amphi Serge Kampf)

Morning session

CHAIRS: JACKIE WOOD & SONIA PELLISSIER

09:00 - 9:40 Physiologic & pharmacologic actions of glucocorticoids
Ludmila Filaretova, St. Petersburg

09:45 - 10:25 Psychological dimension of stress
Cécile Dantzer, Chambéry

10:30 - 10:45 Coffee break

10:45 - 11:25 Allostasis & allostatic load
Frédéric Canini, Brétigny-sur-Orge (Paris)

11:30 - 12:30 Free oral communication session (See: "Free communications" in the book)

CHAIR: OKSANA ZAYACHKIVSKA

12:30 - 13:30 Lunch *(4th floor Grenoble Institute of Neurosciences)*

Afternoon session

CHAIRS: YVETTE TACHE & AMANDINE RUBIO

13:30 - 14:15 Stress & functional GI disorders: Motility disorders, IBS (irritable bowel syndrome)
Bruno Bonaz, Grenoble; Yvette Taché, Los Angeles

14:15 - 15:00 Stress & IBD (Inflammatory bowel disease)
Bruno Bonaz, Amandine Rubio, Grenoble

15:00 - 15:15 Coffee break

15:15 - 16:25 Stress & structural GI diseases: Gastroduodenal ulcers
Sandor Szabo, Irvine/Los Angeles; Jackie Wood, Columbus, Ohio

16:30 - 17:10 Endogenous modulators of stress-induced gastric ulcers
Ludmila Filaretova, St. Petersburg

17:15 - 17:30 General discussion: Comments, questions, answers

Wednesday, July 1, 2015

Grenoble Institute of Neuroscience
(Amphi Serge Kampf)

Morning session

CHAIRS: SONIA PELLISSIER & VASSILIA THEODOROU

8:30 - 9:15 Brain-gut axis & microbiota in relation to stress
Vassilia Theodorou, Toulouse

9:15 - 10:00 New insight into role of melatonin, a key hormone of brain-gut axis, in health & disease
Oksana Zayachkivska, Lviv

10:00 - 10:15 Coffee break

10:15 - 11:00 Hear rate variability (HRV) a marker of the autonomic nervous system: Implication in stress and diseases
Sonia Pellissier, Chambéry

11:00 - 11:45 Stress & brown and white fat cell disorders: Impact of early-life exposure to sedentary life and overloaded sugar on later life health outcomes
Oksana Zayachkivska, Lviv,

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

12:00 - 13:00 Lunch *(4th floor Grenoble Institute of Neurosciences)*

Afternoon session

CHAIRS: STEFAN BRUNNHUBER & JACKIE WOOD

13:00 - 13:40 Do regulatory agencies (e.g., EU, FDA) create psychologic stress?
Arpad Somogyi, Brussels/Berlin

13:45 - 14:25 Stress & mental disorders
Thierry Bougerol, Grenoble

14:30-14:45 Coffee break

14:45 - 15:25 Strength for the journey: Strategies integrating brain, mind, body & spirit for stress resilience & management
Stefan Brunnhuber, Dresden

15:30 - 15:45 General discussion: Comments, questions, answers

15:45 - 16:45 **Poster session**

CHAIRS: JACKIE WOOD & OKSANA ZAYACHKIVSKA

17:00 ***Grenoble sight-seeing tour***
19:45 ***Dinner at the restaurant du Téléphérique***

Thursday, July 2, 2015

Grenoble Institute of Neuroscience
(Amphi Serge Kampf)

Morning session

CHAIRS: SANDOR SZABO, ARPAD SOMOGYI & YVETTE TACHÉ

9:00 - 9:30 Management strategies for stress
Martina Rojnic Kuzman, Zagreb

9:30 - 10:00 Hans Selye: The grandmaster of creativity & originality
Arpad Somogyi, Brussels/Berlin

10:00 - 10:30 Stress in our daily lives – transformation of distress into eustress
Open forum with participation of all registered attendees

10:30 – 10:45 Coffee break

10:45 - 11:30 Putting it all together: Take-home messages
All lecturers & presenters

11:35 - 12:00 Final group discussion, feedback & course evaluation

12:00 End of the Summer School

Lecture outlines

The brain-gut axis: Stress & disease implications

Bruno Bonaz, MD, PhD,

Professor of Gastroenterology, Clinique Universitaire d'Hépato-Gastroentérologie, CHU de Grenoble, Grenoble, France.

BBonaz@chu-grenoble.fr

Rationale

The gut has the capacity to function as an autonomous organ. However, in normal conditions, the gut and the central nervous system talk to each other through the autonomic nervous system (ANS), represented by the sympathetic (i.e. the splanchnic nerves) and the parasympathetic nervous system (i.e. the vagus nerve and the sacral parasympathetic pelvic nerves). The brain is able to integrate inputs coming from the digestive tract inside a central autonomic network organized around the hypothalamus, limbic system and cerebral cortex and in return to modify the ANS and the hypothalamic pituitary adrenal axis (HPA axis). An abnormal functioning of these brain-gut interactions has been described *i)* in functional digestive disorders, such as irritable bowel syndrome (IBS), classically considered as a biopsychosocial model, *ii)* in organic digestive disorders, such as inflammatory bowel disease (IBD) which result from an inappropriate inflammatory response to intestinal microbes in a genetically susceptible host.

The effects of stress on the gastrointestinal tract have been associated with modifications of motility, visceral sensitivity, intestinal permeability, local inflammatory responses and microbiota through the activation of the central and/or peripheral CRFergic system represented by CRF, urocortins 1,2,3 and their receptors (CRF1,2) as well as by modifications of the ANS. Targeting this CRFergic system either by agonists and/or antagonist would be of interest in such digestive disorders. In the same way, restoring a normal equilibrium of the sympatho-vagal balance, as monitored by heart rate variability, either through a drug approach or with complementary medicines or vagus nerve stimulation would be of interest.

Learning objectives

- Stress and functional digestive disorders
- Stress and inflammatory digestive disorders
- Central and peripheral CRFergic system
- HPA axis
- Parasympathetic (vagus nerve) and sympathetic nervous system
- Intestinal permeability
- Vagus nerve stimulation
- Heart rate variability

References

Taché Y, Bonaz B. Corticotropin-releasing factor receptors and stress-related alterations of gut motor function. J Clin Invest. 2007 Jan;117(1):33-40.

Taché Y, Perdue MH. Role of peripheral CRF signalling pathways in stress-related alterations of gut motility and mucosal function. Neurogastroenterol Motil. 2004 Apr;16 Suppl 1:137-42.

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[4]. 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 nociceptive CRD or repeated daily CRD six weeks after the development of colitis, intracolonic infusion of 0.5% acetic acid or a high-anxiety rat strain, the Kyoto. It is actually obvious that stress, i.e. the CRFergic system (either central or peripheral), is a major effector in the pathophysiology of many functional digestive disorders and particularly in IBS Recent studies identified the hippocampus and the central amygdala (CeA) as brain sites of action. CRF microinjected into the CeA induces a hyperalgesic response to CRD and enhances the noradrenaline levels at this site which are blocked by a CRF-R1 antagonist injected into the CeA. Pharmacological interventions targeting the CRFergic system would be of interest in stress-related functional bowel disease. So far non-pharmacologic therapies to reduce the stress component including cognitive behavioral therapy, relaxation therapy, and hypnotherapy, alone or in combination, are reportedly effective for IBS symptoms.

Learning objectives

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

References: Taché Y, Bonaz B. Corticotropin-releasing factor receptors and stress-related alterations of gut motor function. J Clin Invest. 2007 Jan;117(1):33-40. Larauche M Mulak A, Taché Y. Stress and visceral pain: from animal models to clinical therapies. Exp Neurol. 2012 Jan;233(1):49-67. Mayer EA and Gebhart GF. Basic and clinical aspects of visceral hyperalgesia. Gastroenterology 1994; 107: 271-293. Mulak A, Bonaz B. Irritable bowel syndrome: a model of the brain-gut interactions. Med Sci Monit. 2004 Apr;10(4):RA55-62. Pellissier S, Dantzer C, Canini F, Mathieu N, Bonaz B. Psychological adjustment and autonomic disturbances in inflammatory bowel diseases and irritable bowel syndrome. Psychoneuroendocrinology. 2010 Jun;35(5):653-62.

