

# Approach to stress endocrine response: somatization in the context of gastroenterological symptoms: a systematic review

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## Abstract:

**Background:** Stress can be defined as an acute threat to the homeostasis of an organism, and in order to manage stress, and maintain stability, the allostatic systems activate an adaptive response. Stress has been shown to have both short - and long-term effects on the function of the gastrointestinal tract, but long-term exposure to stress is more likely to cause endocrine disorders.

**Objective:** The aim of this study was to investigate the endocrine response to stress, and evaluate the relationship between somatization and gastrointestinal symptoms.

**Methods:** A systematic literature search was conducted on several academic databases, which included, Pubmed, EBSCO and Science Direct. The search was performed using the keywords, “endocrine response to stress”, “somatization” and “gastrointestinal symptoms”.

**Results:** The hypothalamic-pituitary-adrenal (HPA) axis is essential in controlling physiological stress responses. Dysfunction is related to several mental disorders, including anxiety and depression, or somatization. Symptoms associated with genetic, or other traumatic experiences of individuals under stress, can lead to a maladaptive response to stress. These stressful life events were found to be associated with digestive system-related chronic diseases. Gastrointestinal disorders significantly affect millions of people worldwide.

**Conclusion:** This study examined how the endocrine system responds to stress, and the effect this has in causing stress-related gastrointestinal distresses. Our findings indicate that stress-related psychological disorders are strongly associated with the severity of gastrointestinal symptoms.

**Keywords:** Stress, endocrine response, somatization, gastrointestinal symptoms.

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## Introduction

When an organism is confronted with any perceived threat, it reacts by creating a series of behavioural responses. A response that is either extreme, or insufficient, in terms of its specificity, may result in one or more, psychological or physical pathologies. Whilst it is understood that an organism responds to stress, the nature of stress itself is so diverse, that there is no widely accepted defi-

inition. Stress is a condition that manifests itself, in both physiological and psychological forms, when an organism feels threatened. Stress may affect a series of variables relevant to homeostasis and the internal environment. For example, Selye [1976] carried out a series of laboratory experiments on mice, and the results showed that the mice displayed certain physical symptoms when they were subjected to stress.<sup>1,2</sup> There are many stressful situations, both physical and psychological, that can be associated with various medical disorders, surgery or psychological trauma.<sup>3,4</sup> Adaptive mechanisms may be activated in order to provide environmental control and to allow the organism to survive. This adaptive process, and the presence of disease, influence physiological functions.<sup>5,6</sup>

Allostasis is defined as a process that restores homeostasis, or balance, in the internal environment through physiological or behavioural changes. The cost of biological

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responses to adapt to stress is known, in psychiatry, as allostatic load. Allostatic load is low-level in stress-relieved conditions, and high-level in extremely stressful situations, and is triggered in many physical disorders.<sup>7</sup> Allostatic systems become active when changes take place in the hypothalamic-pituitary-adrenal (HPA) axis, the autonomic nervous system (ANS) and in the cardiovascular, metabolic and immune systems.<sup>8</sup>

Hormones and physiological factors are prophylactic, and can help to lessen the severity of the effects of stress in the short term. However, these hormones, and the physiological factors, stay at a consistently high level, or deteriorate, during repeated and prolonged exposure to stress. This situation may result in pathological, physiological or psychological changes.<sup>6,9</sup> Stress response aims to reduce the effects of stress, however, acute and chronic stress responses differ. Current evidence is still insufficient and, therefore, it has not been possible to demonstrate conclusively that stress has a direct effect on endocrine and oncological diseases. Nevertheless, there are quite extensive studies which explore the relationship between psychological stresses and a variety of medical disorders.<sup>10,11</sup>

This brief summary considers stress, the endocrine response to stress, the gastrointestinal stress response, the relationship between stress and somatization, and gastrointestinal symptoms. Some recent clinical experiments have examined endocrine responses and the endocrine effects of stress on the gastrointestinal system. The results of these experiments were assessed in association with somatization. The aim of this study was to investigate the endocrine response to stress, and the relationship between somatization and gastrointestinal symptoms.

