Gut–brain axis biochemical signalling from the gastrointestinal tract to the central nervous system: gut dysbiosis and altered brain function

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ABSTRACT

Background The gut–brain axis facilitates a critical bidirectional link and communication between the brain and the gut. Recent studies have highlighted the significance of interactions in the gut–brain axis, with a particular focus on intestinal functions, the nervous system and the brain. Furthermore, researchers have examined the effects of the gut microbiome on mental health and psychiatric well-being. The present study reviewed published evidence to explore the concept of the gut–brain axis.

Aims This systematic review investigated the relationship between human brain function and the gut–brain axis.

Methods To achieve these objectives, peer-reviewed articles on the gut–brain axis were identified in various electronic databases, including PubMed, MEDLINE, CIHAHL, Web of Science and PsycINFO.

Results Data obtained from previous studies showed that the gut–brain axis links various peripheral intestinal functions to brain centres through a broad range of processes and pathways, such as endocrine signalling and immune system activation. Researchers have found that the vagus nerve drives bidirectional communication between the various systems in the gut–brain axis. In humans, the signals are transmitted from the liminal environment to the central nervous system.

Conclusions The communication that occurs in the gut–brain axis can alter brain function and trigger various psychiatric conditions, such as schizophrenia and depression. Thus, elucidation of the gut–brain axis is critical for the management of certain psychiatric and mental disorders.

INTRODUCTION

The gut–brain axis, commonly referred to as GBA, encompasses bidirectional communication between the enteric nervous system and the central nervous system.[1] This bidirectional communication also links peripheral intestinal function to cognitive and emotional centres of the brain.[2] Recent work shows that bidirectional interaction between the gut–brain axis and the microbiota facilitates communication between humoural, neural, immune and endocrine systems.[2] Some researchers even posit that disruptions and changes in the composition of the gastrointestinal tract microbiome result in mental disorder development and exacerbation.[3] For instance, there is a long history of psychiatric side effects of antibiotic medications, even in patients who do not have a history of premorbid psychiatric conditions.[3]

To achieve clinical benefit, there have been attempts to alter the composition of the gut microbiota with the goal of influencing interactions between the brain and humoural, neural, immune and endocrine systems.[2 3] For example, probiotic preparations containing *Lactobacillus* strains have been developed and used as interventions for improving mental health and managing psychiatric disorders.[4] However, such interventions quickly fell out of favour due to the lack of understanding of the mechanism through which they contribute to mental health.[4] Nonetheless, the medical field has recently witnessed a growing interest in the manner in which the gut microbiome influences mental health and how it can be manipulated to improve mental and psychiatric well-being.[5 6] This systematic review examines existing literature on the gut–brain axis and how it relates to the central nervous system and brain function.

METHODOLOGY

This systematic review considers evidence from previous studies exploring the gut–brain axis as well as biomechanical signalling from the gastrointestinal tract to the central nervous system. In addition, results of studies examining the concept of gut dysbiosis in relation to altered brain function are discussed. To achieve this goal, related peer-reviewed journal articles to the topic of study were retrieved from different electronic databases including PubMed, MEDLINE, CIHAHL, Web of Science, and PsycINFO. The search terms and phrases employed were 'gut-brain axis', 'mechanical signaling from the gastrointestinal tract to the central nervous system', 'gut-brain axis and brain functioning', 'gut dysbiosis', 'gut microbiome' and 'gut dysbiosis and altered brain function'.

The initial search yielded more than 30 results from each of the electronic databases. For simplicity, the search was limited to English articles published between 2011 and 2017. Restricting the search to articles published in the last 5 years facilitated the identification of current research evidence contributing to an understanding the gut–brain axis and its relationship to brain function. After applying this inclusion criterion, the abstracts of the remaining articles were reviewed, and the

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quality and appropriateness of each study was determined by assessing at the purpose, research design, results and conclusions. The final group of articles reviewed consisted of randomised control studies, longitudinal studies, meta-analyses, randomised controlled clinical trial and systematic reviews. A total of 70 peer-reviewed articles were included in this systematic review.