Stress & inflammatory bowel disease (IBD)

Bruno Bonaz, MD, PhD, Professor of Gastroenterology, Clinique Universitaire d'Hépato-Gastroentérologie, CHU de Grenoble, Grenoble, France. BBonaz@chu-grenoble.fr. **Amandine Rubio,** MD, PhD, Department of Pediatry, CHU de Grenoble, Grenoble, France. ARubio@chu-grenoble.fr

Rationale

IBD are organic diseases classically divided in Crohn's disease and ulcerative colitis involving the digestive tract, and particularly the small-bowel and colon, starting early in life (between 15 and 30 years), and evolving by flares alternating with periods of remissions of variable duration. The pathophysiology of IBD is multifactorial involving immunologic, genetic, infectious and environmental factors. Among the latter, the role of stress is evoked based on experimental and clinical data. The autonomic nervous system has a key role in the relation between stress and digestive inflammation and a dysautonomia is reported in IBD. Stress may play a deleterious role in IBD through pathways close to the ones described for irritable bowel syndrome (IBS): 1) Increase of intestinal permeability through an activation of mast cells in the intestinal mucosa, 2) Catecholamines, acting through α- and β-adrenergic receptors, mediate stress-induced increases in peripheral and central inflammatory cytokines and activation of the inflammatory nuclear factor-kB signaling pathway, 3) The cholinergic anti-inflammatory pathway through activation of vagal efferents, 4) An imbalance of the relations between the prefrontal cortex (PFC) and amygdala, 5) A hyporeactive HPA axis and an inhibition of the central response to a chronic interoceptive stress, 6) An activation of the pro-inflammatory peripheral CRFergic system, 7) Stress-induced increased intestinal permeability allows bacteria to cross the epithelial barrier to activate mucosal immune response and to translocate to secondary lymphoid organs to stimulate the innate immune system, 8) Modification of the stress axis early in development, as observed in early life traumas, could induce a maladaptive control of neuro-endocrine immune axis.

Most of the data presented above are described in experimental conditions. However, there are now increasing data arguing for a role of stress in IBD patients. There is consistent evidence that psychological factors play a role both in the pathophysiology and course of IBD and in how patients deal with IBD. In a population based cohort of IBD patients, significantly more people in the persistently inactive disease group indicated they had experienced no stressful events compared to those in the persistently active disease group. Only the psychological factors, including occurrence of a major life event, high perceived stress, and high negative mood during a previous 3 month period were significantly associated with the occurrence of a flare. On multivariate logistic regression analyses of these variables only high perceived stress was associated with increased risk of flare. Perception of stress is a key factor, which incorporates the individual's appraisal of the demands created by stress in general and resources to cope with stress. The interaction between perceived stress and avoidance coping was predictors of earlier relapse in quiescent CD. Recent reviews have concluded that stress has an impact on the course of disease but the jury is still out as to whether cognitive therapies or psychotropic medications can positively influence the course of IBD.

Learning objectives

- Parasympathetic (vagus nerve) and sympathetic nervous system
- Intestinal permeability
- Cholinergic anti-inflammatory pathway and vagus nerve stimulation
- Heart rate variability and HPA axis
- Fronto-amygdaloid complex
- Early life stress, depression and inflammation
- Habituation of the hypothalamic CRFergic system
- Gastro-intestinal CRF and inflammation
- Microbiota-brain-gut axis

References

Bonaz BL & Bernstein CN. Brain-gut interactions in inflammatory bowel disease. Gastroenterology. 2013 Jan;144(1):36-49.

Pellissier S et al. Relationship between vagal tone, cortisol, TNF-alpha, epinephrine and negative affects in Crohn's disease and irritable bowel syndrome. PLoS One. 2014 Sep 10;9(9):e105328.

Taché Y, Perdue MH. Role of peripheral CRF signalling pathways in stress-related alterations of gut motility and mucosal function. Neurogastroenterol Motil. 2004 Apr;16 Suppl 1:137-42.

Coping with stress in daily life and mental health: A psychiatric perspective

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Rationale

Current Global Burden of disease (GBD) data demonstrate the importance of chronic stressors on health. The lecture outlines the importance of daily stress management in healthy subjects and populations with mental health disorders. The phenomenon of "stress" in mental health is explored including the clinical relevance of negative experiences such as adverse childhood experiences (ACE), the trans-generational transmission of stress, the allostatic load resulting from chronic stress exposure and their clinical implications; protective factors or positive responses to stress which render people more stress-resilient are also described.

The second part of the lecture focuses on non-pharmacological interventions and lifestyle-modifications, which positively impact stress and alleviate symptoms in patients suffering from mental disorders. There is mounting evidence that (a) exercise, (b) changes in diet (c) mindfulness-based exercises, (d) social support, (e) sleep hygiene and (f) special forms of hydrotherapy play an important role in the prevention and treatment of stress associated mental health symptoms.

The lecture emphasizes the importance of life-style modifications in addressing chronic psychosocial stressor in healthy subjects and patients suffering from mental symptoms.

Learning objectives

- To review the concept of stress and it's link to mental health disorders.
- To understand risk factors associated to the development of mental health disorders including adverse childhood experiences (ACE), the trans-generational transmission of stress, and allostatic load as well as protective factors leading to resilience.
- To describe the association between perceived stress, emotions and pro inflammatory markers.
- To discuss some of the non-pharmacological interventions preventing or alleviating stress-linked mental health disorders.

References

The references will be handed out at the lecture.

Allostasis & allostatic load

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Rationale

Long term exposure to low grade stressors is known to induce several somatic pathologies such as metabolic syndrome, hypertension, cancer, infection, etc. The relation between stress and pathologies is conceptualized in the frame of the General Adaptation Syndrom by the mechanism of heterostasis, also called "allostasis". The biological consequence of allostasis on the body is called "allostatic load". The consequence of the allostatic load is an increased risk of pathologies. The mechanism linking stress to allostatic load is based on the stress mediator, namely glucocorticoid release, sympathetic activation and low vagal tone. Upstream to the heterostasis is the mechanisms regulating stress. They adjust stress to its minimum amount leaving adaptation to occur. In case of heterostasis, these mechanisms are likely to be less efficient.

Learning objectives

- General Adaptation Syndrome
- Relation between stress and adaptation
- Heterostasis, allostasis and allostatic load concepts
- Relation between stress mediators and allostatic load
- Relation between allostatic load and pathologies through one example
- Brain mechanisms of stress inhibition
- How to act on allostasis to reduce it

The psychology of stress

Cécile Dantzer,

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Rationale

Heath Psychology is a scientific discipline which aims at understanding the role of psychological variables in the etiology and the evolution of the disease. Health Psychology uses correlational and experimental methodologies in psychology to determine the link between psychological variables, stress and illness. It focuses on the promotion of healthy behaviors, prevention and treatment of disease, and the improvement of patient care. This course will present how Health psychology theories are pertinent in understanding stress in clinical or normal populations. In particular we will focus on what we learn from these models, and what we still don't know and need to explore. We will propose examples of psychological interventions based on these models.

Learning objectives

- Definition of Health psychology
- Description of Health Psychology theories
- Contribution of Health Psychology models in the stress response
- Description of psychology-based interventions in clinical and normal populations

References

• Ogden, J. (2008). Health Psychology. A textbook. Open university Press. 2012

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.

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 it's 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 adrenocorical (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 topic 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.

