Research Results in Pharmacology

Research Results in Pharmacology 11(4): 162–174
UDC: 615.015:615.214:616.34:579.61
DOI 10.18413/rrpharmacology.11.587

Review Article

Stress, neurotransmitters, and the microbiota–gut–brain axis: mechanisms of mucosal injury

Khaled A. Abdel-Sater

Faculty of Dentistry, Mutah University, Al-Karak, Jordon

Corresponding Author Khaled A. Abdel-Sater (Kabdelsater@mutah.edu.jo)

Academic editor: Tatyana Avtina ♦ **Received** 17 February 2025 ♦ **Accepted** 01 September 2025 ♦ **Published** 25 December 2025

Citation: Khaled A. Abdel-Sater (2025) Stress, neurotransmitters, and the microbiota–gut–brain axis: mechanisms of mucosal injury. Research Results in Pharmacology 11(4): 162–174. https://doi/org/10.18413/rrpharmacology.11.587

Abstract

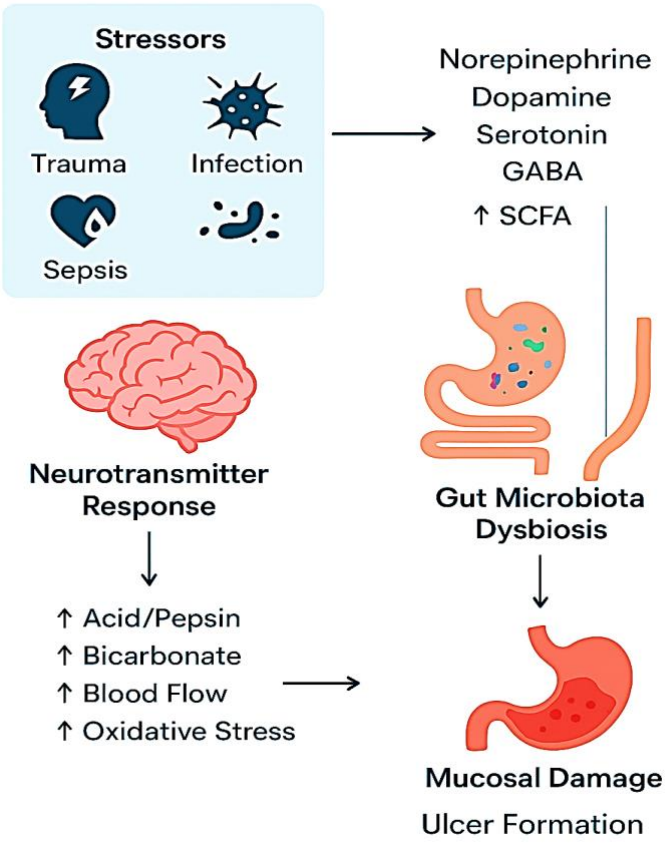
Introduction: Stress-induced mucosal damage is increasingly understood to be mediated by the gut-brain axis, where neurotransmitters serve as essential signaling molecules. This review explores the interplay between gut microbiota and the stress response, highlighting how neurotransmitters mediate the effects of stress on gut health and mucosal integrity. Understanding these mechanisms may open new avenues for therapeutic interventions targeting the gut-brain axis.

Methods: A literature search was completed using PubMed, Web of Science, PsycINFO, and Embase databases for clinical and preclinical studies related to stress ulcer, gut microbiota and gut brain axis published in English until 2024.

Results: The gut microbiota has a role in maintaining gastrointestinal health and influencing the body's stress response through various pathways, including the enteric and autonomic nervous systems. It produces microbial metabolites like short-chain fatty acids, tryptophan, and bile acids, which enter the bloodstream and reach the brain. Microbial neurotransmitters modify the brain's gut axis. Norepinephrine, released as an adrenal hormone and neurotransmitter, plays a role in cognition and attention regulation. Dopamine regulates immune responses, motivation, memory, mood and attention. Serotonin, synthesized in the digestive tract, indirectly impacts brain function. Glutamate, a key neurotransmitter, is synthesized in the brain, while acetate and γ-aminobutyric acid regulate blood pressure and heart rate. Cortisol, acetylcholine, neuropeptide Y, and cholecystokinin influence gut function and emotional regulation. Disturbances to gut microbiota can lead to maladaptive mood and behavior.

Conclusion: The connection between stress ulcer, neurotransmitters, and the gut microbiota was outlined in this review.

Graphical Abstract



Keywords

stress ulcer, microbiota-gut-brain axis, neurotransmitters, SCFAs, glutamate, dopamine, norepinephrine, GABA, CCK

Introduction

Gut microbiota is important in many nutrition and physiological functions. It regulates gastrointestinal tract (GIT) and central nervous system functions. It regulates food digestion, energy metabolism, inflammatory response, systemic immunity, intestinal motility, and nutrient absorption, memory, and learning (Cristofori et al. 2021).

The gut-brain axis is a bidirectional communication network between the brain and GIT. The nervous system (autonomic and enteric systems), endocrine system, immune system (by producing cytokines and chemokines from both peripheral and central infiltrating immune cells), and neurotransmitters cooperate to regulate digestion, cognition, learning, and anxiety (Góralczyk-Bińkowska et al. 2022).

Dysbiosis refers to an imbalance in the gut microbiota, where the community of microbes is disrupted, leading to a predominance of pathogenic species over beneficial ones (Cristofori et al. 2021). It may disrupt the communication between the gut and the brain, altering stress response pathways (Góralczyk-Bińkowska et al. 2022). This dysfunction can exacerbate psychological stress and lead to increased gastric acid secretion, further contributing to ulcer formation (Karl et al. 2018).

Normally, there is a balance between the protective mucosal defense factors (e.g., mucus barrier, bicarbonate secretion, prostaglandins, and normal blood flow, cell renewal, endogenous antioxidants, and nitric oxide) and damaging factors (e.g., *Helicobacter pylori* infection, acid plus pepsin, stress, free radicals, nonsteroidal anti-inflammatory drugs, smoking, and alcoholism). Peptic ulcers develop when aggressive factors overcome the protective mechanisms (Işık et al. 2024). It is the most common GIT disease and is a serious

medical problem that causes morbidity and mortality despite therapeutic intervention (Périco et al. 2020).

Stress ulcers are acute mucosal lesions that occur in the GIT, primarily in the stomach and duodenum, due to physiological stress (Karl et al. 2018). Stressors may be sepsis, shock, serious bacterial infections, burns (of more than 35% of the total body surface), trauma, organ failure, postoperative and psychological conditions (Işık et al. 2024).

The development of stress ulcers can be explained through several interrelated mechanisms: Decreased gastric blood flow is due to vasoconstriction (mediated by the alpha-adrenergic nervous system, angiotensin II, and the neuroendocrine system) or to hypotension. The resulting ischemia causes decreased secretion of bicarbonate in the stomach and duodenum, decreased mucosal proliferation, and increased permeability of the gastric epithelium. Reperfusion damage leads to the formation of reactive oxygen species levels, leading to oxidative damage (Popovic et al. 2023).

Stress may increase the secretion of gastric acid and pepsin, damaging the gastric mucosa. Acid secretion is increased by stress-induced elevation of acetylcholine (ACh) and histamine levels (Martínez-Augustín et al. 2000).

Decreased protective mechanisms of the gastric lining (including mucus and bicarbonate secretion) may be compromised during stress. Decreased bicarbonate secretion allows gastric acid to damage the epithelium, as hydrogen ions diffuse into an epithelium made more permeable by ischemia, resulting in intramural acidosis, cell death, and ulceration (Jia et al. 2023).