## Methods

In this study, we identified a number of earlier publications which focused on the endocrine response to stress and, more precisely, the assessment of stress, somatization and gastrointestinal symptoms. A systematic search was conducted on several academic databases which included, Pubmed, EBSCO and Science Direct. The search was carried out using the keywords “endocrine response to stress”, “somatization” and “gastrointestinal symptoms”. Publication dates were not specified, however, the final search was carried out in February 2016. A search using the keywords “somatization, stress and gastrointestinal symptoms” revealed 11,300 web pages on Google Scholar (this search was completed on 5 June 2016). A further 34,500 articles were found on Science Direct, of

these, 12,500 articles were found between the years 2005 and 2010, and another 22,000 articles were found between 2011 and 2018. These figures confirm that interest in this field of study has grown considerably and clearly show an increase in the number of articles being published. We focused on studies that provided information on how endocrine response to stress was defined, its prevalence, its predictors, and its relation to gastrointestinal symptoms. We used the keywords, ‘gastrointestinal symptoms, and somatization’, and confined our search to those studies only published in English and Turkish.

**Inclusion criteria**-only articles measuring endocrine responses to stress, stress- gastroenterology response and somatization-gastroenterological symptoms were included.

**Exclusion criteria**-studies undertaken and published before 2005 were excluded.

## Results

### Endocrine responses to stress

Sensitivity to stress may differ in cases where there has been a lifetime of exposure to extreme stress. The reason for this can be associated with factors such as, the level of response to stress, past experiences, and genetic factors. The evaluation and detection of stress is effective for both psychological and biological mechanisms. The amygdala, prefrontal cortex (PFC) and hippocampus may regulate the stress response by interacting, directly or indirectly, with the prefrontal cortex (PFC) when the amygdala is charged, thereby activating the emotional memory which contains inhibition and responses to fear.<sup>2</sup> The amygdala is responsible for the perception of emotions, and helps to store memories involving stress-related events that occurred in the past. It perceives the severity of a stressful situation based on a previous experience and triggers stimuli, in separate regions of the memory, to focus on, and manage threatening situations. The sympathetic-adrenomedullary-system and the hypothalamic-pituitary-adrenal axis also have a role in stress response and are regulated by the amygdala, hippocampus and the orbital/medial PFC. Acute or repetitive stress may produce functional and structural alterations in the PFC, amygdala and hippocampus.<sup>13,14</sup>

When acute stress occurs, the locus coeruleus becomes active, and the noradrenergic system releases catecholamines in the autonomic nervous system (ANS). During

periods of chronic stress, tyrosine hydroxylase is released and noradrenaline (NA) synthesis is further increased. Consequently, chronic stress may reduce the autonomic nervous system response to a particular stress but it may also improve sensitivity. Increased levels of postsynaptic serotonin have been found during recurrent brief, or long-term, adaptation to stress.<sup>15,16</sup>

The endocrine response to stress causes change in the hypothalamic-pituitary-adrenal (HPA) axis function. The direction and intensity of this function alters with the frequency and duration of exposure. The genes responsible for the secretion of corticosteroids in stress-related situations come from Chromosome 3 (in the genomic region).<sup>6,17</sup> One of these genes, Rs6318c-allele, was found to increase in subclinical depressive symptoms in non-depressed teenagers, and was also seen to disrupt the effectiveness of the neuroendocrine stress response.<sup>18</sup> In addition to the HPA function, prolactin and growth hormone secretion from the anterior pituitary gland, and antidiuretic hormone secretion from the posterior pituitary gland, (ADH) are affected during stress. Furthermore, the thyroid hormone is also suppressed during stress especially after reproduction and growth has stopped.<sup>19</sup>

Chronic stress is known to suppress cellular immunity. It is also known that helper and suppressor T cell counts decrease, and that the proliferations of lymphocytes stop. HPA activation, which leads to increased levels of cortisol are also known to suppress immune function. The functions of CRF are central to how the immune system responds to stress.<sup>20,21</sup>

Some individuals cannot tolerate stress-related bodily sensations. This low tolerance threshold suggests that the reason for neural and psychobiological sensitivity can be defined as 'prolonged (sustained) attention', and this assumption is defined as 'stress-related cognitive activation theory' (CATS).<sup>22,23,24</sup> According to this theory, a particular stimulus is activated and forms a message that is then transmitted to the cortex via the thalamus and hypothalamus. The cortex alerts the hypothalamus to respond to this stimulus (or stimuli), and triggers a series of events in the periphery. At the same time, changes in the periphery are sent to the cortex via the thalamus-hypothalamus, and the events are perceived. This perception, which deals with emotions and emotional attitude, are produced at the cortex.<sup>22,25</sup>