Heart rate variability (HRV) a marker of the autonomic nervous system (ANS): Implication in stress and diseases

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Rationale

The autonomic nervous system, with the sympathetic and parasympathetic branches, plays a major role in homeostasis and regulation of stress responses. Therefore it seems important to measure the autonomic nervous system activity with the most reliable and efficient parameters. Heart rate variability, derived from the electrocardiogram, is an effective method which takes into account numerous methodological constraints. Heart rate variability corresponds to the degree of fluctuation in the length of intervals between successive heartbeats. The amplitude of this fluctuation is mainly driven by the parasympathetic nervous system and it is a reliable indicator of the vagal tone. Therefore, HRV could be a marker of vagal withdrawal under stress but also a marker of recovery and parasympathetic rebound after the completion of stress. In case of disease, especially in chronic disease, HRV could be used as a marker of the disease load, but could also be seen as a marker of flexibility in the regulation of homeostasis from a physiological and emotional point of view. The vagus nerve also exerts an anti-inflammatory modulation on the immune system through the cholinergic anti-inflammatory pathway, meaning that HRV is a marker of this pathway especially in inflammatory diseases. Finally, the measure of HRV combine with that of cortisol could provide also indications about the functional coupling between the HPA axis and ANS which reflects the coupling between the prefrontal cortex and the amygdala at the level of the brain. As such, HRV provides a window to understand firstly, stress and health processing and secondly, the beneficial effects of vagus nerve reinforcement techniques such as vagus nerve stimulation.

Learning objectives

- Parasympathetic and sympathetic nervous system
- The parasympathetic control of heartbeats
- Heart rate variability and power frequency parameters
- Inflammatory bowel diseases and stress, anxiety and depression
- HRV and pro-inflammatory cytokines
- Vagus nerve stimulation
- HRV and HPA axis

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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

Stress & gastroprotection: Endogenous peptides from the stomach

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Rationale

We aim to highlight the controversies related to Selye's stress concept and practical realization of Selye's stress coping response where the stable gastric pentadecapeptide BPC 157 (a prototype of endogenous peptides from the stomach) activities might be perceived as an effective realization of the Selye's stress coping response. Namely, the mediator that integrates adaptive bodily stress response, and thereby, would exhibit an integrative beneficial effect applicable in the therapy is still unrealized legacy of the Selye's stress concept, general adaptive response to various noxious events. Therefore, to bypass concept limitations, we presented Selye's subsequent work, particularly with corticosteroids beneficial effects; Selye established the stress-diseases (cardiovascular, inflammatory, peptic ulcer); Selye claimed an innovative approach to understanding "mosaic of life in health and disease"; along with these, Selye performed a permanent search for the mediator that integrates adaptive bodily stress response. To next ways close to the solution, we briefly reviewed the search toward the mediator that integrates adaptive bodily stress response that was provided by Selye's students, Tache (TRH, CRF, brain-gut axis), Szabo (dopamine combining Parkinson's and peptic ulcer disease), Robert (PGs, cytoprotection, cell protection, adaptive cytoprotection, extended by Szabo to organoprotection). But, the extent of the beneficial effects that may be exhibited by the proposed agents, i.e., CRF (Tache), PGs (Robert), Szabo (dopamine), separately or together, did not reach an integrative beneficial effect supposed for the mediator that integrates adaptive bodily stress response, thereby general beneficial effect, applicable in the therapy. Concluding, we presented the stable gastric pentadecapeptide BPC 157 as the agent that may fulfill - at the best way - all of the requirements for the supposed Selye's mediator that integrates adaptive bodily stress response and large range of the beneficial effects, suited for practical application in therapy, within the Robert's cytoprotection, adaptive cytoprotection and organoprotection, Tache's brain-gut axis activity, and Szabo's dopamine as integrative systems.

Learning objectives

Selye's stress concept and practical realization of Selye's stress coping response; Review: the controversies related to Selye's stress concept and practical realization of Selye's stress response; the birth of the Selye's concept (syndrome produced by diverse nocious agents); Selye's search for the mediator that integrates adaptive bodily stress response, and thereby, would exhibit an integrative beneficial effect applicable in the therapy; the next ways close to the solution, the search toward the mediator that integrates adaptive bodily stress response that was provided by Selye's students, Tache (TRH, CRF, brain-gut axis), Szabo (dopamine combining Parkinson's and peptic ulcer disease), Robert (PGs, cytoprotection, cell protection, adaptive cytoprotection, extended by Szabo to organoprotection); Discuss the possibility and mechanisms - that the stable gastric pentadecapeptide BPC 157 may be the agent that may fulfill - at the best way - all of the requirements for the supposed Selye's mediator that integrates adaptive bodily stress response and large range of the beneficial effects, suited for practical application in therapy, within the background of the Robert's cytoprotection, adaptive cytoprotection and organoprotection, Tache's brain-gut axis activity, and Szabo's dopamine as integrative systems.
Selye's stress concept and practical realization.

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

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 Chrirurgie expérimentales that Hans Selye founded and made world famous could not survive its creator.

Learning objectives

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

The major discoveries of Hans Selye

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Rationale

Hans Selye is mostly known for his identification of biologic stress syndrome, but he also made numerous seminal discoveries that are as valid today as when they were made several decades ago. It's not a coincidence that Selye was often called the 'Einstein of medical sciences'… Selye's most significant 'other discovery' is the first modern classification & naming of steroid hormones as well as the first identification of anti-inflammatory action of glucocorticoids & pro-inflammatory effect of mineralocorticoids in animal models in the early & mid-1940s. As we now know, the anti-inflammatory glucocorticoids ("steroids") are wildly used in clinical medicine, both in inpatient & outpatient settings. It's just a sad irony that despite his well-documented first demonstration of inflammatory modulatory effects of corticoids in animal models by Hans Selye in the 1940s, the 1950 Nobel Prize was given to a Mayo Clinic physician who did the 'next obvious step' by showing the efficacy of ACTH & cortisone in patients with rheumatoid arthritis as well as to two chemists who isolated & synthesized cortisone (by Nobel's will, only three persons may get the prize for one topic in one year)…
Selye was also the first to introduce an i.v. anesthetic in the 1940s; after serendipitous discovery that rats, injected intraperitonealy with a large dose of progesterone, 'slept like a baby'… Until then only inhalation anesthesia (e.g., ether, chloroform, halothane) were used in surgery. It's not surprising that the pharmaceutical industry jumped on these steroid-related discoveries of Hans Selye & developed various non-steroidal anesthetic & anti-inflammatory drugs (e.g., indomethacin, ibuprofen, naproxen).

Learning objectives

- Chronologic review of Selye's "other" discoveries.
- Brief description of "Selye Symposium 2013" at the Hungarian Academy of Sciences on the 70 year anniversary of his seminal discoveries (e.g., naming & classification of steroids, first reference to human 'stress ulcers' during air raids on London in 1943).
- Lessons & practical, long-lasting implications of these discoveries.
- Homage to Selye's repeated insistence on creativity & the daily importance of originality & 'peripheral vision' in research, especially in biomedical sciences.

Historic origins of the stress concept

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Rationale

Although it's commonly know that the stress concept has been introduced in biomedical sciences with the first description of the non-specific 'general adaption syndrome' (GAS) by Hans Selye in his historic short article in Nature (1936), it's not widely appreciated that non-specific adaptive responses were described in the medical literature before. Even Selye gave generous credit to his predecessors, often comparing his "discovery" of stress with Columbus discovery of America which was visited by other explorers (e.g., Vikings) many years ago. He used to say that 'it does not matter who saw what, the important thing is who made a quantum jump in our knowledge about our understanding & importance of the topic/event'. Thus, without denying the creativity & originality of Hans Selye, this presentation will put his seminal discovery in historic perspectives. We also have to underline that the word "stress" was not used for several years after his first publications on the subject in the late 1930s & 1940s, but his first-ever book on the subject, published in Montreal in 1950, had the title "Stress". Furthermore, because of the popularity of the subject that was widely investigated & his initial findings had been widely reproduced, his historic monograph was followed by "Annual Reports on Stress" (1951-1956). These books contained hundreds of new publications every year, carefully listed & commented on by Selye, - without any bias if the other publication confirmed, expanded or challenged his findings & interpretations.