Decreased gastric motility may, in theory, facilitate bile reflux and breakdown of the mucosal barrier (Işık et al. 2024). Activation of the sympathetic nervous system and the neurohormonal system, triggered by stress, in turn causes decreased gastric motility, decreased gastric blood flow, and decreased bicarbonate secretion (Martinou et al. 2022).

There is a link between gut microbiota and stress ulcers, but the exact mechanisms underlying the role of gut microbiota in this condition remain unclear. According to this review's hypothesis, gut microbiota homeostasis is crucial for preventing and treating stress ulcers, especially through neurotransmitter activity. Therefore, this study was designed to understand the link between gut bacteria and stress response neurotransmitters.

Therefore, the purpose of this review is to synthesize evidence on how gut microbiota and neurotransmitter signaling interact in stress-induced mucosal injury, with the aim of identifying novel mechanistic insights and potential therapeutic strategies targeting the gut–brain axis.

Methods

Role of microbiota-gut-brain axis in prevention of stress ulcer

1. Maintains GIT mucosal integrity

One of the key ways in which gut microbiota influences stress ulcers is through the regulation of gut barrier function. It produces by modulating immunity, producing short-chain fatty acids (SCFAs), and influencing the production of mucous and antimicrobial peptides (Li et al. 2024). Beneficial bacteria such as *Lactobacillus* and *Bifidobacterium* species help in creating a protective barrier that shields the mucosal lining from pathogens and inflammatory stimuli (Tremblay et al. 2021). Disruption of the gut barrier can lead to increased permeability (leaky gut), allowing harmful substances such as bacteria and toxins to enter the bloodstream and exacerbating the inflammatory response, thereby increasing the risk of mucosal injury and ulceration. Imbalances in intestinal flora can impair mucosal regeneration and repair (Talarico et al. 2024).

2. Immune activation

The gut is an immunological organ that acts as a protective barrier between the internal biological environment and infections originating from the outside (Talarico et al. 2024). Gut microbiota secretes cytokines and other immunological chemicals that play a role in stress-induced mucosal damage (Houser & Tansey 2017). Studies have shown that stress can alter the balance between pro-inflammatory and anti-inflammatory cytokines in the gut, leading to increased levels of cytokines such as interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α), and IL-6 (Tremblay et al. 2021). These cytokines can disrupt the intestinal epithelial barrier, promote mucosal inflammation, and contribute to the development of GIT disorders (Wu et al. 2023). This inflammation can be exacerbated by dysbiosis, leading to increased vulnerability to ulceration. Dysbiotic bacteria can also produce toxins that contribute to inflammation and mucosal injury, promoting ulcer formation (Houser & Tansey 2017).

3. Microbial Metabolites (Table 1)

Microbial metabolites such as SCFAs, tryptophan, and bile acid (BA) can cross the blood-brain barrier (BBB). SCFAs are produced by the fermentation of dietary fiber by gut bacteria and have been shown to have anti-inflammatory and protective effects on the gut mucosa. Studies have shown that stress can alter the production of SCFAs in the gut, leading to dysbiosis and impairment of mucosal integrity (Tremblay et al. 2021). Dysbiosis can reduce the production of SCFAs, compromising mucosal repair and increasing vulnerability to ulceration (Li et al. 2024).

They stimulate the secretion of noradrenaline (NE), dopamine, serotonin (5-HT), and neuropeptide Y (NPY), which further regulates neuroinflammation (Talarico et al. 2024). They are essential for the growth of microglia and BBB integrity (Iftikhar et al. 2020).

Gut microbiota plays a vital role in defending against excessive oxidative stress through regulating the production of SCFAs and antioxidant enzymes (Sun et al. 2024).

A necessary amino acid, tryptophan is a building block of several physiologically active substances, including the neurotransmitter 5-HT (Wang et al. 2020). Tryptamine and indoles are only two of the many tryptophan metabolites that the gut microbiota produces (Rothhammer et al. 2018). This can affect astrocyte transcriptional programs and reduce central nervous system inflammation (Kennedy et al. 2017). Indoles control neuronal growth, differentiation, and neuro-depressive-like effects on behavior (Kaur et al. 2019).

Liver and brain produce BA that can cross the BBB. It influences cognition, memory, and motor skills (Han et al. 2021). It plays a role in the modulation of cortisol production through inhibiting corticotropin-releasing hormone (CRH) release (McMillin & DeMorrow 2016).

Microbial neurotransmitters (Table 1)

They are composed of two types: small-molecule neurotransmitters and large-molecule neuromodulators. Small-molecule neurotransmitters include monoamines (e.g., epinephrine, NE, dopamine, and 5-HT), amino acids [e.g., glutamate and γ-aminobutyric acid (GABA)], glucocorticoids, and ACh. Large-molecule neuromodulators include neuropeptides, e.g., CRH, orexin, vasoactive intestinal peptide (VIP), and substance P. The need for multiple mediators in the stress response system arises from the complexity and variability of stressors that organisms encounter (Teleanu et al. 2022). Dysregulation of these chemicals due to stress can impair gut function, increase gastric acid secretion, and contribute to ulcer development (Strandwitz 2018).

1. Monoamines

Through the enzymatic activity of aromatic amino acid decarboxylase, intestinal bacteria create dopamine (Liu et al. 2021). Most dopamine peripherally is produced from the gut, and gut bacteria can control peripheral dopamine levels (Jia et al. 2023).

NE is made from dopamine. Epinephrine and NE are involved in the rapid stress response. Epinephrine ensures adequate energy supply through glycogen and fatty acid mobilization, while NE is vital for maintaining sympathetic tone and behavioral responses to stress (Baik 2020). Both hormones can supply sufficient blood to reach the brain, muscles, and lungs to deal with the situation (Privitera et al. 2024). It has a role in sensation, cognition, and attention and appetite regulation (Borodovitsyna et al. 2017). In GIT, they increase gastric acid production and tighten the gut barrier, which can contribute to mucosal damage and ulcer formation. Activation of the sympathetic nervous system can release NE, resulting in decreased blood flow to the gastric mucosa, thereby impairing its ability to heal and maintain integrity (Sgambato et al. 2016). In addition, NE can modulate energy intake, thermal homeostasis, and gut motility (Rusch et al. 2023).

Dopamine has functions in motivation, memory, mood, attention, risk assessment, and decision-making. After being exposed to stress, the dopaminergic reward system must be regulated to monitor and choose the best coping mechanism for stressful situations (Belujon & Grace 2015). In GIT, it stimulates secretions and mucosal blood flow and inhibits gut motility. It has a protective role against gastroduodenal ulcers (Belujon & Grace 2017). Stress-induced dysbiosis may decrease dopamine production, affecting both GI motility, blood flow, and mucosal barrier function (Baik 2020).

Most 5-HT is formed in GIT. Gut bacteria stimulate the intestine to secrete 5-HT (Strandwitz 2018). It does not cross the BBB but increases BBB permeability, which indirectly impacts brain function. Sleep, anxiety, mood, hunger, sickness, social and sexual behavior are all regulated by it (Baik 2020). 5-HT has an anti-immunity property. It inhibits the expression of major histocompatibility complex class II and the ability of macrophages to present antigens. It stimulates the generation of pro-inflammatory cytokines (Wan et al. 2020). In GIT, it influences motility and mucus and bicarbonate secretions (Jia et al. 2023). Under

stress, dysbiosis reduces 5-HT levels, impairing mucosal integrity and enhancing vulnerability to inflammation and ulceration (Strandwitz 2018).

2. Amino acids

Excitatory glutamate is secreted from brain cells and neurons (Brekke et al. 2016). Acute stress stimulates glutamate secretion by the activation of glucocorticoid receptors (Pal 2021). Its function is learning, memory, appetite, and right concentration in the right places at the right time (Bailey & Cryan 2017). In GIT, it influences motility, endocrine function, mucus, and bicarbonate secretions. Furthermore, glutamate stimulates 5-HT secretion by enteroendocrine cells (San Gabriel & Uneyama 2013). Preperfusion of L-glutamate prevented acid-induced cellular injury, suggesting that L-glutamate protects the mucosa by enhancing mucosal defenses (Akiba et al. 2009).