THE GUT–BRAIN AXIS

The gut–brain axis is a term used to refer to the biochemical signalling that occurs between the central nervous system and the gastrointestinal tract.[7] The term has been expanded to include interaction between the gut flora and the central nervous system and the gastrointestinal tract.[8–10] According to a definition by Wang and Kasper, the gut–brain axis comprises the central nervous system, the neuroimmune and neuroendocrine systems, the parasympathetic and sympathetic sections of the autonomic nervous system and the gut microbiota.[7] Other researchers posit that the gut–brain axis plays the important role of integrating and monitoring bowel functions and linking the cognitive and emotion centres of the brain to various peripheral intestinal mechanisms. The gut–brain axis also functions in enteroendocrine signalling, intestinal permeability, enteric reflexes and immune activation.[7] Figure 1 illustrates the structure of the gut–brain axis.

Research on the gut–brain axis has revealed the existence of a *complex communication and interaction system* that contributes to the proper maintenance of gastrointestinal homeostasis.[7 11] Furthermore, the autonomic system drives efferent signals from the central nervous system to the intestinal walls.

In contrast, the *hypothalamic–pituitary–adrenal system (HPA)* coordinates the adaptive response of organisms to stressors of any type. Moreover, it is a component of the limbic system and supports emotional response and memory.[7] The system is usually activated by environmental stress and high levels of proinflammatory cytokines through corticotropin-releasing factor (CRF) secreted from the hypothalamus.[7] It is well known that *cortisol* is a primary stress hormone that affects different human tissues and organs such as the brain.[7] Therefore, both hormonal and the neural communication lines converge to enable the human brain to directly influence the activities of various intestinal functional effector cells such as enterochromaffin cells, enteric neurons, epithelial cells, interstitial cells of Cajal and immune cells.[12–15] The gut microbiota also influences the intestinal functional effector cells controlled by the brain.[1 16 17] Therefore, components of the gut microbiota *facilitate a reciprocal communication* between the brain and gut.[18 19]

BIOCHEMICAL SIGNALLING FROM THE GASTROINTESTINAL TRACT TO THE CENTRAL NERVOUS SYSTEM

Among the principle mechanisms underlying biochemical signalling in the gastrointestinal tract are the modulation of intestinal barriers and high integrity of tight junctions.[1]

Researchers have linked probiotic species-specific central outcomes with restoration of the integrity of tight junctions as well as to protection of intestinal barriers.[20] In studies involving pretreatment of animals with probiotics, it has been reported that *Bifidobacterium longum* R0175 and *Lactobacillus helveticus* R0052 were able to restore the integrity of the junction barrier while also attenuating autonomic nervous systems activity. Moreover, probiotics can hinder expression in hypothalamic genes and changes in hippocampal neurogenesis.[1]

A second mechanism involves modulation of afferent sensory nerves. Some studies have reported that enhancement of *Lactobacillus reuteri* excitability through inhibition of calcium-dependent potassium channel opening can modulate pain perception and gut motility.[1] In this case, changes in gut motility will facilitate bidirectional communication between the spinal cord, brain, central nervous system, HPA system and enteric nervous system. The autonomic system, together with the parasympathetic and sympathetic limbs, drives afferent signals from the lumen and transmitted through the vagal, enteric and spinal pathways to the central nervous system.[1]

The third major mechanism involves the production, expression and turnover of neurotransmitters. Researchers have reported that the microbiota has the ability to influence enteric nervous system (ENS) activity through the production of unique molecules with the ability to alter the function of various neurotransmitters such as γ-aminobutyric acid (GABA), melatonin, histamine, serotonin and acetylcholine. Evidence from a study by Sampson and Mazmanian shows that communication between the central nervous system and the gastrointestinal tract involves the vagus nerve.[21] Those researchers reviewed articles exploring the topic of the gut–brain axis, with a particular focus on the neurological relationship between the central nervous system and the gastrointestinal tract.