Another theory which assesses the relationship between stress and the brain, is the 'thalamic theory of emotion'. In 1931, Cannon-Bard focused on the role of the thalamus and sensation. According to this study, the thalamus acts as a centre for integrating emotions. This theory also concludes that emotional stimuli are processed in the first instance by the thalamus. It also goes on to suggest that there is a correlation between emotional response and sensation. In the study, Cannon referred to the spontaneous 'fight or flight' reaction to intense emotional changes. He also stated that two subcortical structures, the hypothalamus and thalamus, are responsible for the regulation of emotional changes.<sup>26,27</sup>

### **Stress- gastroenterology response**

Stress is known to be associated with, not only psychiatric disorders, but with all diseases. The gastrointestinal system is innervated by sympathetic nerves from the lateral hypothalamus, and innervated by parasympathetic nerves from the periventricular and lateral hypothalamus, and the dorsal vagal nucleus. The brain-GI axis is controlled by the amygdala and the limbic system. Acute and short-term stress responses inhibit gastric emptying and colonic transit stimulation. The corticotrophin releasing factor (CRF) acts as a key component in stress and GIS interaction. The CRF-2 receptor regulates the inhibition of the upper gastrointestinal tract, and the CRF-1 receptors are responsible for colonic response, and have an anxiogenic effect in the lower gastrointestinal tract. Elevated central CRF levels increase the risk of stress-related psychiatric, physiological, and behavioural disorders.<sup>22,28</sup>

The increased activation of 5HT<sub>3</sub> in colonic motility also occurs through the CRF. Furthermore, how the intermediary role of CRF in stress, and GIS interaction, affect the role of early life events in gastrointestinal disorders, has also been considered. However, how the motility response in people with functional gastrointestinal complaints compares to healthy individuals has not been determined. It is not clear if these complaints were caused by sensitivity to stress, or if they resulted from a failure of the nervous system.<sup>22,29</sup>

Stress affects many functions such as, microbiota motility, secretion, permeability, and sensitivity in the gastrointestinal tract. Normally, stress stimulates secretion and colonic transit, delays gastric emptying time, increases intestinal permeability and visceral sensitivity, and modifies intestinal microbiota. These effects on the gastrointesti-

nal system show that stress plays a role in the pathogenesis of ulcerative colitis and Crohn's disease, irritable bowel syndrome, functional gastrointestinal disorders, and inflammatory bowel diseases. Physical stimuli to the thalamus, insula, anterior cingulate and the amygdala activation responses were higher in patients with inflammatory bowel syndrome than in healthy individuals. The 5HT<sub>3</sub> gene polymorphism has been associated with amygdala response.<sup>15,22,30</sup>

Selye (1976), with reference to the general theory of adaptation, stated that stress will lead to adjustment disorders such as ulcers and constipation.<sup>1</sup> William Beaumont (1833), however, reported that anger and fear affect gastric acid secretion.<sup>31</sup> In a study conducted by Walter Cannon in 1902, which observed cats being confronted by aggressive dogs, gastrointestinal motility disorders were seen to occur.<sup>26,32,33</sup>

Currently, CRF and the associated peptides, urocortin cytokines and their receptors of CRF, regulate the effects of stress on the gastrointestinal system. CRF is secreted by the hypothalamus and is mobilized by a series of adaptive physiological, and behavioural, responses to stress. Anterior pituitary hormones are controlled by CRF, and supra hypothalamic stimuli affect gastrointestinal functions. Abnormal levels of CRF<sub>1</sub> play a significant role in the pathology of irritable bowel syndrome as well as in anxiety and depression. CRF is present in the myenteric and submucosal plexuses along the gastrointestinal tract, in epithelial cells of the colonic mucosa, as well as in epithelial and submucosal immune cells of the gastrointestinal tract, including endocrine cells.<sup>22</sup> In humans, CRF<sub>2</sub> and CRF<sub>1</sub> are located in the lamina propria colon, and specifically, in the colonic myenteric plexus.<sup>22,34</sup>