By antibiotic treatment, NMDA receptor levels decrease, so intestinal flora may be involved in the metabolic activity of NMDA (Bailey & Cryan 2017).

Parabacteroides, *Eubacterium*, and *Bifidobacterium* produce GABA (Woo et al. 2021). In addition to controlling heart rate and blood pressure, GABA is essential for several GIT processes, including inflammation, motility, and gastric emptying (Wu & Sun 2015). It also has a significant impact on immunological response, anxiety, depressive symptoms, and pain perception (Chen et al. 2021). Stress-induced dysbiosis may reduce GABA levels, impairing the mucosal barrier and exacerbating inflammation in the GI tract (Szpręgiel et al. 2021). Reduced GABA signaling under stress can lead to heightened anxiety and stress responses, which may exacerbate gastric mucosal damage and increase ulcer risk (Strandwitz 2018).

3. Glucocorticoids

Glucocorticoids are one form of long-term stress adaptation (Kageyama et al. 2021). Normal cortisol secretion protects the body from stress by distributing salt and water between cells and fluid in tissues, increasing the vascular response to circulating catecholamines (Keskitalo et al. 2021). Dysbiosis elevates cortisol levels, which can activate mast cells. They secrete tryptase, proteases, proinflammatory cytokines, heparin, and histamine from these granules. Histamine secreted from mast cells, which plays an important role in the pathogenesis of stress-related diseases, activates the H2 receptor in parietal cells, leading to excessive secretion of stomach acid and may cause peptic ulcers (Işık et al. 2024). Cortisol also alters the gut environment, promoting the growth of pathogenic bacteria over beneficial ones (Périco et al. 2020).

4. Acetylcholine (ACh)

ACh is a parasympathetic neurotransmitter that is produced in reaction to stress (Kageyama et al. 2021). ACh helps in both acute physiological responses to stress and memories of stressful events that may have an impact on long-term behavioral patterns (Mineur & Picciotto 2021).

In GIT, it is a metabolite derived from bacteria (Martínez-Augustín et al. 2000). It regulates GIT secretions and motilities, and enteric neurotransmission. Also, it is an important neuromodulator involved in stress coding, memories, and cognition (Popovic et al. 2023). Stress can lead to dysregulation in ACh signaling, resulting in gut motility issues and contributing to the development of ulcers (Kageyama et al. 2021).

5. Neuropeptides (Table 1)

Enteroendocrine cells (EECs) in the gut produce various neuropeptides in response to bacterial by-products. These neuropeptides, such as NPY, peptide YY (PYY), cholecystokinin (CCK), glucagon-like peptide-1 and -2, and substance P, can influence gut motility, secretion, and even emotional regulation by diffusing into the bloodstream or acting locally on the enteric nervous system (ENS) (Cani & Knauf 2016). In GIT, increased levels of substance P have been associated with heightened pain sensitivity and inflammation in the gut, potentially exacerbating mucosal injury and ulceration during stressful situations (Iftikhar et al. 2020).

Under moderate stress, CRH is used to adjust humoral and behavioral reactions and memory (Kageyama et al. 2021), while, under severe stress, it causes hyperexcitability and seizures (Leistner & Menke 2020). In the GIT, colon and ileum cells are the primary sources of CRH secretion (Liu et al. 2016). According to Rodiño-Janeiro et al. (2015), it slowed down gastric emptying, stimulated colonic motility, and damaged the intestinal epithelial barrier. These effects were not reliant on a stressful environment (Yang et al. 2016).

Table 1. Role of gut microbiota neurotransmitters in prevention stress ulcer

Category	Item	Mechanism	Mechanism of Action	References
Monoamines	Dopamine	Regulates GI motility, blood flow, and mucosal barrier; protects against gastroduodenal ulcers.	Increase in dopamine enhances mucosal protection and reduces ulcer risk.	Liu et al. 2021; Jia et al. 2023; Belujon & Grace 2017
	Norepinephrine (NE)	Tightens gut barrier; modulates energy intake, thermal homeostasis, and gut motility.	NE increases gastric acid secretion but reduces mucosal blood flow under stress.	Baik 2020; Privitera et al. 2024; Rusch et al. 2023
	Epinephrine	Ensures energy supply via glycogen and fatty acid mobilization; involved in rapid stress response.	Epinephrine mobilizes energy but may exacerbate mucosal damage under prolonged stress.	Baik 2020; Privitera et al. 2024
	Serotonin (5-HT)	Regulates sleep, mood, anxiety, and GI motility; increases BBB permeability; stress-induced dysbiosis reduces 5-HT, impairing mucosal integrity.	Decrease in 5-HT reduces mucosal repair and increases ulcer susceptibility.	Strandwitz 2018; Baik 2020; Wan et al. 2020
Amino Acids	Glutamate	Influences learning, memory, and GI motility; stimulates 5-HT secretion; protects mucosa by boosting mucosal defenses.	Glutamate enhances mucosal defenses and reduces acid-induced damage.	Brekke et al. 2016; Bailey & Cryan 2017; Akiba et al. 2009
	GABA	Regulates heart rate, blood pressure, GI motility, and inflammation; stress-induced dysbiosis reduces GABA, exacerbating inflammation.	Decrease in GABA exacerbates inflammation and mucosal damage.	Woo et al. 2021; Wu & Sun 2015; Szpręgiel et al. 2021
Glucocorticoids	Cortisol	Long-term stress adaptation; cortisol protects against stress but dysbiosis increases cortisol.	Increased cortisol promotes pathogenic bacterial growth and mucosal damage.	Kageyama et al. 2021; Keskitalo et al. 2021; Périco et al. 2020
Acetylcholine	Acetylcholine (ACh)	Regulates GI secretion, motility, and enteric neurotransmission; stress-induced dysregulation contributes to ulcers.	Dysregulation of ACh signaling disrupts gut motility and mucosal integrity.	Kageyama et al. 2021; Popovic et al. 2023; Martínez-Augustín et al. 2000
Neuropeptides	CRH	Slows gastric emptying, stimulates colonic motility, and damages intestinal epithelial barrier.	CRH increases intestinal permeability and mucosal damage.	Kageyama et al. 2021; Rodiño-Janeiro et al. 2015
	Orexin	Regulates intestinal permeability and immune cell activation; promotes mucosal regeneration and gastric blood flow for ulcer healing.	Orexin enhances mucosal regeneration and blood flow, promoting ulcer healing.	Couvineau et al. 2021; Grafe & Bhatnagar 2018; Mediavilla 2020
	Ghrelin	Regulates gastric secretion and gut motility; aids in ulcer healing through mucosal regeneration and blood flow.	Ghrelin promotes mucosal repair and reduces inflammation.	Akalu et al. 2020; Mediavilla 2020
	NPY	Released in response to stress; regulates hunger, pain, mood, and memory; has antibacterial and neuroprotective properties.	NPY reduces stress-induced mucosal damage and inflammation.	Zhang et al. 2024; Lach et al. 2018; Henry et al. 2017
	PYY	Regulates food intake and memory; penetrates BBB to influence brain function.	PYY modulates gut-brain signaling and reduces stress-induced mucosal damage.	Lach et al. 2018; Henry et al. 2017
	CCK	Regulates pain, cognition, and feeding behavior; accelerates ulcer healing via somatostatin release and hyperemia.	CCK promotes ulcer healing through hyperemia and somatostatin release.	Bauer et al. 2016; West et al. 2003
	Glucagon-like peptide (GLP)	Inhibits gastric movement and insulin secretion; has anti-inflammatory and anti-apoptotic functions; microbial metabolites increase GLP secretion.	GLP enhances mucosal blood flow and reduces inflammation.	Abdalqadir & Adeli 2022; Diz-Chaves et al. 2020; Zeng et al. 2024
	VIP	Reduces vascular sensitivity to NE and angiotensin II; protects stomach tissue from lipid peroxidation and ulcers; has anti-inflammatory and antioxidant functions.	VIP reduces oxidative stress and protects mucosal integrity.	Withana & Castorina 2023; Tunçel et al. 1998