Learning objectives

- Better understand the origins of concept of biologics stress, based on historical background.
- Give credits to major personalities in the development of human medicine.
- Compare & contrast the first attempts to identify nonspecific defensive reactions (e.g., Claude Bernard's 'stability of our internal environment', Pavlov's conditional & non-conditional reflexes, Cannon's 'fight or flight syndrome), with Selye's GAS & the biologic stress reaction as we know today.
- Although GAS-like adaptive or defensive reactions have described by a few scientists before Selye, to appreciate that he was the first one to mechanistically implicate the neural & endocrine system.
- To acknowledge that the causes of diseases have been connected with mythical forces for the initial five millennia of human history, followed by implications of specific etiologic factors (e.g., microbes, chemicals, physical agents like radiations), Selye was the first to identify that despite their specific actions, these agents also trigger similar adaptive-defensive reactions in our body that unfortunately may also result in maladaption or disease.
- Emphasize that the above reactions have been connected only with one internal system, e.g., blood chemistry, nervous system or release of catecholamines only, while Selye identified the involvement of all these factors, regulated primarily by the neuroendocrine system, especially the pituitary & adrenal glands.

What is stress, what is not: Distress vs. eustress

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Rationale

Hans Selye was pleased to know that despite the initial criticism & objections, in the last decades of his life (he died in Montreal in 1982), his 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 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 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 through transtress into moderate eustress or to chemical induction of eustress…

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 H. pylori that markedly delays healing, hence it requires the elimination of these bacteria by antimicrobial drugs. It's important to note that in rodents (e.g., rats, mice) even the most intensive distress produces only gastric lesions & not duodenal ulcers, for the reproduction of which specific duodenal ulcerogenic chemicals are needed in rodents. In humans, on the other hand, the stress- & drug-induced duodenal ulcers are more frequent than gastric ulcers, at least in most countries of the world. It's almost unbelievable that about 80 years after their description, the cause & pathogenesis of these lesions are still debated. Nevertheless, it is generally agreed that they are triggered by the increased secretion of catecholamines & glucocorticoids during severe stress, where vascular & motility factors play a critical role, with a small, if any, contribution by enhanced gastric acid secretion. IBD refers to ulcerative colitis (UC), which may often lead to colonic cancer, & Crohn's disease (CD) that often involves parts of small intestines, in addition to the colon. Stress & environmental factors play a role in the pathogenesis of UC, while genetic & immunologic elements are more important for the development of CD.

Learning objectives

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

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

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

Brain-gut axis & microbiota in relation to stress

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Rationale

The brain-gut axis can be defined as an integrated bidirectional entero-cortical activity. The regulation of the brain-gut axis is essential for maintaining gut but also central nervous system homeostasis. Striking and pioneer experimental evidences illustrating the role of the brain-gut axis in the regulation of the digestive functions include the Pavlovian conditioning on the gastric acid secretion, the stress-induced colonic transit acceleration and the changes in gut motility induced by centrally administered gut hormones. More recently, a new actor has been integrated in the brain-gut axis, namely the intestinal microbiota. The rationale of this integration comes from experimental data showing that descending information from the brain is able to modify gut motility and intestinal barrier function, leading to changes of the commensals habitat resulting to alterations of their composition and metabolic profile. Conversely, the microbiota-host interactions can influence the intestinal barrier function resulting to modulation of neural afferent pathways able to modulate the enteric nervous system, spinal and supraspinal neurochemistry. Consequently, the brain-gut axis concept has been nowadays extended to the microbiota-gut-brain one. The stress is a major environmental factor illustrating the bidirectional microbiota-gut-brain interplay[1] and it is largely incriminated in the pathophysiology of chronic digestive diseases, such as inflammatory bowel diseases (IBD)[2] and irritable bowel syndrome (IBS)[3]. Interestingly, both pathologies are characterized by visceral pain, "leaky" intestinal barrier dysbiosis and psychiatric cormobidity[4]. Animal models of stress result to similar features allowing the mechanistic approaches contributing to a better understanding of the IBD and IBS pathophysiology. On this basis modulation of the gut microbiota may lead to promising therapeutic strategies in these diseases.

Learning objectives

- Stress-related changes in intestinal barrier function and visceral hypersensitivity
- Microbiota modulation, stress visceral sensitivity and intestinal barrier function
- Microbiota modulation and HPA axis response to stress
- Microbiota modulation , brain neurochemistry changes and behavior
- Microbiota modulation and IBS

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Neurogastroenterology of functional gastrointestinal disorders: Brain-in-the-gut, enteric mast cells, 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?

New insight into 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 contribute 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 transmeridian 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.

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STRESS & BROWN AND WHITE FAT CELL DISORDERS: IMPACT OF EARLY-LIFE EXPOSURE TO SEDENTARY LIFE AND OVERLOADED SUGAR ON LATER LIFE HEALTH OUTCOMES

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Rationale

Although the very first description of adipose tissue, more specifically brown adipose tissue – as an important organ was done by the Swiss naturalist Conrad Gessner in 1551, recently were discovered a growing body of evidences demonstrates involvement of white, brown and brite adypocytes in a variety of physiologic and pathologic processes, which can initiate ectopic fat formation, as well as different diseases. One of them is obesity, often named as lifestyle disease, pathogenesis of which is complex. The modern sedentary lifestyle is a major contributor to increased risks of incident of lifestyle diseases. Sitting is the "new smoking" which causes different health problem. Carrying out sitting more than 6 hours in day, we increase risk of death in the next 15 years by 40% in comparison with those who sits less than 3 hours. Overloaded sugar in diet, other escalating world public health problem, with the sedentary life do us fat. More recent inquiry has been directed toward environmental causes ("obesogenic environment") and gene-environment impacts on early fetal development. According to Barker's "fetal programming hypothesis", the importance of maternal lifestyle and conditions on early fetal development is undoubted, when changes in organism are caused by different environmental stimuli, including nutrition. Moreover, there is an association between prenatal stress exposure and subsequent shorter telomere length, a predictor of aging and mortality (Entringer S., 2011-2014). Thus, the elucidation of new triggers and biomarkers of early stages of alterations induced by adipocytes is urgently needed. The approaches to evaluate the role of obesogenic environment during early-life exposure (*in utero)* in humans are limited. Thus, to evaluate the impact of maternal stress and imbalanced nutrition on changes in brown and white adipocyte physiological activities, hepatocellular organization in offspring, and their resistance to stress injury are urgently needed. Moreover, identification of new non-invasive alternative biomarker to assess early fat tissue, liver changes will be useful for prognosis of ectopic and intrahepatic fat accumulation, as early diagnostic biomarker vs. to the invasive "gold standard" methods of liver assessment by biopsy.

Learning objectives

- Review of functional role of brown, beige and white adipocytes.
- Discuss the functional connections between the hallmarks of adipocyte's activities.
- Briefly discuss how the sedentary life destroys an organism.
- Explain the association between maternal combined stress and unbalanced hypercaloric feeding on fat tissue activity and hepatocellular injury & inflammation in adult offspring during physiological conditions and stress.