Other researchers report that the *vagus nerve aids communication* in the human gut–brain axis by transmitting signals from the luminal environment to the central nervous system.[21] Indeed, *through the vagus nerve*, the intestinal microbiota can influence different processes such as the production of metabolic precursors, neurotransmitters and active metabolites.[21] Chemical signalling and involvement of the vagus nerve in communication between the gastrointestinal tract and the central nervous system have further been supported by a study that explored the manipulation of the gut microbiota by antibiotics and probiotics.[22] An important systematic review reported that probiotic treatments, including the use of *Bifidobacterium infantis*, altered brain neurochemistry by creating region-dependent alterations in GABA mRNA,[22] demonstrating that the gastrointestinal tract affects brain neurochemistry and the HPA system through the vagus nerve.[22]

Another study explored biochemical signalling from the gastrointestinal tract to the central nervous system by analysing the GABAergic signalling process occurring in the intestinal epithelium.[23] GABA, a primary inhibitory neurotransmitter in the central nervous system, is usually produced through enzymatic activities involving glutamic acid decarboxylase.[23] The authors further noted that GABA provides rapid biological signalling via type A receptors. Based on analysis of the intestine epithelial GABAergic signalling process, they pointed out that the microbiota can influence central nervous system activity through the production of molecules that function as local neurotransmitters, including serotonin, melatonin, GABA, acetylcholine and histamine.[23]

The authors also concluded that the microbiota can influence the central nervous system through the generation of active catecholamines in the gut.[23] However, it has been reported that the gastrointestinal tract microbiota can influence the central nervous system, for example, through *Lactobacillus* strains that use nitrate to produce nitric oxide and hydrogen sulfide.[24 25] The same researchers posit that hydrogen sulfide production can modulate gut mobility through interactions with vanilloid receptors found in capsaicin-sensitive nerve fibres.[25] In a different study, it was demonstrated that gut microbes were able to communicate with the brain and influence the central