Excitatory neuropeptides known as orexins, or hypocretins, are produced from the prepro-orexin precursor and are found in cells located in the lateral and posterior hypothalamus regions. Also, orexin has been detected in neurons and mucosa of all gut regions, of the enteric nervous

system, and in the enteroendocrine gut cells in animals and humans (Couvineau et al. 2021). Ghrelin – the hunger hormone – is produced and released mainly by the stomach, with small amounts also released by the small intestine, pancreas, and brain. It can cross the BBB (Akalu et al. 2020). Orexin and ghrelin have been shown to regulate the stress response. The acute behavioral and neuroendocrine response to stress is enhanced by orexin. It regulates intestinal permeability, prevents the activation of immune cells, and protects against systemic and central inflammation (Grafe & Bhatnagar 2018). Ghrelin has a role in reward processes, mood, memory, learning, and stress response. It also has a role in the stimulation of gastric and pancreatic secretions and gut motility (Akalu et al. 2020).

Ghrelin and orexin contribute to the process of chronic gastric ulcer healing, cooperating with nitric oxide and sensory afferent nerve endings releasing vasoactive neuropeptide calcitonin gene-related peptide. Orexin has a protective effect via the vagal pathway. Furthermore, it plays an essential role in the healing process of chronic gastric ulcers by activating the gastric blood flow at the ulcer margin and mucosal regeneration (Mediavilla 2020).

The control of hunger, pain, emotion, mood, cognition, stress, intake, and energy balance are all impacted by NPY. It is released in response to stress and can have anxiolytic effects (Zhang et al. 2024). NPY is also produced in the GIT (Lach et al. 2018). PYY is mostly secreted by colon and ileum cells. while pancreatic polypeptide (PP) is produced by the vagus nerve and is released in response to food. By using transmembrane diffusion, PYY and PP may both penetrate the BBB and attach to cognate receptors in the postrema region (Henry et al. 2017). NPY was formed in the brain from medulla to cortex. Its receptors (Y1, Y2, Y3, Y4, Y5) are expressed on brain neurons, gut primary afferents, immunological cells, sympathetic neurons, and the hypothalamus (Lach et al. 2018). The NPY family has antibacterial, neuroprotection, neurogenesis, and neuroinflammation properties. It has a role in memory retention, control of blood pressure, and regulation of food intake (Henry et al. 2017).

CCK has a role in pain, cognition, anxiety, depression, and feeding behavior (Bauer et al. 2016). By modifying the makeup of the gut environment and food digestion, gut microbiota can affect the production of CCK. Certain bacterial species may enhance the release of CCK in response to dietary fats and proteins, thereby promoting satiety and digestive processes (Wang et al. 2020). CCK accelerates ulcer healing by the mechanism involving upregulation of specific CCK-A receptors, enhancement of somatostatin release, stimulation of sensory nerves, and hyperemia in the ulcer area, possibly mediated by nitric oxide (West et al. 2003).

Glucagon-like peptide 1 (GLP-1) – a hormone stimulating glucose-dependent insulin secretion – is also involved in the modulation of the stress response (Abdalqadir and Adeli 2022). In the gut, it inhibits both gastric movements and insulin secretion (Diz-Chaves et al. 2020). In the brain, it has anti-inflammatory and anti-apoptosis functions (Stenman et al. 2015). Microbial metabolites (e.g., SCFAs and lipopolysaccharide) increase glucagon-like peptide secretion (Zeng et al. 2024). GLP-2 protects the gastric mucosa by increasing gastric mucosal blood flow and regulating the linoleic acid metabolic pathway (Zhang et al. 2022).

VIP is one of the regulators of the stress response. It appears to activate factors responsible for sustained responses to stressors rather than immediate reactions. It is a potent vasodilator agent and reduces the sensitivity of the aorta smooth muscle to NE and angiotensin II (Withana & Castorina 2023). Gut microbiota is essential for normal myenteric VIP levels. This effect is dependent on microbiota-innate immune system crosstalk and enteric glia cells. VIP prevented stress-induced ulcers and mast cell degranulation and protected gastric tissue from lipid peroxidation. It is an anti-inflammatory and antioxidant agent (Tunçel et al. 1998).

Potential therapeutic strategies for stress ulcer targeting the microbiota-gut-brain axis
dietary modification

In critically ill patients, stress ulcers are common due to prolonged mechanical ventilation, hemodynamic instability, and the use of medications that affect gastric mucosal integrity. Dietary strategies should focus on minimizing acid hypersecretion, supporting mucosal protection, and reducing systemic inflammation (Sheneni et al. 2023).

The Mediterranean diet, known for its antioxidant, anti-inflammatory, and neuroprotective properties, may benefit critically ill patients by enhancing gut microbial diversity and short-chain fatty acid (SCFA) production. However, modifications are needed to accommodate enteral feeding and patient-specific nutritional needs (Sofi et al. 2013). High-fiber diets, including fruits (apple, banana, mango, melon, and papaya), vegetables (spinach, carrot, bean, beet, kale, and leek) (Rahantasoa et al. 2020), cereals (brown rice, bulgur, millet, oatmeal), and legumes (bean soup, lentils, chickpeas, and soybean), promote mucin formation and gut barrier integrity. Fiber and essential fatty acids help mitigate stress-induced peptic ulcers and support immune function (Kulshreshtha et al. 2017).

For critically ill patients, diets combining elements of the Mediterranean and Dietary Approaches to Stop Hypertension (DASH) diets, rich in vegetables, whole grains, fruits, low-fat dairy, and lean protein, may offer additional protective effects against ulcer formation and improve clinical outcomes (Prasad 2009). Micronutrients such as zinc, selenium, vitamin C, β-carotene, and vitamin E play critical roles in wound healing and oxidative stress reduction. Zinc promotes mucosal repair and immune function (Prasad 2009), selenium enhances ulcer healing and infection control, and β-carotene and vitamin C contribute to gastric mucosal protection (Kulshreshtha et al. 2017). Vitamin E aids in ulcer treatment and enhances mucosal recovery (Yousaf et al. 2014).

Intermittent fasting may have potential benefits in critically ill patients by modulating gut microbiota, reducing systemic inflammation, and decreasing gastric acid secretion. However, its application requires careful consideration in ICU settings (Paoli et al. 2019).

Prebiotics

Prebiotics support gut health by promoting the growth of beneficial bacteria, which is particularly crucial for critically ill patients at high risk of gut dysbiosis (Al-garni et al. 2021).

Yeast beta-glucan enhances SCFA production, restores gut microbiota balance, and reduces systemic and neuroinflammation. It also promotes epithelial hyperplasia, ulcer healing, fibroblast proliferation, and angiogenesis (Medeiros et al. 2012). Mannan oligosaccharides stimulate SCFA synthesis while reducing oxidative stress and pro-inflammatory cytokines (TNF-α, IL-6, IL-10), thereby protecting the gastric mucosa in critically ill patients (Ashaolu 2020).