Free communications

Oral presentations

New cytoprotection/adaptive cytoprotection: Oral strong alcohol in rats improves regular eating/drinking habits and mucosal integrity. the effect of BPC 157, L-arginine AND L-NAME

T Becejac, V Cesearec, A Zenko Sever, A Sepac, L Batelja, A Kokot, D Stancic Rokotov, D Drmic, S Seiwerth, P Sikiric

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Stress in cardiovascular diseases

E.A. Datsomor

Danylo Halytskylviv National Medical University – Lviv – Ukrainia

The Hans Selye Club in Bratislava

B. Gálffy, K. Váradi, K. Füssi, L. Vendégh, Cs. Eke, M. Csóka, Z. Tóth, Faculty of Medicine, *Comenius University, Bratislava, Slovakia. balazs@galffy.com, selyejanosklub*

Stress-induced gastric damage: gaseous mediator hydrogen sulfide as an important factor for the gastric mucosal barrier

Magierowski Marcin*, Magierowska Katarzyna, Surmiak Marcin, Kwiecien Slawomir, Brzozowski Tomasz

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Poster session

Pretreatment with H2S-derivative NSAIDS attenuated esophageal and gastric mucosa integrity against stress injury

Ali Masri, Nazar Bula, Dzvinka Khyrivska, Elena Gavrilyuk, Oksana Zayachkivska

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Prenatal maternal stress: comparative analysis of sociodemographic and lifestyle maternal risk factors in preterm birth rates and prevalence in Ukraine and Germany

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NO system-dependent atropine mydriasis, L-NAME- and L-arginine-induced miosis: Counteraction by pentadecapeptide BPC 157 in rats and in guinea pigs

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The role of stress, as link between risk factors of osseointegration problem and fat–bone interactions

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Cortiricotropin-releasing factor (CRF) receptor type 1 blockade resulted in transformation of non-ulcerogenic stress stimuli into gastric ulcerogenic ones

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Opioid as a stress trigger: Cerebellum and the eyeball

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Effect of gastric pentadecapeptide BPC 157 therapy in liver fibrosis and cirrhosis and portal hypertension

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The effect of pentadecapeptide BPC 157 on system circulation and thrombogenesis after ligation of vena cava inferior

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Abstrcts

NEW CYTOPROTECTION / ADAPTIVE CYTOPROTECTION: ORAL STRONG ALCOHOL IN RATS IMPROVES REGULAR EATING/DRINKING HABITS AND MUCOSAL INTEGRITY. THE EFFECT OF BPC 157, L-ARGININE AND L-NAME.

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We compared the effect of oral (drinking) versus Robert's intragastric administration of strong alcohol in rats, and the consequences thereof, the immediately presented overlapping cytoprotection/adaptive cytoprotection, in unbroken sequence, only with minor gastric lesions instead the huge post-alcohol stomach lesions. Methods: We gave strong, 96%-ethanol: (i) orally (1 ml/rat on the tongue, sacrifice at the 1, 5, 15, 30min; 1, 2 and 24h), where tongue was the first target, then esophagus, stomach and duodenum (this sequence was not investigated before); (ii) intragastrically (1 ml/rat, sacrifice at 1h); (iii) orally 1 ml/rat, and then immediately intragastrically, 1 ml/rat, (sacrifice at 1h). We assessed lesion areas (mm2), lower esophageal and pyloric sphincter pressure (cmH2O). Tested agents (/kg intraperitoneally immediately after alcohol) were: stable gastric pentadecapeptide BPC 157 10 ug, 10 ng, NOS-blocker L-NAME, 5 mg, L-arginine, NOS-substrate, 100 mg, applied alone and/or together. Results: 96%-alcohol induced: (i) orally, 1 min-24h, widespread, but only minute esophageal, gastric and duodenal lesions with intact mucosa, but markedly fallen sphincter pressures; (ii) intragastrically, extensive stomach ulcers, widespread tongue, esophagus, duodenum redness; further fallen sphincter pressures, particularly failed lower esophageal sphincter; (iii) orally, and then immediately intragastrically, only small gastric lesions, less tongue, esophagus, duodenum redness; attenuated sphincter pressures drop resembles the attenuated lesions. In addition, strong mucosal beneficial effect of with BPC 157 was found, including at least partially rescued sphincter pressures, slight effect of L-arginine (protection) and L-NAME (aggravation) (and thereby, the NO-system seems to be involved); however not involving changes in sphincter pressure. Conclusion: These effects and the oral strong alcohol-model show improvement of regular eating/drinking habits and maintenance of mucosal integrity.

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. The guests of these medical discussions are always speakers who are the best scholars of Medicine. Among our guests have already been: geneticist Endre Czeizel, neonatologist Ferenc Bauer, psychiatrist Péter Hunčík, pediatric nephrologist László Kovács, transplantologist Filip Danninger, and rheumatologist Emőke Šteňová.
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. 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. We are pleased that a club member whose scientific work is

considered to be the best by a professional committee can participate in the annual scientific meeting of HMAA in Sarasota. This possibility is 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. It is truly mirrored in the above mentioned activities. Our mutual aim is to establish a Selye alumni, where we could utilize professional and human relations between medical students and specialists.

PRENATAL MATERNAL STRESS: COMPARATIVE ANALYSIS OF SOCIODEMOGRAPHIC AND LIFESTYLE MATERNAL RISK FACTORS IN PRETERM BIRTH RATES AND PREVALENCE IN UKRAINE AND GERMANY

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According to WHO (2008), the reproductive health (RH) is tightly related to state of complete physical, mental and social well-being and not merely the absence of disease or infirmity, in all matters relating to the reproductive system and to its functions and processes. From H. Selye time until to now stress-related disorders via biological, behavioral, environmental and nutritional factors play key role in RH. Modern societies characterized by diversity and many different socioeconomic disadvantages, as well as lifestyle factors could be replicated factor in RH in civilian populations. The aim of this study was to explore social-demographical and lifestyle maternal factors in preterm birth rates in Ukraine and Germany and effect of population migration, as maternal risk factor on preterm delivery. Methods: Relevant publications were identified through electronic searches on PubMed, Google Scholar, using keywords "socio-demographic and lifestyle characteristics", "stress," "migration" and "preterm birth" and semi-structured, in-depth interviews of socio-demographic characteristics, data of pregnancy-related variables and comorbidities were conducted in women with preterm births who had long time (5 years and more) or less than 1 year short time of residence in Lviv from Obstetrics Gynecology Departments in Lviv Regional Hospital (Ukraine) (n=20) or EU citizenship or had migrated from non-EU countries (Germany) (n=20). Results: According to the academic literature data the key risk maternal characteristics associated with preterm delivery risk are age, socioeconomic status, migration status, body weight index, smoking, bad habits, short interpregnancy intervals, previous preterm birth, preexisting medical conditions, and previous induced abortions. Compared to long residence women recent immigrants were at higher risk of preterm delivery during pregnancy (17%) and the highest prevalence of postpartum depression (20%). Our data revealed that women with short term of residence who has broken long-standing family relationships, extended family networks, and circles of friends has higher stress perception level than average, as well as sitting work or life style (75%), and sleeping problems (35 %). Conclusions: Preterm births are the complex problems. The length of stay in new place, as chronic psychosocial stressor could be considered as additional prenatal maternal risk factor of pre-term birth and postpartum depression. Future studies should consider their potential role in the association reproductive health.

STRESS IN CARDIOVASCULAR DISEASES

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Two major components of the auto regulatory stress response in vertebrates are known thus far, and they are both connected with the nervous system and its associated glands: the hypothalamic-pituitary-adrenal (HPA) axis and the sympatho-adrenal medullary (SAM) system [Cannon]. Frequently, the SAM is equated with the sympathetic nervous system (SNS). These two systems – HPA and SAM – are normally operating to maintain a delicate state of balance (homeostasis), in order to continue the organism's integrity even under highly challenging conditions (allostatic load, perturbations).