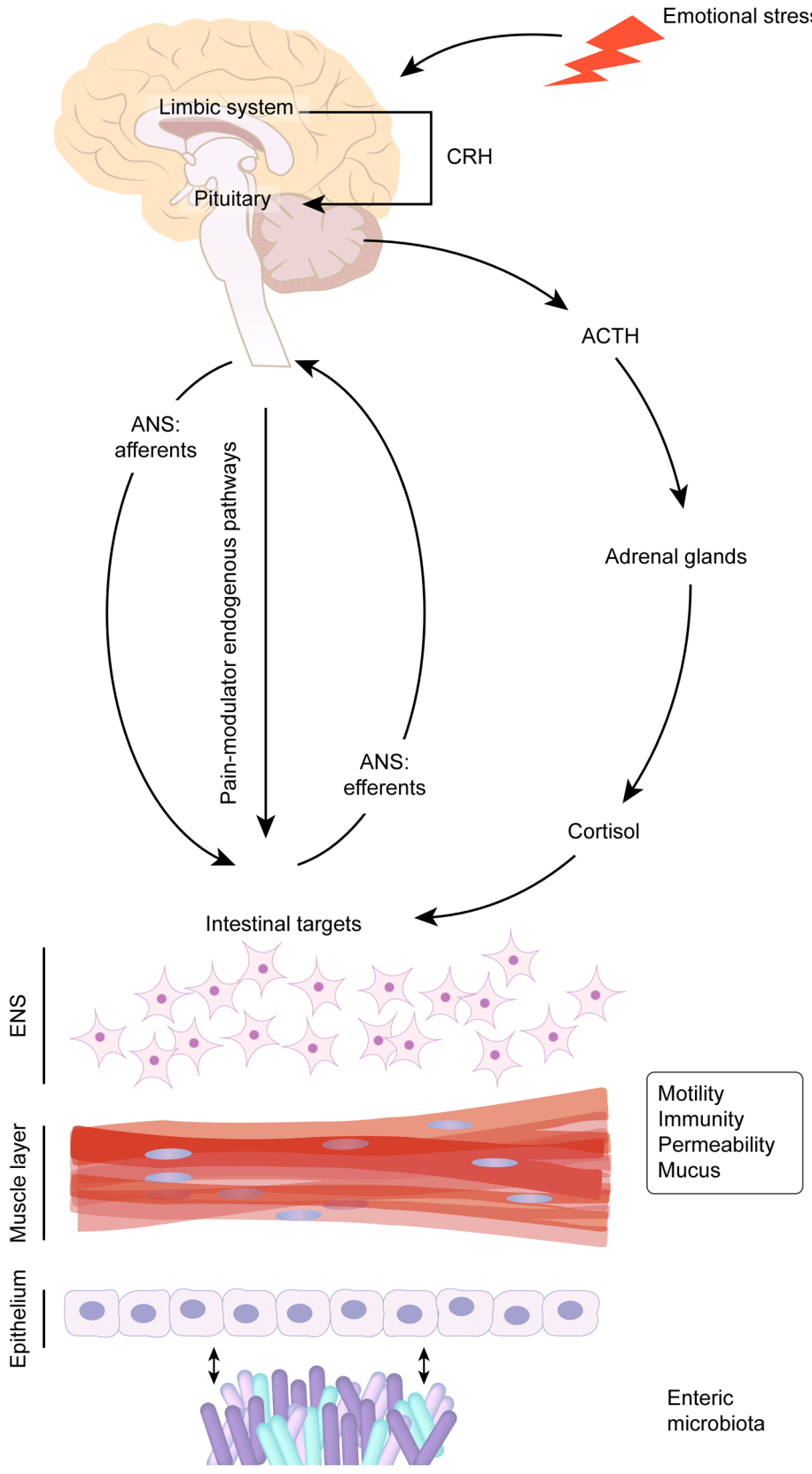

Figure 1 Schematic structure of the constitution of the gut–brain axis. The microbiological flora of the intestine stays in contact with the epithelium of the intestine. The intestine is surrounded by muscles and nerve cells (so-called enteric nerve system (ENS)). These nerve cells are in contact with the autonomic nervous system (ANS). The autonomic nervous system consists of ANS afferents and ANS efferent fibres. Thereby the autonomic nervous system provides the connection of the ENS to the brain. In addition, the system is under control of hormones. Here, the ACTH cortisol system is the most important one.ACTH, adrenocorticotropin; CRH, corticotropin releasing hormone.

nervous system by directly altering neurotransmitter levels.[26] As an example, the human gastrointestinal tract contains most of the body's serotonin (5-hydroxytryptamine (5-HT)).[26]

Regardless, the actual mechanism that controls the metabolism and functioning of 5-HT derived from the gut remains largely unclear. The aim of a recent study was to demonstrate that the microbiota directly regulates 5-HT via metabolic signalling.[26] The authors found out that introduction of spore-forming bacteria into the gut leads to the breakdown of short-chain fatty acids and *reduced* serotonin production; decreased serotonin levels in the gut then trigger neurochemical signalling to both the brain and the central nervous system. Furthermore, the authors concluded that the gastrointestinal tract is an important site for the biosynthesis of 5-HT, which in turn influences the levels of both blood and colon 5-HT and facilitates communication between the microbiota and the central nervous system via signalling to host cells.[26]

Another review demonstrated a direct link between the microbiota and the HPA axis as well as *direct neurological activation* of stress circuits by the microbiota.[27] The review reported that by activating stress circuits and vagal pathways, administration of food-borne pathogens such as *Campylobacter jejuni* and *Citrobacter rodentium* contributes to signalling between the gastrointestinal tract and the central nervous system.[27] The authors of that review stated that in the acute stage of *C. jejuni* infection, neuronal activation markers such as *cFOS* are present in vagal sensory neurons, even in the absence of a systemic immune response.[27] Stress-induced *cFOS* and *c-Jun* form *AP-1*, an transcription factor that is important for apoptosis and cell differentiation. That study also revealed that the central brain region exhibits cFOS activation after oral administration of *C. rodentium*.[27–29] In the case of infections by two *Escherichia coli* strains, cFOS activation of neurons is strong and can be accompanied by a robust cytokine response, suggesting the involvement of both immune and neural routes in HPA activation.[27 29 30]