Lactulose plays a crucial role in modulating gut microbiota composition, reducing inflammation, and improving insulin sensitivity. Additionally, it inhibits inflammatory carcinogenesis and restores intestinal barrier integrity (Hiraishi et al. 2022). Ferulic acid exerts potent anti-inflammatory and antioxidant effects, supporting nerve growth factor production and reinforcing gastric mucosal integrity. By blocking neutrophil infiltration and lipid peroxidation, it has gastroprotective properties that are particularly relevant in ICU patients with stress ulcers (Ermis et al. 2023). Despite these benefits, further research is necessary to standardize prebiotic use in clinical practice, considering individual factors such as diet, age, and comorbidities (Barbosa & Vieira-Coelho 2020).

Probiotics

Probiotics modulate the gut microbiota toward a favorable balance, making them an essential adjunct therapy for stress ulcers in critically ill patients (Al-garni et al. 2021). *Lactobacillus* and *Bifidobacterium*, the most widely studied probiotics, regulate the host immune response, reduce inflammation, prevent pathogen overgrowth, and enhance antioxidant enzyme activity (Paoli et al. 2019; Al-garni et al. 2021).

In critically ill patients, probiotics help restore mucosal integrity by inhibiting apoptosis, stabilizing mast cells, and preventing excessive activation of the hypothalamic-pituitary-adrenal (HPA) axis, which contributes to gastric mucosal protection (Mal et al. 2024). Combining probiotics with prebiotics enhances their therapeutic potential, promoting epithelial cell proliferation, particularly at ulcerated margins (You et al. 2022).

Probiotic and prebiotic therapies have shown efficacy in reducing oxidative stress, pro-inflammatory cytokines, and gastric mucosal injury. Studies suggest that probiotics may be the most effective therapeutic group for stress ulcer prevention in ICU patients (Al-garni et al. 2021). However, the harsh physiological conditions in critically ill patients, including acidic gastric pH, mechanical stress, and digestive enzymes, may limit probiotic colonization in the gut. Further research is needed to optimize probiotic strains, dosages, and delivery methods tailored to ICU settings (Khoder et al. 2016).

Fecal microbiota transplantation (FMT)

FMT is an emerging therapy for restoring gut microbiota diversity and function in critically ill patients with severe dysbiosis (Allegretti et al. 2019). It involves transplanting prescreened donor feces via colonoscopy, enema, or capsule to enhance SCFA production and reestablish gut microbial homeostasis (Mullish et al. 2018).

In critically ill patients, FMT may support gut barrier repair, regulate mucosal immune responses, and restore secondary bile acid metabolism, which plays a crucial role in gastrointestinal health (Khoruts & Sadowsky 2016). However, concerns regarding safety, infection risk, and treatment standardization require further investigation before widespread clinical implementation (Feng et al. 2023).

Table 2. Possible treatment approaches for stress ulcers that focus on the gut-brain-microbiota axis

Category	Item	Mechanism	Notes	References
Prebiotics	Yeast Beta-Glucan	Increases SCFA production; balances anti- and pro-inflammatory bacteria; reduces neuroinflammation.	Promotes ulcer healing, fibroblast proliferation, and angiogenesis.	Medeiros et al. 2012
	Mannan Oligosaccharides	Enhances SCFA synthesis; reduces oxidative stress and pro-inflammatory cytokines (TNF-α, IL-6, IL-10).	Reduces gastric injury and inflammation.	Ashaolu 2020
	Lactulose	Reduces neuroinflammation; promotes insulin sensitivity; restores gut microbiota composition.	Inhibits inflammatory carcinogenesis and reduces inflammation.	Hiraishi et al. 2022
	Ferulic Acid	Anti-inflammatory and antioxidant effects; increases nerve growth factor and brain-derived neurotrophic factor; blocks NF-κB, reducing tissue damage.	Protects gastric mucosa and maintains structural integrity.	Ermis et al. 2023
Probiotics	*Lactobacillus* & *Bifidobacterium*	Modulates immune response; reduces inflammation and reactive oxygen species; enhances antioxidant enzymes and inhibits apoptosis.	Stabilizes mast cells and protects gastric mucosa from stress-induced damage.	Paoli et al. 2019; Al-garni et al. 2021
Fecal Microbiota Transplantation (FMT)	FMT	Restores gut microbial diversity and SCFA production; repairs gut barrier and restores secondary bile acid metabolism.	Administered via colonoscopy, enema, or capsule; safety concerns require further research.	Allegretti et al. 2019; Mullish et al. 2018; Khoruts & Sadowsky 2016

Conclusion

The gut microbiota affects stress ulcers through multiple mechanisms, including the generation of neurotransmitters and metabolites, immune activation, and repair of intestinal damage. Potential treatment approaches that could influence gut microbiota and stress ulcers include diet, probiotic and prebiotic supplements, and fecal transplantation. The gut microbiota may be a future preventive and curative treatment for stress ulcers.

Additional Information

Conflict of interest

The authors declare the absence of a conflict of interests.

Funding

No specific funding agency grant was provided for this research. The author did not receive any funding to assist in this work. No funding was received for this study.

Data availability

All of the data that support the findings of this study are available in the main text.

References

- Abdalqadir N, Adeli K (2022) GLP-1 and GLP-2 orchestrate intestine integrity, gut microbiota, and immune system crosstalk. Microorganisms 10(10): 2061. https://doi.org/10.3390/microorganisms10102061 [PubMed] [PMC]
- Akalu Y, Molla MD, Dessie G, Ayelign B (2020) Physiological effect of ghrelin on body systems. International Journal of Endocrinology 2020: 1385138. https://doi.org/10.1155/2020/1385138 [PubMed] [PMC]
- Akiba Y, Watanabe C, Mizumori M, Kaunitz JD (2009) Luminal L-glutamate enhances duodenal mucosal defense mechanisms via multiple glutamate receptors in rats. American Journal of Physiology-Gastrointestinal and Liver Physiology 297(4): G781-G791. https://doi.org/10.1152/ajpgi.90605.2008 [PubMed] [PMC]
- Al-garni AA, Khalifa FK, Zeyadi MA (2021) Comparative study of the efficacy of prebiotics and probiotics as dietary supplements in rats with gastric ulcer. Journal of Pharmaceutical Research International 33(28A): 137–145. https://doi.org/10.9734/jpri/2021/v33i28A31518