However, while the allostatic stress response represents a complex and sensible instrument, it is susceptible to pathophysiological factors or processes and further has an impact upon many biological functions [Esch].
STRESS-RELATED CARDIOVASCULAR DISEASES
Hypertension: The etiology and pathophysiology of hypertension are complex. Besides primary, essential, or idiopathic forms, symptomatic (secondary) forms exist. Aging, atherosclerosis, risk factors, and sympathetic nervous system activity (stress) may play a critical role in secondary hypertension [Curtis]. Stress may even, in part, cause or contribute to the clinical onset of arterial hypertension in certain cases. In particular, acute stress is capable of immediately increasing the arterial blood pressure. This is probably due to vasoconstriction, triggered by enhanced SNS activity. Additionally chronic stress may lead to hypertension and prolonged lasting side effects, eventually fixating vascular lesions and facilitating cardiovascular complications [Strawn].
Atherosclerosis: The pathophysiology of atherosclerosis seems to be multifaceted and many etiological factors may be of importance. High-fat diets can induce atherosclerosis. Atherosclerosis caused by moderate hyperlipoproteinemia is highly susceptible to the influence of psychosocial stress [Kaplan]. Since oxidative stress may induce endothelial dysfunction and injury, and since endothelial injury has been considered an initiating event in atherogenesis [Skantze], oxidative stress/free radical activity may also contribute to the pathophysiology of atherosclerosis. Mental or psychosocial stress is associated with endothelial dysfunction and atherosclerosis in many ways. The atherosclerosis-associated endothelial dysfunction has been shown to ‘cause’ abnormal vascular responses to stress, leading to a paradoxical constriction, especially at points of a preexisting stenosis.
Myocardial Infarction: Myocardial infarction describes an ischemic event that follows an acute interruption of a sufficient coronary blood supply, usually going along with CAD, coronary spasm, thromboembolism, arrhythmia, trauma etc. [Heusch]. Stress clearly has the potential to actively trigger this threatening cardiac event and here, mental stress appears to be exceptionally potent [Dakak]. In particular, mental stress may cause paradoxical constrictions in patients with CAD/atherosclerosis, especially at points of stenosis – a response that correlates with the extent of atherosclerosis (plaque) and with the endothelium-dependent response to an infusion of acetylcholine (verification of endothelial dysfunction): Local failure of dilation causes unopposed constriction [Yeung].
CONCLUSION: Stress has a major impact upon the circulatory system. It plays a significant role in susceptibility, progress, and outcome of cardiovascular diseases. Subjective or individual differences have also to be taken into account. Stress, especially 'adequate' acute stress – stress that is not 'overwhelming' – may improve performance and thus be beneficial in certain cases. The close relationship between stress and cardiovascular diseases may represent an important aspect of modern medicine.

NITRIC OXIDE (NO) SYSTEM-DEPENDENT ATROPINE MYDRIASIS, L-NAME- AND L-ARGININE-INDUCED MIOSIS: COUNTERACTION BY PENTADECAPEPTIDE BPC 157 IN RATS AND IN GUINEA PIGS

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To extend the role of NO in regulating ocular function, we investigated the effect of the stable gastric pentadecapeptide BPC 157, NOS-blocker L-NAME, and NOS-substrate L-arginine in normal pupils and with atropine-induced mydriasis that was hitherto not previously investigated. In rats and guinea pigs with normal pupils and atropine-mydriasis (2 drops of 1% atropine/eye), we administered locally (2 drops/eye) or systemically (intraperitoneally/kg) (application at the maximal atropine-mydriasis): stable gastric pentadecapeptide BPC 157 (0.4 μg/eye; 10 μg, 10 ng, 10 pg/kg), L-NAME (0.1 mg/eye; 5 mg/kg), L-arginine (2 mg/eye; 100 mg/kg) alone and in combination. Local and systemic effects were long-lasting, mostly congruent in both species and both species act similarly. All agents counteracted atropine-mydriasis; thus, L-NAME-miosis, L-arginine-miosis, and atropine-mydriasis were NO-sensitive. L-NAME and L-arginine shortened, and attenuated each other´s responses in animals with normal pupil, when combined (L-NAME+L-arginine) (except to guinea pigs treated locally) while in atropine-animals (atropine+L-NAME+L-arginine) a rather consistent shift toward the left regularly appeared. In both species, applied locally or systemically (in all regimens), BPC 157 alone had no influence on normal pupils but distinctively affects miosis and consistently counteracts atropine-mydriasis (illustrative is a counteracting effect (in rats treated intraperitoneally), even in small regimens).

With normal pupils, BPC 157 occasionally augmented the miotic effects of L-arginine (in rats treated intraperitoneally and in guinea pigs treated locally) and almost invariably neutralized the miotic effects of L-NAME (except to L-NAME+L-arginine+BPC 157-guinea pigs treated intraperitoneally). In atropine-mydriasis, BPC 157 always shifted L-arginine toward the left in both species (atropine+L-arginine+BPC 157) as well as L-NAME (atropine+L-NAME+BPC 157) (except to guinea pigs treated intraperitoneally), and L-NAME+L-arginine (atropine+L-NAME+L-arginine+BPC 157) in rats treated intraperitoneally and in guinea pigs treated locally. Thus, in rats and guinea pigs, we demonstrated for the first time the effect of BPC 157, L-NAME, and L-arginine in normal pupils and in atropine-mydriasis.

STRESS – INDUCED GASTRIC DAMAGE: GASEOUS MEDIATOR HYDROGEN SULFIDE AS AN IMPORTANT FACTOR – THE GASTRIC MUCOSAL BARRIER

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Exposure to acute and chronic stress is known to evoke gastric mucosal erosions damage that may lead to peptic ulcers collectively called stress ulcerations. H2S exerts vasodilatory and anti-inflammatory effects on gastric microcirculation but the mechanism by which this gaseous mediator affects the gastric mucosal defense against stress-induced gastric damage has been little elucidated.
Our study was designed to determine the effect of the H2S precursor L-cysteine, H2S-donor NaHS, the H2S synthesizing enzyme (CSE) activity inhibitor- D, L-propargylglycine (PAG) and the gastric H2S production by CSE/CBS/3-MST activity in water immersion and restraint stress (WRS) ulcerogenesis and the accompanying changes in gastric blood flow (GBF). Rats were pretreated 30 min before the 3.5 hrs of WRS either with: A) L-cysteine (2 - 80 mg/kg) and B) NaHS (0.1-10 mg/kg i.g.) with or without the combination with the inhibitor of CSE activity, D,L-propargylglycine (PAG 30 mg/kg i.g.) or the combination with 1) the non-selective (indomethacin, 5 mg/kg i.p.) or selective COX-1 (SC-560, 5 mg/kg i.p.) and COX-2 inhibitors (celecoxib, 30 mg/kg i.g.), and 2) blockade of sensory nerves by capsaicin (125 mg/kg s.c.) or inhibition of vanilloid receptor (VR-1) by capsazepine (10 mg/kg i.g.). The number of gastric lesions was measured by planimetry, the gastric blood flow (GBF) determined by H2-gas clearance technique, the mucosal production of H2S was assessed by methylene blue method. Expression of mRNA and protein levels for COX-1, COX-2 and CGRP were assessed by RT-PCR and ELISA, respectively. Both NaHS and L-cysteine dose-dependently attenuated severity of WRS-induced gastric lesions and significantly increased GBF. The inhibition of COX-1 and COX-2 activity significantly diminished NaHS- and L-cysteine-induced protection and hyperemia. The protective activity of NaHS and L-cysteine were significantly reduced by pretreatment with PAG and capsazepine. NaHS increased gastric H2S production and mRNA expression of COX-1, COX-2 and CGRP in gastric mucosa.

THE ROLE OF STRESS, AS LINK BETWEEN RISK FACTORS OF OSSEOINTEGRATION PROBLEM AND FAT–BONE INTERACTIONS

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Concerning to the last data, health is a multi-dimensional model, taking how people feel, and how they function from the individual to the cellular level, and what ability of an organism to respond adaptively to environmental challenges (D. Kuh, 2013). Moreover, according to statistic prognosis (2014), the EU population aged 65+, which is 11% from total population will increase to 23% in 2035. Research on the factors that influence health and premature ageing has become a priority in medicine. Review of PubMed, Google Schoolar data indicate that physical fitness, nutrition and lifestyle are key components in development lifestyle diseases, which are causes of premature ageing and cluster of diseases. Two of them, obesity and osteoporosis are growing in prevalence and closely related to physical inactivity, unbalanced nutrition and low-grade inflammation. Despite of pandemic character of overweight in human population, and recent data that around of 70 millions people from EU, USA and Japan are suffering of osteoporosis and this number is going to be double within in next 50 years, the link between body weight, bone mineral density, osteoporosis and bone active factors from adipocytes (i.e. estrogen, leptin, adiponectin) is still unclear. CJ Rosen and ML Bounxen (Nature, 2005) reflected osteoporosis, as “obesity of bone”, indicating on central regulation bone metabolism through the

hypothalamus and sympathetic nervous system, a pathway that also regulates stress response and adaptation, metabolic outcome and distribution of adipose tissue. To associate the risk factors with clinical, radiological, and patient-centered outcomes of periimplantitis after dental implant placement the retrospective study was done in 10 patients from Dental Departments from LNMU. Early detection of risk factors of bone destruction, as well as monitoring progression of bone loss, transformation of osteopenia to osteoporosis is important to indicate and prevent clinical problem with osteointegration titanium implants to the surrounding host bone.