The other commonly studied mechanism involves *bacterial metabolites* and *mucosal immune regulation*. Due to the ability of the gut microbiota to change the availability of nutrients and to the close association between peptide secretion and nutrient sensing, interactions in the gut–brain axis may involve secretion of biologically active components such as bacterial metabolites. For instance, *galanin* can stimulate secretion of adrenocorticotropic hormone and CRF.[1] From the mucosal immune regulation perspective, researchers have reported that muscal inflammation can enhance expression of activating signalling in the ENS, whereas *Lactobacillus paracasei can attenuate* antibiotic-linked visceral hypersensitivity.

GUT DYSBIOSIS AND ALTERED BRAIN FUNCTION

The potential contribution of bidirectional communication and interaction between the central nervous system and the gut is suggested by the increasing rates of comorbidity between psychiatric and gastrointestinal illnesses.[1 31] A study by Foster and McVey Neufeld,[32] for instance, reported that mood disorders affect more than half of those who suffer from irritable bowel syndrome.

More specifically, the researchers noted that patients continue to suffer from the commensal intestinal microbiota that influences stress-related behaviour. Moreover, different bacteria, such as pathogenic, commensal and probiotic microbes, found in the gastrointestinal tract can activate the central nervous system signalling process and neural pathways and contribute to the development of mental illnesses such as depression and anxiety.[32–34] Other agents that have been referred to when examining directional interactions occurring between the central nervous system and the gut include *Lactobacillus rhamnosus*, *Helicobacter pylori*, *L. paracasei*, *Pseudomonas*, *E. coli* and *B. longum*.[35–37] In recent years, researchers have become increasingly interested in the contribution of the gut microbiome to the regulation and influence of metabolism and immunity and how it alters brain function.[38–40] The human microbiome affects the functioning and development of the central nervous system through its interaction with the gut–brain axis.[41] Furthermore, factors such as *diet*, *sleep patterns* and *exposure to antimicrobials* have proven to alter brain function through changes in the gut microbiome.[42–44]

A recent review reported that administration of a single course of antibiotics among patients with gastrointestinal complications increased the risks of developing depression and anxiety.[1] Additionally, the researcher indicated that oral administration or the delivery of non-absorbable antimicrobials increased brain-derived neurotrophic factor-mediated hippocampal experience-dependent learning.[1] Based on the findings, the researchers concluded that the gut microbiome contributes to alteration in brain function and immune system dysfunction.[1]

Mood disorders and anxiety are some of the specific conditions that investigators have focused on when evaluating the relationship between gut dysbiosis and altered brain function. Although research on the relationship between anxiety disorders, mood disorders, depression and the gut flora is still in the early stage, evidence from a study by Schneiderhan, Master-Hunter and Locke showed that gastrointestinal problems are common among patients suffering from anxiety and depressive disorders.[10] In fact, these authors noted that the existence of depressive disorders among patients with gastrointestinal illnesses demonstrates that bidirectional communication occurs in the gut–brain axis and the effect of the microbiome on the HPA stress response.[10] Another study examined faecal samples obtained from 46 patients with depressive disorder and 30 healthy controls,[45] with higher levels of Actinobacteria, Proteobacteria and Bacteroidetes and a reduced level of Firmicutes in the former.[45] Despite the suggested correlation between depressive symptoms and gastrointestinal problems, the study did not speculate on the exact physiological implications and mechanism of the relationship between gut dysbiosis and altered brain function.[45]