- Allegretti JR, Mullish BH, Kelly C, Fischer M (2019) The evolution of the use of faecal microbiota transplantation and emerging therapeutic indications. The Lancet 394(10196): 420-431. https://doi.org/10.1016/S0140-6736(19)31266-8 [PubMed]
- Ashaolu TJ (2020) Immune boosting functional foods and their mechanisms: A critical evaluation of probiotics and prebiotics. Biomedicine & Pharmacotherapy 130: 110625. https://doi.org/10.1016/j.biopha.2020.110625 [PubMed]
- Baik JH (2020) Stress and the dopaminergic reward system. Experimental & Molecular Medicine 52(12): 1879–1890. https://doi.org/10.1038/s12276-020-00531-5 [PubMed] [PMC]
- Bailey MT, Cryan JF (2017) The microbiome as a key regulator of brain, behavior and immunity: Commentary on the 2017 named series. Brain, Behavior, and Immunity 66: 18-22. https://doi.org/10.1016/j.bbi.2017.08.001 [PubMed]
- Barbosa RSD, Vieira-Coelho MA (2020) Probiotics and prebiotics: Focus on psychiatric disorders – A systematic review. Nutrition Reviews 78(5): 437–450. https://doi.org/10.1093/nutrit/nuz080 [PubMed]
- Bauer PV, Hamr SC, Duca FA (2016) Regulation of energy balance by a gut –brain axis and involvement of the gut microbiota. Cellular and Molecular Life Sciences 73(4): 737–755. https://doi.org/10.1007/s00018-015-2083-z [PubMed] [PMC]
- Belujon P, Grace AA (2015) Regulation of dopamine system responsivity and its adaptive and pathological response to stress. Proceedings of the Royal Society B: Biological Sciences 282: 20142520. https://doi.org/10.1098/rspb.2014.2520 [PubMed] [PMC]
- Belujon P, Grace AA (2017) Dopamine system dysregulation in major depressive disorders. International Journal of Neuropsychopharmacology 20(12): 1036–1046. https://doi.org/10.1093/ijnp/pyx056 [PubMed] [PMC]
- Borodovitsyna O, Flamini M, Chandler D (2017) Noradrenergic modulation of cognition in health and disease. Neural Plasticity 2017: 6031478. https://doi.org/10.1155/2017/6031478 [PubMed] [PMC]
- Brekke E, Morken TS, Walls AB, Waagepetersen H, Schousboe A, Sonnewald U (2016) Anaplerosis for glutamate synthesis in the neonate and in adulthood. Advances in Neurobiology 13: 43–58. https://doi.org/10.1007/978-3-319-45096-4_3 [PubMed]
- Cani PD, Knauf C (2016) How gut microbes talk to organs: the role of endocrine and nervous routes. Molecular Metabolism 5(9): 743-752. https://doi.org/10.1016/j.molmet.2016.05.011 [PubMed] [PMC]
- Chen Y, Xu J, Chen Y (2021) Regulation of neurotransmitters by the gut microbiota and effects on cognition in neurological disorders. Nutrients 13(7): 2099. https://doi.org/10.3390/nu13072099 [PubMed] [PMC]
- Couvineau A, Voisin T, Nicole P, Gratio V, Blais A (2021) Orexins: A promising target to digestive cancers, inflammation, obesity and metabolism dysfunctions. World Journal of Gastroenterology 27(44): 7582-7596. https://doi.org/10.3748/wjg.v27.i44.7582 [PubMed] [PMC]
- Cristofori F, Dargenio VN, Dargenio C, Miniello VL, Barone M, Francavilla R (2021) Anti-Inflammatory and immunomodulatory effects of probiotics in gut inflammation: a door to the body. Frontiers in Immunology 12: 578386. https://doi.org/10.3389/fimmu.2021.578386 [PubMed] [PMC]
- Diz-Chaves Y, Herrera-Pérez S, González-Matías LC, Lamas JA, Mallo F (2020) Glucagon-Like peptide-1 (GLP-1) in the integration of neural and endocrine Responses to Stress. Nutrients 12(11): 3304. https://doi.org/10.3390/nu12113304 [PubMed] [PMC]
- Ermis A, Aritici Colak G, Acikel-Elmas M, Arbak S, Kolgazi M (2023) Ferulic acid treats gastric ulcer via suppressing oxidative stress and inflammation. Life 13(2): 388. https://doi.org/10.3390/life13020388 [PubMed] [PMC]
- Feng J, Chen Y, Liu Y, Lin L, Lin X, Gong W, Xia R, He J, Sheng J, Cai H, Xiao C (2023) Efficacy and safety of fecal microbiota transplantation in the treatment of ulcerative colitis: a systematic review and meta-analysis. Scientific Reports 13(1): 14494. https://doi.org/10.1038/s41598-023-41182-6 [PubMed] [PMC]
- Góralczyk-Bińkowska A, Szmajda-Krygier D, Kozłowska E (2022) The microbiota-gut-brain axis in psychiatric disorders. International Journal of Molecular Sciences 23(19): 11245. https://doi.org/10.3390/ijms231911245 [PubMed] [PMC]
- Grafe LA, Bhatnagar S (2018) Orexins and stress. Frontiers in Neuroendocrinology 51: 132–145. https://doi.org/10.1016/j.yfrne.2018.06.003 [PubMed] [PMC]
- Han GH, Kim SJ, Ko WK, et al. (2021) Transplantation of tauroursodeoxycholic acid-inducing M2-phenotype macrophages promotes an anti-neuroinflammatory effect and functional recovery after spinal cord injury in rats. Cell Proliferation 54(6): e13050. https://doi.org/10.1111/cpr.13050 [PubMed] [PMC]
- Henry MS, Gendron L, Tremblay ME, Drolet G (2017) Enkephalins: Endogenous analgesics with an emerging role in stress resilience. Neural Plasticity 2017: 1546125. https://doi.org/10.1155/2017/1546125 [PubMed] [PMC]
- Hiraishi K, Zhao F, Kurahara LH, et al. (2022) Lactulose modulates the structure of gut microbiota and alleviates colitis-associated tumorigenesis. Nutrients 14(3): 649. https://doi.org/10.3390/nu14030649 [PubMed] [PMC]
- Houser MC, Tansey MG (2017) The gut-brain axis: is intestinal inflammation a silent driver of Parkinson's disease pathogenesis? NPJ Parkinson's Disease 3: 3. https://doi.org/10.1038/s41531-016-0002-0 [PubMed] [PMC]
- Iftikhar K, Siddiq A, Baig SG, Zehra S (2020) Substance P: A neuropeptide involved in the psychopathology of anxiety disorders. Neuropeptides 79: 101993. https://doi.org/10.1016/j.npep.2020.101993 [PubMed]
- Işık M, Özbayer C, Dönmez DB, Erol K, Çolak E, Üstüner MC, Değirmenci İ (2024) Dose-dependent protective effects of Lactobacillus rhamnosus GG against stress-induced ulcer. Journal of the Science of Food and Agriculture 104(13): 8109-8119. https://doi.org/10.1002/jsfa.13641 [PubMed]
- Jia X, He Y, Li L, Xu D (2023) Pharmacological targeting of gastric mucosal barrier with traditional Chinese medications for repairing gastric mucosal injury. Frontiers in Pharmacology 14: 1091530. https://doi.org/10.3389/fphar.2023.1091530 [PubMed] [PMC]

