MAKING SENSE FOR STRESS: FROM HANS SELYE'S ANIMAL STUDY TO THE MOLECULAR PHYSIOLOGY OF STRESS AND ITS PHYSIOLOGICAL CONSEQUENCES ON HEALTH AND WELL-BEING (TO 110-ANNIVERSARY FROM BIRTH OF H.SELYE)

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Professor Hans Selye (1907, Vienna – 1982, Montreal) is one of the greatest scientists of the 20th century who stood at the cradle of studies of the manifestation of the stress and stress-related conditions. He is often named as father of "biologic stress" concept but he is still unknowing in XXI century to a wide audience. Selye's fate was closely tied to the history of region of former Austro-Hungarian empire where he was born and grow up. He graduated German Medical School in Prague, and later moved to New World where performed his influential investigations at the Université de Montréal (Canada) and where during 35 years he was a scientific mentor of more than 60 MSc and PhD students, including the Nobel Laureate Roger Guillemin (1977) as well as hundreds of visiting scientists from all over the world. H. Selye was author of about 1700 original and review articles, as well as 39 books. The first monograph with the short title "Stress" was published in 1950 in Montreal (Canada) and author supposed "stress" to be a non-specific neuroendocrine reaction of the body on two and more stressors (agents which cause stress) of different nature (physical, chemical, biologic and psychologic). Selye also distinguished three stages of stress response: alarm reaction, resistance and exhaustion and introduce term 'eustress" and "distress". It is important to note that the research of Selye was not limited to stress, but he also worked in the field pharmacology and was first who introduced term "glucocorticoids". However, Selye's groundbreaking work and ideas were done in the time when tools for investigation molecular mechanisms were unknown. His PhD students Yvette Tache and Sandor Szabo followed stress-related research and now they are recognized leading experts in neurobiology of stress and gastroenterology, as well as brain-gut interactions, the role of peptides and growth factors in the underlying mechanisms of stress-related gut dysfunction. These data provided the preclinical groundwork showing potential benefit of blocking corticotropin releasing (CRF) or angiogenesis signaling pathways in experimental models of irritable bowel syndrome. 2017 is the 110th anniversary of his birth which is internationally celebrated and it is good reason to reminder historical lessons of life story and work H.Selye on modern physiology, psychology, and medicine.

THE ROLE OF STRESS IN GERD – WHAT DO WE KNOW?

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Key words: stress, GERD, gastric acid, acid reflux

Various studies evaluated the effect of stress on the gastrointestinal tract. More recent studies have focused on the relationship between stress and reported symptoms of GERD. However, when evaluating these studies, one should consider the stressors used, if the stress is acute or chronic, if the complaints are subjective or objective and, most importantly, the subjects being evaluated. There are a variety of stressors that have been used in these

studies, including white noise, exposure to cold temperature, loud noises and anticipation of stressful situations such as giving a speech. Overall, these stressors result in acute stressful situations. Other studies screened for subjects who experience a prolonged stressful situation such as being primary caregiver to a terminal loved one.

It has been shown that subjects who have been exposed to prolonged life stressors are more likely to complain of symptoms of GERD. One study demonstrated a correlation between discussion of emotionally charged topics and nonpropulsive activity in the esophagus. Another study assessed gastric acid output in relation to personality traits. It was found that subjects who were considered to have a higher level of impulsivity and expressed emotions more freely were more likely to react with an increase in gastric acid output when subjected to stress simulated by a problem-solving session than patients with low level of impulsivity. In fact, subjects with low level of impulsivity reacted to this stress with a decrease in gastric acid secretion. Increased gastric acid secretion has been seen in subjects with a higher tendency towards emotional lability. One study evaluated the relationship among stress, psychological traits associated with chronic anxiety, acid reflux parameters and perceptions of reflux symptoms. The researchers found that stress tasks did not influence objective measurements of acid reflux (total acid exposure, number of acid reflux events and duration of longest acid reflux event). Another significant finding was that reflux patients who were chronically anxious and exposed to prolonged stressful stimuli may be more likely to perceive low-intensity esophageal stimuli as painful reflux symptoms. Therefore, even normal esophageal acid exposure could trigger complaints of GERD symptoms. Also, it is not a specific psychiatric disorder that may be responsible for gastrointestinal distress but the presence of psychological distress that predisposed a patient to have clinical manifestations of GERD.

A study by Naliboff et al. found that 'vital exhaustion', which is a measure of sustained stress symptoms, was most closely correlated with symptoms of heartburn. Fass et al. have shown that acute auditory stress can exacerbate heartburn symptoms in GERD patients by enhancing perceptive response to intra-oesophageal acid exposure. This greater perceptual response is associated with greater emotional responses to the stressor.

EFFECTS OF STRESS ON BEHAVIOUR AND SLEEP

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Key words: stress, glucocorticoid receptor, cortisol, memory, cognition

Psychologists Yerkes and Dodson described already in 1908 the inverted-U shaped relationship between arousal and performance. When the level of arousal heightens, behavioural performance increases but only to a certain point. When the level of arousal, produced by stress, becomes too high, adequacy of behaviour decreases while sleep is affected. Physical and mental performance generally follows the level of circulating stress hormones, in particular the glucocorticoid hormone cortisol. The secretion of cortisol in response to a stressful event triggers a chain of events, ultimately leading to energy for fight-or-flight behaviour. Under non-stressed basal conditions, the level of cortisol follows a circadian pattern: a maximum in the morning, necessary for daily activities, with slowly declining levels during the day, and a trough during sleep. Cortisol binds to two glucocorticoid receptor subtypes: Type I with a high affinity and Type II with a lower affinity for cortisol. There are also differences in brain location between the types. The differences between the two subtypes results in a discrepancy of receptor occupation. During the nocturnal sleep trough all Type I receptors are occupied by the endogenous hormone, while during the morning wake peak Type 1 receptors are fully saturated and Type 2 receptors come into action. The mix of Type I and Type II occupation is also the situation by stressful events. The differential qualities