PROTECTIVE ROLE OF H2S-DERIVATIVE NSAIDS AGAINST STRESS-RELATED ESOPHAGEAL AND GASTRIC MUCOSAL INJURY

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Introduction: Hydrogen sulfide (H2S) is a critical mediator of gastro-intestinal mucosal protection and repair in preclinical models of GERD and peptic ulcer. It has been proven also that the addition of a H2S-releasing moiety to classical NSAID structures results in NSAID-H2S with anti-inflammatory activity. Thus, we review effects of H2S derivate of NASID: H2S-naproxen (ATB-346) and H2S-aspirin (ATB-340) vs classical naproxen and aspirin during long-term administration on esophageal and gastric injury.
Methods: Rats were treated with vehicle (control), naproxen, aspirin, ATB-346, ATB-340 during 28 days with or without being subjected to water immersion restricted stress (Takagi et al. 1964). Subgroups of rats were pre-treated with an inhibitor of H2S synthesis cystathionine γ-lyase (PAG; 25 mg/kg) or cystathionine β-synthase (CHH, 20 mg/kg). Damage of the esophageal mucosa and esophagogastric junction, as well as gastric mucosa was estimated and scored using a histological damage index, according to the EsoHisto, 2011 recommendations for microscopic esophagitis and gastritis.
Results: Treatment with naproxen and aspirin resulted in the development of severe esophagitis and damage to the esophagogastric junction with disorganization of the muscle plate and irregular submucosal oedema and induction of erosive gastritis. The NSAID-related damage of esophageal and gastric mucosa was exacerbated by inhibitors of H2S biosynthesis PAG and CHH and attenuated by treatment with H2S-NSAID.
Conclusions: Inhibition of endogenous H2S synthesis provides a novel experimental model that can be useful in preclinical studies of NSAID-related non-reflux esophagitis or erosive gastritis. H2S-NSAID exerts potent vasoactive and anti-inflammatory activities, which contribute significantly to esophageal and gastric mucosal integrity against stress injury.

HISTAMINE-CORTISOL CORRELATIONS: NEW LINK OF MULTIFACIAL REGULATION OF INFLAMMATION

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Histamine is a mediator of inflammatory process. It influences tissues through four receptors, affecting nerve transmission gastric acid synthesis and allergy formation. Histamine was first received by A. Windaus and W. Vogta in 1907. In 1920 Leon Popielski, one of the XX century leading scientists in gastrointestinal (GI) Physiology and Pharmacology and co-author of humoral concept in GI secretion, which is still unknown to wide medical society, stated that after subcutaneous introduction, histamine acts directly on secretory cells in stomach stimulated more potently than cephalic conditioned impact. During his subsequent research in 1909 on wazodilatine Prof. Popielski established the difference between two compounds. Intravenous administration of histamine causes hypotension without immunization or coagulation impartment, in contrast to vasodilatine. On base of these researches in 1922 Steusing published his work in which he for the first time indicates histamine-containing tissues and compound. Interestingly histamine is everywhere, where plant or animal peptides get fermented. Histamine levels increase especially during stress. Histamine-cortisol correlation is responsible for induction inflammation in all part of GI tract. After the detection of histamine H2 receptors and their innovative role in the healing of gastroduodenal ulcer, the research on GI histamine was considered to be established.

Conversely, restarted interested in the amine began in the ‘90s with the detection of the histamine H3 receptor (H3R), and subsequently, in the early 2000 when the H4 receptor (H4R) was detected. As a consequence, novel therapeutic fields have been unravelled for antihistamine drugs: where¬as histamine H3R antagonists may represent new therapeutic options for cognitive, sleep and memory disorders and for obesity, H4R antagonists are currently the object of intensive research, as potential candidates in the therapy of allergy, inflammatory disorders, neuropathic pain and pruritus which have common pathogenic mechanism related to involving stress (Adami, Corruzzi, 2014). It is influenced not only by stress but also diet, contact with allergens, genetic predispositions and activity of histamine-breaking enzymes like diamine oxidase or histamine N-methyltransferaze (Shari Cheves, 2012). Except obvious symptoms of histamine level disturbances, there are also nonspecific symptoms like behavioral changes, depression or psychosis, change of sleeping pattern, sexual hyper- or hypoactivity.

CORTIRICOTROPIN-RELEASING FACTOR (CRF) RECEPTOR TYPE 1 BLOCKADE RESULTED IN TRANSFORMATION OF NON-ULCEROGENIC STRESS STIMULI INTO GASTRIC ULCEROGENIC ONES

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Background/Aim: It has been demonstrated previously in our laboratory that stress-induced activation of the HPA axis is gastroprotective component of stress reaction and glucocorticoids released in response to acute stress or exogenous CRF are gastroprotective factors. In the present study we hypothesized that mild stressors does not damage the gastric mucosa due to gastroprotective action of glucocorticoids released in response to these stimuli. Methods: Experiments were performed in preliminary fasted male rats. To verify the hypothesis the effects of normally non-ulcerogenic mild stimuli (30 min cold-restraint) on the gastric mucosa have been studied under the circumstances of CRF receptors type 1 blockade. For the blockade the selective CRF1 receptor antagonist NBI 27914 (10 mg/kg, ip) was injected 15 min before the onset of cold-restraint stress. Results: Acute exposure to 30 min cold-restraint did not cause gastric injury but induced plasma corticosterone rise in rats. Cold-restraint-induced corticosterone rise was inhibited by NBI 27914 injection and these results confirm the critical role of CRF1 receptors in the activation of the HPA axis. After NBI 27914 pretreatment of rats acute exposure to 30 min cold-restraint caused the gastric erosion. Additionally, NBI 27914 pretreatment significantly aggravated gastric erosion produced by 3 h cold-restraint. Conclusions: The results obtained demonstrate that in rats with glucocorticoid deficiency non-ulcerogenic stress stimuli are transformed into ulcerogenic ones and confirm the hypothesis. The data suggest that endogenous CRF may protect the gastric mucosa against cold-restraint injury through involvement of CRF1 receptors and glucocorticoids. The findings further support for the point of view that glucocorticoids released during acute stress are gastroprotective factors. The study was supported by Program PRAN P7 and the Russian Scientific Foundation grant N 14-15-00790.

OPIOID AS A STRESS TRIGGER: CEREBELLUM AND THE EYEBALL

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“Stress is the non-specific response of the body to any demand for change” (Selye). Opioid, as a chronic factor of stress leads to the disability and distress resulting usually in the contraction of chronic diseases or death. Our study deals with the establishment of these changes in the structural organization of cerebellar cortex and the vascular tunic of the rat’s eyeball resulting from injection of Nalbuphine during 6 weeks.
Methods: These investigations were carried out on 15 adult rats. Nalbuphine was injected to the experimental animals in doses 15.24 mg/kg during 6 weeks. Histological and electron microscopic methods of investigation were used. All experiments were approved by the University Animal Care and Use Bioethical Committee (Protocol #2/2012).