- Kageyama K, Iwasaki Y, Daimon M (2021) Hypothalamic regulation of corticotropin-releasing factor under stress and stress resilience. International Journal of Molecular Sciences 22(22): 12242. https://doi.org/10.3390/ijms222212242 [PubMed] [PMC]
- Karl JP, Hatch AM, Arcidiacono SM, Pearce SC, Pantoja-Feliciano IG, Doherty LA, Soares JW (2018) Effects of psychological, environmental and physical stressors on the gut microbiota. Frontiers in Microbiology 9: 2013. https://doi.org/10.3389/fmicb.2018.02013 [PubMed] [PMC]
- Kaur H, Bose C, Mande SS (2019) Tryptophan metabolism by gut microbiome and gut-brain-axis: An in silico analysis. Frontiers in Neuroscience 13: 1365. https://doi.org/10.3389/fnins.2019.01365 [PubMed] [PMC]
- Kennedy PJ, Cryan JF, Dinan TG, Clarke G (2017) Kynurenine pathway metabolism and the microbiota-gut-brain axis. Neuropharmacology 112: 399–412. https://doi.org/10.1016/j.neuropharm.2016.07.002 [PubMed]
- Keskitalo A, Aatsinki AK, Kortesluoma S, Pelto J, Korhonen L, Lahti L, Lukkarinen M, Munukka E, Karlsson H, Karlsson L (2021) Gut microbiota diversity but not composition is related to saliva cortisol stress response at the age of 2.5 months. Stress 24(5): 551-560. https://doi.org/10.1080/10253890.2021.1895110 [PubMed]
- Khoder G, Al-Menhali AA, Al-Yassir F, Karam SM (2016) Potential role of probiotics in the management of gastric ulcer. Experimental and Therapeutic Medicine 12(1): 3-17. https://doi.org/10.3892/etm.2016.3293 [PubMed] [PMC]
- Khoruts A, Sadowsky MJ (2016) Understanding the mechanisms of faecal microbiota transplantation. Nature Reviews Gastroenterology & Hepatology 13(9): 508-516. https://doi.org/10.1038/nrgastro.2016.98 [PubMed] [PMC]
- Kulshreshtha M, Srivastava G, Singh MP (2017) Pathophysiological status and nutritional therapy of peptic ulcer: An update. Environmental Disease 2(3): 76–86. https://doi.org/10.4103/ed.ed_11_17
- Lach G, Schellekens H, Dinan TG, Cryan JF (2018) Anxiety, depression, and the microbiome: a role for gut peptides. Neurotherapeutics 15(1): 36-59. https://doi.org/10.1007/s13311-017-0585-0 [PubMed] [PMC]
- Leistner C, Menke A (2020) Hypothalamic-pituitary-adrenal axis and stress. Handbook of Clinical Neurology 175: 55–64. https://doi.org/10.1016/B978-0-444-64123-6.00004-7
- Li J, Cai H, Zhang Y, et al. (2024) Dysbiosis of gut microbiota is associated with pathogenesis of peptic ulcer diseases through inflammatory proteins: A Mendelian randomization study. Medicine 103(39): e39814. https://doi.org/10.1097/MD.0000000000039814 [PubMed] [PMC]
- Liu C, Goel P, Kaeser PS (2021) Spatial and temporal scales of dopamine transmission. Nature Reviews Neuroscience 22(6): 345-358. https://doi.org/10.1038/s41583-021-00455-7 [PubMed] [PMC]
- Liu S, Chang J, Long N, Beckwith K, Talhouarne G, Brooks JJ, Qu MH, Ren W, Wood JD, Cooper S, Bhargava A (2016) Endogenous CRF in rat large intestine mediates motor and secretory responses to stress. Neurogastroenterology & Motility 28(2): 281–291. https://doi.org/10.1111/nmo.12724 [PubMed] [PMC]
- Mal S, Das TK, Pradhan S, Ghosh K (2024) Probiotics as a therapeutic approach for non-infectious gastric ulcer management: a comprehensive review. Probiotics and Antimicrobial Proteins. https://doi.org/10.1007/s12602-024-10348-7 [PubMed]
- Martínez-Augustín O, Sánchez de Medina F Jr, Sánchez de Medina F (2000) Effect of psychogenic stress on gastrointestinal function. Journal of Physiology and Biochemistry 56(3): 259-274. https://doi.org/10.1007/BF03179794 [PubMed]
- Martinou E, Stefanova I, Iosif E, Angelidi AM (2022) Neurohormonal changes in the gut-brain axis and underlying neuroendocrine mechanisms following bariatric surgery. International Journal of Molecular Sciences 23(6): 3339. https://doi.org/10.3390/ijms23063339 [PubMed] [PMC]
- McMillin M, DeMorrow S (2016) Effects of bile acids on neurological function and disease. FASEB Journal 30: 3658–3668. https://doi.org/10.1096/fj.201600275R [PubMed] [PMC]
- Medeiros SDV, Cordeiro SL, Cavalcanti JEC, et al. (2012) Effects of purified Saccharomyces cerevisiae (1→3)-β-glucan on venous ulcer healing. International Journal of Molecular Sciences 13(7): 8142–8158. https://doi.org/10.3390/ijms13078142 [PubMed] [PMC]
- Mediavilla C (2020) Bidirectional gut-brain communication: A role for orexin-A. Neurochemistry International 141: 104882. https://doi.org/10.1016/j.neuint.2020.104882 [PubMed]
- Mineur YS, Picciotto MR (2021) The role of acetylcholine in negative encoding bias: Too much of a good thing? European Journal of Neuroscience 53(1): 114-125. https://doi.org/10.1111/ejn.14925 [PubMed] [PMC]
- Mullish BH, Quraishi MN, Segal JP, McCune VL, Baxter M, Marsden GL, Moore D, Colville A, Bhala N, Iqbal TH, Settle C, Kontkowski G, Hart AL, Hawkey PM, Williams HR, Goldenberg SD (2018) The use of faecal microbiota transplant as treatment for recurrent or refractory Clostridium difficile infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines. Gut 67(11): 1920–1941. https://doi.org/10.1136/gutjnl-2018-316818 [PubMed]
- Pal MM (2021) Glutamate: The master neurotransmitter and its implications in chronic stress and mood disorders. Frontiers in Human Neuroscience 15: 722323. https://doi.org/10.3389/fnhum.2021.722323 [PubMed] [PMC]
- Paoli A, Tinsley G, Bianco A, Moro T (2019) The influence of meal frequency and timing on health in humans: the role of fasting. Nutrients 11(4): 719. https://doi.org/10.3390/nu11040719 [PubMed] [PMC]
- Périco LL, Emílio-Silva MT, Ohara R, et al. (2020) Systematic analysis of monoterpenes: advances and challenges in the treatment of peptic ulcer diseases. Biomolecules 10(2): 265. https://doi.org/10.3390/biom10020265 [PubMed] [PMC]
- Popovic D, Stojanovic M, Milosavljevic T, Stojkovic-Lalosevic M, Glisic T, Savic P, Filipovic B (2023) Oxidative stress in gastrointestinal ulcer disease: a gastroenterologist's view. Journal of Gastrointestinal and Liver Diseases 32(3): 277-282. https://doi.org/10.15403/jgld-5172 [PubMed]