It has also been reported that any pathological process that either increases or decreases food intake can affect the microbiome and compromise brain function and development by altering the synthesis of neuromodulators and neurotransmitters such as dopamine, serotonin and GABA.[6] Moreover, changes in the microbiome can affect the production of chemicals that regulate appetite and mood, such as ghrelin, leptin and tryptophan.[6 46 47] The ability of the gut microbiome to influence and alter brain function has also been studied by focusing on the development of schizophrenia among patients with gastrointestinal diseases.[48 49] A recent review reported that the homeostatic microbial community in the digestive tract disrupts and influences the development of schizophrenia by activating both innate and adaptive immunity.[48] The process involves interaction of a brain active immune component know as *Complement C1q* with various schizophrenia risk factors such as food intolerances, exposure to *Toxoplasma gondii*, inflammation and cellular barrier defects.[48 50 51]

The interaction of *Complement C1q* with schizophrenia risk factors a state of immune dysregulation that leads to the occurrence of schizophrenia symptoms among patients with

gastrointestinal diseases.[48 52–54] A review of previous studies suggests that patients with gastrointestinal disorders may also have an increased risk of developing Parkinson's disease and vice versa.[55–59] Parkinson's disease is usually characterised by so-called alpha-synucleinopathy, which can affect every level of the gut brain axis, including enteric nervous, autonomic, and central nervous systems.[60 61] As the symptoms of the disease massively affect quality of life, it is not surprising that researchers strive to understand the pathophysiological aspects of the condition and its relationship with the gut–brain axis.[6 62] A different study determined that changes in the composition of the gut microbiota can alter intestinal permeability and gut barrier function. Furthermore, microbiota compositional changes can affect the immune system, GI epithelial cells and both glial cells and neurons in the nervous system.[56 63–65] Changes in the composition of the gut microbiota can either precede or occur during Parkinson's disease.[66] Therefore, the authors speculate that the peripheral premotor symptoms of Parkinson's disease may even originate from the intestine and demonstrate that alterations in microbiome composition can alter brain function.[66]

TAKE HOME MESSAGE

The communication occurring in the gut–brain axis contributes to the proper coordination as well as the maintenance of gastrointestinal function. Furthermore, this communication permits feedback from the human gut. In this process, the gut–brain axis supports and influences mood, cognitive function and motivated behaviour. Available research suggests that communication and interaction in the brain–gut axis occur through efferent and afferent neural pathways and signalling from the gut to the brain. The gut–brain axis can also influence the function of the neuro-immuno-endocrine pathways such as those participating in enteric sensorimotor reflex modulation. For instance, short-term exposure to stressors can influence the profile of the microbiota community by altering the proportions of main microbiota phyla and patterns. Similarly, gut microbiota changes can affect anxiety-like behaviour, responsiveness and activation of the HPA system. Thus, the gut–brain axis substantially affects the function of the central nervous system as well as that of the gastrointestinal tract through biochemical signalling. The current review shows that interaction between the gut–brain axis and the microbiota can be explained on the basis of four major mechanisms: adjustment of intestinal barriers as well as high junction integrity; modulation of afferent sensory nerves; neurotransmitter production, expression and turnover; and regulation of bacterial metabolites and mucosal immunity. Table 1 provides a summary of the four major mechanisms identified from a review of the literature.

Table 1 Summary of mechanisms that underlie interaction between the gut–brain axis and the microbiota

Mechanism	Description
Modulation of intestinal barriers and high junction integrity	*Bifidobacterium longum* R0175 and *Lactobacillus helveticus* R0052 can restore the integrity of the junction barrier and attenuate autonomic nervous system activities.
Modulation of afferent sensory nerves	Changes in gut motility can facilitate communication between the nervous system and other systems in the body.
Production, expression and turnover of neurotransmitters	The microbiota can influence the ENS activity. The impact occurs through the production of neurotransmitters such as GABA and melatonin.
Bacterial metabolites and mucosal immune regulation	Interactions in the gut–brain axis may involve secretion of biologically active components such as bacterial metabolites.

ENS, enteric nervous system; GABA, γ-aminobutyric acid.