It has been established that intestinal permeability is affected by childhood trauma, acute stress, or chronic stress. Stress increases mast cell protease II and mucin which are released from colonic explants. Following acute stress, however, these increases return to normal after 24 hours. A new member of the CRF family, UCN (urocortin), is seen to increase dramatically when *H. pylori* is absent. When this happens, the UCN can be associated with psychological factors which impact the gastric epithelium of the gastrointestinal tract.<sup>22,35</sup> Currently, the microbiota of the gastrointestinal tract is known to have an effect on obesity, diabetes mellitus, atherosclerosis, and

non-alcoholic fatty liver disease pathogenesis. CRF and gut microbiota could play important roles in the development of stress-related disorders such as depression and anxiogenic behaviours.<sup>36</sup>

Microorganisms (microbiota) in the gastrointestinal tract were seen to have several important functions such as: 1) ensuring the maturation of the epithelium; 2) metabolic transformation; and 3) protecting against enteric infections. It is thought that the intestinal microbiota play a role in the pathogenesis of motility-related disorders like bowel disease, and diseases associated with inflammations such as, inflammatory bowel disease. It has been shown that commensal microbiota affect the postnatal development of the brain and the endocrine response to stress.<sup>37,38</sup> In a study carried out on rats, Ait-Belgnaoui et al. showed that prevention of intestinal barrier impairment by a probiotic reduces the HPA response to acute psychological stress.<sup>39</sup> CRF<sub>1</sub> reduces colonic sensitivity against colonic distention.<sup>22,40</sup>

### **Stress related gastrointestinal disorders**

The major functions of the gastrointestinal tract include swallowing, motility, emptying (of every section), assimilation and elimination. Motility enables swallowing, transit, emptying and elimination. All of these functions are essential for proper assimilation. Abnormal gastric emptying is thought to be a clinical marker for gastric or intestinal motility disorder. This would suggest that there is a direct relationship between stress and gastric emptying. Gastroesophageal reflux, with symptoms of heartburn, is more common in patients with mental disorders such as neurosis, anxiety, and depression than in healthy patients.<sup>41</sup> In non-erosive esophagitis patients, anxiety was found to weaken the response to the proton pump inhibitor.<sup>42</sup>

Chronic stress has an important role in the etiology and prognosis of irritable bowel syndrome. While stress can increase dysbiosis and bacterial wall adhesions, the interaction between host and microbiota can modulate neuro-immune-endocrine systems. The alteration of microbiota in the gut, due to stress, plays a critical role in the pathogenesis of irritable bowel syndrome.<sup>43</sup> However, stressful life events can negatively affect the prognosis of IBS, abdominal pain and abdominal distention, and can exacerbate these disorders in patients.<sup>44</sup>

A higher incidence of mood disorders were found in patients with gastrointestinal dysfunctions, such as Crohn's disease and ulcerative colitis, compared to the general population. Furthermore, depression and anxiety can also affect the course and the severity of the underlying bowel disease.<sup>45</sup> Psychosocial stresses can increase inflammation and may compromise both the integrity of the gastrointestinal mucosal barrier, and the role of the sympathetic nervous system. Therefore, stress can stimulate the passage of the bacterial pathogens on the epithelial barrier and activate mucosal immune responses.<sup>46</sup> Psychosocial stress causes an increase in inflammatory cytokines, and prolonged exposure to cytokines leads to an increase in cortisol concentrations. This may also impede the integrity of the bowel barrier, allowing the commensal bacteria to cross the gastrointestinal mucosa and assist the formation of inflammatory bowel disease.<sup>47</sup>

## Discussion

### Somatization-gastroenterological symptoms

It is possible to describe physical symptoms as an external expression of psychic conflicts in somatization. In other words, somatization as an emotional dysphoria, has a tendency to manifest itself in the form of physical symptoms.<sup>48</sup> According to MacLean et al<sup>35</sup>, emotions are symbolic expressions that cannot be converted into verbal pathways which would otherwise connect with the neocortex. Therefore, they are expressed autonomously, and appear as physical symptoms which are then converted into body language in a psychosomatic person.<sup>42</sup> Psychosomatic feelings do not reach the cortex through the hypothalamus and so remain in the amygdala.<sup>49</sup> The concept of somatization was originally proposed and defined by Stekel<sup>50</sup>, as a physical disorder symptomatic of underlying deep neuroses. In other words, somatization should be considered as a temporary stress reaction that extends beyond the apparent disorder or diagnostic categories.<sup>51</sup>