- Prasad AS (2009) Zinc: role in immunity, oxidative stress and chronic inflammation. Current Opinion in Clinical Nutrition and Metabolic Care 12(6): 646–652. https://doi.org/10.1097/MCO.0b013e3283312956 [PubMed]
- Privitera M, von Ziegler LM, Floriou-Servou A, Duss SN, Zhang R, Waag R, Leimbacher S, Sturman O, Roessler FK, Heylen A, Vermeiren Y, Van Dam D, De Deyn PP, Germain PL, Bohacek J (2024) Noradrenaline release from the locus coeruleus shapes stress-induced hippocampal gene expression. eLife 12: RP88559. https://doi.org/10.7554/eLife.88559 [PubMed] [PMC]
- Rahantasoa Finaritra CFP, Andrianjafiarivony C, Randrianasolo F, Rajaonera AT, Samison LH (2020) The role of diet and hygiene in the management of digestive haemorrhages on peptic ulcer disease. American Academy of Science Research Journal for Engineering, Technology, and Sciences 71(1): 207–211.
- Rodiño-Janeiro BK, Alonso-Cotoner C, Pigrau M, Lobo B, Vicario M, Santos J (2015) Role of corticotropin-releasing factor in gastrointestinal permeability. Journal of Neurogastroenterology and Motility 21(1): 33–50. https://doi.org/10.5056/jnm14084 [PubMed] [PMC]
- Rothhammer V, Borucki DM, Tjon EC, Takenaka MC, Chao CC, Ardura-Fabregat A, de Lima KA, Gutiérrez-Vázquez C, Hewson P, Staszewski O, Blain M, Healy L, Neziraj T, Borio M, Wheeler M, Dragin LL, Laplaud DA, Antel J, Alvarez JI, Prinz M, Quintana FJ (2018) Microglial control of astrocytes in response to microbial metabolites. Nature 557(7707): 724–728. https://doi.org/10.1038/s41586-018-0119-x [PubMed] [PMC]
- Rusch JA, Layden BT, Dugas LR (2023) Signalling cognition: the gut microbiota and hypothalamic-pituitary-adrenal axis. Frontiers in Endocrinology 14: 1130689. https://doi.org/10.3389/fendo.2023.1130689 [PubMed] [PMC]
- San Gabriel A, Uneyama H (2013) Amino acid sensing in the gastrointestinal tract. Amino Acids 45(3): 451-461. https://doi.org/10.1007/s00726-012-1371-2 [PubMed]
- Sgambato D, Capuano A, Sullo MG, Miranda A, Federico A, Romano M (2016) Gut-brain axis in gastric mucosal damage and protection. Current Neuropharmacology 14(8): 959-966. https://doi.org/10.2174/1570159X14666160223120742 [PubMed] [PMC]
- Sheneni VD, Shaibu IE, Akomolafe AP (2023) Peptic ulcer disease: a look into diet therapy. Journal of Digestive Diseases and Hepatology 8: 195. https://doi.org/10.29011/2574-3511.100095
- Sofi F, Macchi C, Abbate R, Gensini GF, Casini A (2013) Mediterranean diet and health. Biofactors 39(4): 335–342. https://doi.org/10.1002/biof.1096 [PubMed]
- Stenman LK, Waget A, Garret C, Briand F, Burcelin R, Sulpice T, Lahtinen S (2015) Probiotic B420 and prebiotic polydextrose improve efficacy of antidiabetic drugs in mice. Diabetology & Metabolic Syndrome 7: 75. https://doi.org/10.1186/s13098-015-0070-z [PubMed] [PMC]
- Strandwitz P (2018) Neurotransmitter modulation by the gut microbiota. Brain Research 1693(Pt B): 128–133. https://doi.org/10.1016/j.brainres.2018.03.015 [PubMed] [PMC]
- Sun Y, Wang X, Li L, Zhong C, Zhang Y, Yang X, Li M, Yang C (2024) The role of gut microbiota in intestinal disease: from an oxidative stress perspective. Frontiers in Microbiology 15: 1328324. https://doi.org/10.3389/fmicb.2024.1328324 [PubMed] [PMC]
- Szpręgiel I, Wrońska D, Kmiecik M, Pałka S, Kania BF (2021) Glutamic acid decarboxylase concentration changes in response to stress and altered availability of glutamic acid in rabbit (oryctolagus cuniculus) brain limbic structures. Animals 11(2): 455. https://doi.org/10.3390/ani11020455 [PubMed] [PMC]
- Talarico F, Tilocca B, Spagnuolo R, Abenavoli L, Luzza F, Roncada P (2024) The effects of stress on gut virome: Implications on infectious disease and systemic disorders. Microbiology Open 13(5): e1434. https://doi.org/10.1002/mbo3.1434 [PubMed] [PMC]
- Teleanu RI, Niculescu AG, Roza E, Vladâcenco O, Grumezescu AM, Teleanu DM (2022) Neurotransmitters-key factors in neurological and neurodegenerative disorders of the central nervous system. International Journal of Molecular Sciences 23(11): 5954. https://doi.org/10.3390/ijms23115954 [PubMed] [PMC]
- Tremblay A, Lingrand L, Maillard M, Feuz B, Tompkins TA (2021) The effects of psychobiotics on the microbiota-gut-brain axis in early-life stress and neuropsychiatric disorders. Progress in Neuro-Psychopharmacology and Biological Psychiatry 105: 110142. https://doi.org/10.1016/j.pnpbp.2020.110142 [PubMed]
- Tunçel N, Erkasap N, Sahintürk V, Ak DD, Tunçel M (1998) The protective effect of vasoactive intestinal peptide (VIP) on stress-induced gastric ulceration in rats. Annals of the New York Academy of Sciences 865: 309-322. https://doi.org/10.1111/j.1749-6632.1998.tb11191.x [PubMed]
- Wan M, Ding L, Wang D, Han J, Gao P (2020) Serotonin: A potent immune cell modulator in autoimmune diseases. Frontiers in Immunology 11: 186. https://doi.org/10.3389/fimmu.2020.00186 [PubMed] [PMC]
- Wang SZ, Yu YJ, Adeli K (2020) Role of gut microbiota in neuroendocrine regulation of carbohydrate and lipid metabolism via the microbiota-gut-brain-liver axis. Microorganisms 8(4): 527. https://doi.org/10.3390/microorganisms8040527 [PubMed] [PMC]
- West SD, Helmer KS, Chang LK, Cui Y, Greeley GH, Mercer DW (2003) Cholecystokinin secretagogue-induced gastroprotection: role of nitric oxide and blood flow. American Journal of Physiology-Gastrointestinal and Liver Physiology 284(3): G399-G410. https://doi.org/10.1152/ajpgi.00130.2002 [PubMed]
- Withana M, Castorina A (2023) Potential crosstalk between the PACAP/VIP neuropeptide system and endoplasmic reticulum stress-relevance to multiple sclerosis pathophysiology. Cells 12(22): 2633. https://doi.org/10.3390/cells12222633 [PubMed] [PMC]
- Woo E, Sansing LH, Arnsten AFT, Datta D (2021) Chronic stress weakens connectivity in the prefrontal cortex: Architectural and molecular changes. Chronic Stress 5: 24705470211029254. https://doi.org/10.1177/24705470211029254 [PubMed] [PMC]
- Wu C, Sun D (2015) GABA receptors in brain development, function, and injury. Metabolic Brain Disease 30(2): 367–379. https://doi.org/10.1007/s11011-014-9560-1 [PubMed] [PMC]

- Wu Y, Guo Y, Huang T, Huang D, Liu L, Shen C, Jiang C, Wang Z, Chen H, Liang P, Hu Y, Zheng Z, Liang T, Zhai D, Zhu H, Liu Q (2023) Licorice flavonoid alleviates gastric ulcers by producing changes in gut microbiota and promoting mucus cell regeneration. Biomedicine & Pharmacotherapy 169: 115868. https://doi.org/10.1016/j.biopha.2023.115868 [PubMed]
- Yang H, Zhao X, Tang S, Huang H, Zhao X, Ning Z, Fu X, Zhang C (2016) Probiotics reduce psychological stress in patients before laryngeal cancer surgery. Asia-Pacific Journal of Clinical Oncology 12(1): e92–e96. https://doi.org/10.1111/ajco.12120 [PubMed]
- You S, Ma Y, Yan B, Pei W, Wu Q, Ding C, Huang C (2022) The promotion mechanism of prebiotics for probiotics: A review. Frontiers in Nutrition 9: 1000517. https://doi.org/10.3389/fnut.2022.1000517 [PubMed] [PMC]
- Yousaf A, Ali S, Bokhari ZH, Khalid AM, Sheikh MA (2014) Protective effect of vitamin e on indomethacin induced gastric ulcers. Journal of Rawalpindi Medical College 18(2): 123-126. https://www.journalrmc.com/index.php/JRMC/article/view/362
- Zeng Y, Wu Y, Zhang Q, Xiao X (2024) Crosstalk between glucagon-like peptide 1 and gut microbiota in metabolic diseases. mBio 15(1): e0203223. https://doi.org/10.1128/mbio.02032-23 [PubMed] [PMC]
- Zhang J, Ning J, Hao X, Han X, Fu W, Gong Y, Meng Q, Ding S, Zhang J (2022) Glucagon-like peptide-2 protects the gastric mucosa via regulating blood flow and metabolites. Frontiers in Endocrinology 13: 1036559. https://doi.org/10.3389/fendo.2022.1036559 [PubMed] [PMC]
- Zhang Y, Shen J, Xie F, et al. (2024) Feedforward inhibition of stress by brainstem neuropeptide Y neurons. Nature Communications 15(1): 7603. https://doi.org/10.1038/s41467-024-51882-0 [PubMed] [PMC]

Author Contribution

- **Khaled A. Abdel-Sater**, MD, Professor of Medical Physiology, Faculty of Dentistry, Mutah University, Jordan; e-mail: Kabdelsater@mutah.edu.jo; **ORCID ID:** https://orcid.org/0000-0001-9357-4983. Conceptualization, Data Curation, Formal analysis, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Validation, Visualization, Writing – Original Draft, Writing – Review & editing. HH: Conceptualization, Data Curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Validation, Visualization, Writing – Original Draft, Writing – Review & editing.