CONCLUSION

There is increasing awareness among medical and scientific communities regarding the robust and significant link between the functioning of the central nervous system and the intestinal environment. More specifically, the existing body of research evidence shows that the gut–brain axis incorporates constant interaction and bidirectional communication between the gut, the central, endocrine and enteric nervous systems, and the brain. This systematic review reveals that gut dysbiosis can alter brain function and trigger the development of psychiatric

Main messages

- Data obtained from previous studies showed that the gut–brain axis links various peripheral intestinal functions to brain centres through a broad range of processes and pathways, such as endocrine signalling and immune system activation.
- In humans, signals are transmitted from the luminal environment to the central nervous system.
- Researchers have found that the vagus nerve drives bidirectional communication between the various systems in the gut–brain axis.
- Psychiatric and/or neurological diseases might be treated by using special probiotic bacteria and/or yogurt in the near future.

Current research questions

- Are there links between gut microbiota and gut-brain axis in different diseases?
- Is there an association between gastrointestinal disorders and the gut microbiota?
- Is there an association between behavioural disorders and the gut microbiota?
- Is there an association between metabolic disorders and the gut microbiota?

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Self assessment questions

1. What is the significance of the gut–brain axis?
   A. The gut–brain axis facilitates critical bidirectional link and communication between the brain and the nervous system and the gut.
   B. Supporting neuronal plexus activity.
   C. Initiating all brain signalling processes.
   D. Supporting the body.
   E. Facilitating movement.
2. Which systems comprise the gut–brain axis?
   A. Lymphatic system, skeletal system and renal system.
   B. Renal system, neuroendocrine systems and skeletal system.
   C. Central nervous system, neuroimmune and neuroendocrine systems, parasympathetic and sympathetic sections of the autonomic nervous system, and gut microbiota.
   D. Autonomic nervous system, musculoskeletal system, integumentary system and respiratory system.
   E. Reproductive system, respiratory system, cardiovascular system and digestive system.
3. What are the mechanisms that underlie biochemical signalling the gut–brain axis?
   A. Production, expression, and turnover of neurotransmitters and neurotrophic factor (BDNF), protection of the intestinal barrier and tight junction integrity, modulation of enteric sensory afferents, release of bacterial metabolites and mucosal immune regulation.
   B. Cell signalling and intercellular signalling.
   C. Mitochondrion-controlled signalling, activation of succinate-specific receptors and Notch signalling.
   D. Erythroblast transformation and transcription factor expression.
   E. Anabolic signalling mechanisms, lipid peroxidation, release of glucose-dependent insulinotropic peptide and heterodimeric signalling.
4. What is the relationship between gut dysbiosis and altered brain function?
   A. There is no direct relationship between gut dysbiosis and altered brain function.
   B. Neurochemical interactions and communication between the gut and brain prevent disorders.
   C. Gut dysbiosis hinders proper brain function.
   D. Gut dysbiosis causes mental diseases and impedes brain function.
   E. There are reports to date that gut dysbiosis can alter brain function and trigger the development of psychiatric disorders such as depression, schizophrenia and Parkinson's disease.
5. What is the role of the gut–brain axis in the development of psychiatric disorders such as depression and schizophrenia?
   A. The gut microbiome appears to contribute to an alteration in brain function and immune system dysfunction.
   B. The gut–brain axis hinders metabolism.
   C. The gut–brain axis increases immunity to diseases.
   D. The gut–brain axis causes the release of hormones that facilitate the development of psychiatric disorders.
   E. The gut–brain axis plays no role in the development and subsequent progression of the gut–brain axis.

disorders such as depression, schizophrenia and Parkinson's disease. However, much remains to be elucidated with regard to the mechanism and impact of the interaction between the nervous system and the gastrointestinal system. Future studies are required to explore how targeting of premotor intestinal stages of psychiatric disorders such as Parkinson's disease and depression can halt the progression of these diseases and alter brain function.

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Answers:

1. A, True.
2. C, True.
3. A, True.
4. E, True.
5. A, True.