In brain imaging studies it has been determined that women with somatization have decreased glucose utilization in the brain. It has also been shown that caudate and putamen metabolism decreased in women with somatization when compared to healthy volunteers.<sup>52</sup> Somatic symptoms were associated with peripheral physiological changes. For example, a tension headache is the most common type of headache, in which the muscle

contractions can be a response to stress or depression. The electromyographic potential of painful muscles was higher than the other muscles. The burning sensation associated with esophageal motility, and the contraction of muscles on the gastrointestinal tract that patients with gastric complaints experience, is another physiological activity that causes stress-related somatic symptoms. These sensations occur due to changes in endocrine activity. Adrenal functions are affected by fear, which in turn cause biochemical changes leading to alkalosis, and as a consequence somatic symptoms are triggered.<sup>53</sup> Patients with dysmotility and GI symptoms show comorbidity with affective disorders, and their symptoms are influenced by psychological stress.<sup>36</sup>

In present day medicine, a psychosomatic syndrome opposes other disease syndromes because it does not appear to have a significant organic cause. Nevertheless, it is a chronic disease which severely affects an individual's life causing considerable pain and restriction. It is also one that has a huge financial impact on health services all over the world. It is often the case that this group of disorders lacks a defined etiology, resulting in the failure to provide patients with improved methods of treatment.<sup>54</sup> Furthermore, because somatoform disorders lack subjective emotional awareness, a factor that is normally present, and one that can be determined in other psychiatric disorders, they are defined simply as 'physical distress syndrome'.

According to the study, changes in physiological activity that cause the somatization is idiosyncratic, in that it is specific to each individual, and it tends to worsen during times of stress. According to Panksepp's<sup>55</sup> basic emotion of the command system, medically unexplained symptoms can be understood by referring to one of these emotions. In particular, anger caused by frustration in childhood, is transformed into somatization in adulthood.<sup>56</sup> In a systematic study in which 4640 patients participated, it was determined that the diagnosis of functional gastrointestinal disorders is high in patients with a history of childhood sexual abuse.<sup>57</sup> Somatoform symptoms are considered to be the process of dissociation from the anxiety created by the conscious awareness resulting from traumatic experiences in childhood.<sup>58</sup> Dissociation was determined to be a highly effective factor in the relation-

ship between trauma and somatization in patients with irritable bowel syndrome.<sup>6,59</sup>

However, there is not enough data to support how the differentiation of motility response in people with functional gastrointestinal complaints compares to healthy individuals. Therefore, this case is not clear enough, whether due to a deficiency in the nervous system, or increased stress sensitivity, but some personality types have been shown to support the somatization. The concentration of catastrophic helplessness beliefs, in particular, supports somatization in individuals with neurotic negative self-perception.<sup>60</sup> Individuals experiencing neuroticism are unable to overcome the stress effectively, and it then becomes a traumatic dissociation.<sup>61</sup> It has been determined that somatization is more prevalent in patients with alexithymia who lack emotional awareness.<sup>62</sup> Somatization may also be related to unrealistic expectations about being healthy. It is also possible that bodily sensation is over-exaggerated, and that maladaptive reactions develop in response to normal body sensations. In other words, interpretation concerning bodily sensations becomes confused and chaotic. Somatosensory amplification increases, and the ability to process information becomes more difficult.<sup>63</sup> Undetected sensations with a neural filtering system in healthy people, are easily sensed by individuals who frequently experience somatization. This is also the basis of the "gate control theory" in pain research, which recognizes the importance of the mind and brain in pain perception. Primary stress response causes an increased activation of physiological signals, and bodily sensations increase so long as the physiological activation continues. In fact, this situation may be considered to be a hypersensitization process. Sensitization occurs when the perceived signal is overly magnified.<sup>63</sup> Jones et al<sup>64</sup>, found quite high alexithymia and somatic amplification scores in patients with dyspepsia. Anxious people were seen to experience catastrophic bodily sensations which were attributed to being symptoms of severe physical illness.<sup>65</sup> According to the attachment theory, somatization is defined as the care-seeking behaviour in individuals who develop an insecure attachment to parents.<sup>66</sup>

## Conclusion

We believe that there is a strong association between gastrointestinal symptoms and psychological disorders triggered by stress. The body reacts to severe somatic stress responses which can cause serious gastroenterological

symptoms. Psychiatric comorbidity is common in gastrointestinal disorders, so psychiatric evaluation is important. Psychological evaluation of the gastrointestinal disease may increase compliance with treatment. It should be noted that optimal treatment for patients with gastrointestinal disorders requires a multidisciplinary approach involving psychiatric intervention.

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