Results: Pathological changes in the vascular tunic of the eyeball resulting from injection of Nalbuphine during 6 weeks were manifested by edema and polymorphonuclear infiltration of the iris, ciliary body, choroidea also by the far-going destructive changes in the hemomicrocirculatory bloodstream elements of the eyeball. Thin-walled, elongated venules prevail. Arterioles' walls were thickened due to sclerotization, choriocapillar layer was destroyed. There was also observed a reduced number of capillaries with occasionally damaged walls and microhemorrhages. Characteristic was the manifested paravasal edema. Ultrastructural study of the vascular tunic of the eyeball had shown, that cytoplasm of endotheliocytes was filled with precipitates and coagulates. Basal membrane of hemocapillaries was thickened, laminated, contained electron-dense deposits. Heterochromatin was prevailed in the nuclei of damaged endotheliocytes in the state of karyorrhexis, their nucleolemma was damaged. Destructive changes were also observed in histological specimens of cerebellar cortex. In the molecular layer were present basket and stellate cells of altered form which testifies to vacuolar degeneration. Cytoplasm of some ganglion layer cells was narrow, unevenly stained. Piriform cells were disorganized. Pericellular edema was found around the cells. Formation of elongated cavities that we have considered to be microcysts were observed in the granular layer. The layer was lost, had an uneven thickness which indicated focal necrotic changes in cells. Sharpness of the boundaries between the layers was lost. Morphological signs of pathologic changes have been found in perikaryons of the neurons of all layers in ultrathin sections of the cerebellar cortex. The cell's form was distorted. Occasional neurocytes occur with an increased electron density of nucleo- and neuroplasm. The nuclei were of irregular form, occupied the entire cell. Nucleolemma formed protuberances. Few round-shaped mitochondrions with a lucid matrix have been seen against the background of compaction and vacuolization. The contours of internal mitochondrial membrane were blurred, cristae were disrupted. Canaliculi of granular endoplasmic were dilated unevenly, fragmented.
Conclusions: Thus, micro- and electron microscopic study of the white rats' cerebellar cortex and vascular tunic of the eyeball after prolonged injection of opioid as a stress factor has shown the signs of degenerative changes of a varying degree of development in the cerebellar cortex neurons. Development of angiopathy in the eyeball under such conditions is triggering mechanism for the rise of destructive processes.

EFFECT OF GASTRIC PENTADECAPEPTIDE BPC 157 THERAPY IN LIVER FIBROSIS AND CIRRHOSIS AND PORTAL HYPERTENSION

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We investigated stable gastric pentadecapeptide BPC 157 as a potential therapy for liver fibrosis and portal hypertension, acutely and chronically. Since BPC 157 affects wound healing, liver lesions and blood vessels via egr-1, naB2, FAK-paxillin, and JAK-2 pathways involved in fibrogenesis/fibrolysis, we studies the beneficial effect in rats with long standing bile duct ligation with portal hypertension and in rats with portal triad clamping-induced huge increase of portal vein pressure. After bile duct ligation (sacrifice at 2, 4, 6, 8 week) medication was (i) BPC 157 orally (10 μg/kg, 10ng/kg, 0.16 μg/ml, 0.16 ng/ml, 12ml/rat/day) till the sacrifice; (ii) BPC 157 intraperitoneally (10μg/kg/day, 10ng/kg/day, first at 30 min post-ligation, last at 24h before sacrifice) or (iii) BPC 157 orally (10μg/kg, 0.16 μg/ml, 12ml/rat/day)since 4 week. For immediate effect on bile duct ligation-portal hypertension, medication (local bath (5ml/kg) of saline or BPC 157 10 μg/kg) was given immediately after establishing portal hypertension values. BPC 157 therapy after bile duct ligation initiated was initiated to see the effect on perilous gross presentation (e.g., jaundice, ascites, nodular, steathotic liver, bile duct dilatation, increased liver and/or cyst weight, body weight loss). All BPC 157 rats had more hepatocytes, more hepatocytes with double nuclei, less portal inflammation, and no picemal necrosis and focal lythic necrosis, apoptosis and focal inflamation, smaller intensity of architectural changes, fibrosis and cirrhosis, lower Ishak score, smaller α-SMA lobular and porto-septal distribution. Decreased were bilirubin, ALP, AST, ALT, AP, GGT serum values, preserved serum albumin. BPC 157-bile duct ligated rats had no portal hypertension. BPC 157 therapy in bile duct-ligated rats since 4 week improved subsequent gross, microscopy and biochemistry presentation. BPC 157 initial administration at 4, 6, or 8 bile duct ligation-week instantly counteracted and normalized portal hypertension. Likewise, given locally as bath at the clamped area, BPC 157 consistently counteracted portal triad clamping-induced huge increase of portal vein pressure (60±5 (control) vs. 23±3 (BPC 157 given before), or BPC 157 after clamping: 20±3 (given at 5min), 27±3 (given at 30min); likewise, BPC 157 (given at 5min after clamping) counteracted decreased pressure in inferior caval vein (5±1 (control) vs. 9±1 (BPC 157), abdominal aorta (30±3) (control) vs. 66±6 (BPC 157), and change in jugular vein pressure (4±1) (control) vs. 1±0 (BPC 157). Also, BPC 157 counteracted remained increase of portal

pressure after removal of portal clamping (15.0±1) (control) vs. 7±1 (BPC 157 (iv)). The same effectiveness was seen with both BPC 157 µg- and ng-regimens. This is likely due to the effect on small blood vessels (i.e., 4th branches). Along with severe portal hypertension, in controls, the number 4th branches rapidly decreased in both intestines (1stmin 40±3. 10thmin 18±2, 20thmin 14±3) and caecum (1stmin 93±4, 10thmin 78±3, 20thmin 60±3) while in BPC 157-rats with portal hypertension was attenuated, the number 4th branches rapidly increased in both intestines (1stmin 42±2, 10thmin 51±2, 20thmin 56±3) and caecum (1stmin 91±4, 10thmin 135±5, 20thmin 167±80). Even after reperfusion, BPC 157 rats showed markedly less gross and microscopic intestinal injury, only slight edema, less epithelial cell degeneration and markedly less necrosis in mucosal villi.

THE EFFECT OF PENTADECAPEPTIDE BPC 157 ON SYSTEM CIRCULATION AND THROMBOGENESIS AFTER LIGATION OF VENA CAVA INFERIOR

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In this study we analyzed the effect of pentadecapeptide BPC 157 on systemic circulation and thrombogenesis after ligation of vena cava inferior (ICV). We used female Wistar rats (200g) which underwent ICV ligation just above the right vena ovarica. Immediately after, controls received 1 ml of saline bath and the BPC 157 rats received 1 ml of BPC 157 (10 µg/kg) bath. The thrombi from the vein were evaluated macroscopically after extraction and the pressure in the abdominal aorta and vena cava was assessed after 1h and 24h. Control group at 1h had the thrombi lenght of 0.83±0.15 cm and the thrombi mass of 0.04±0.01g, and the control group at 24h had length of 1.60 ± 0.43 cm and mass of 0.074 ± 0.006 g, with blood pressure in abdominal aorta of 70.50 ± 2.12 mmHg after 24h and 72.4± 3.1 mmHg after 1h, while the pressure in vena cava inferior was 27± 1.2 mmHg after 1h and after 24h 26.3± 1.4 mmHg. BPC 157 treated group at 1h had the thrombi lenght of 0.4± 0.05cm and the mass of 0.01± 0.004 g, and the 24h BPC 157 group had length of 0.78 ± 0.07cm and mass of 0.032 ± 0.003g, with pressure in abdominal aorta of 98.0 ± 1.40 after 1h and after 24h it was 96.5± 1.8 mmHg, while the pressure in the vena cava inferior was 13± 1.5 mmHg after 1h, and after 24h 15± 0.8 mmHg. As a conclusion, this study has shown significant beneficial effect of pentadecapeptide BPC 157 on systemic circulation and decrease both in thrombi size as well as blood pressure in vena cava inferior. Supported by Grant 108-1083570-3635, Croatia.