Review article

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Nutritional modulation of the "brain–gut axis"

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Abstract

The "brain–gut axis" is a multicomponent conceptual model describing the bidirectional communication pathways connecting cognitive and emotional centres in the brain with neuroendocrine centres, the enteric nervous system and the immune system. This model enables novel explanations for the comorbidity of affective disorders, especially concerning mood and anxiety, in functional gastrointestinal disorders, the visceral hypersensitivity, as well as the effect of various acute and chronic stressors on gastrointestinal function. Furthermore, it offers the possibility to develop new biomarkers of integrated brain–gut function. This review discusses the possibilities to modify brain–gut interaction by nutritional means, offered by the brain–gut axis concept. Dietary interventions directed at serotonergic metabolism and its action in the brain, the hypothalamic–pituitary–adrenal axis, the metabolism of long-chain polyunsaturated fatty acids affecting both brain function and inflammatory cytokine profiles, and gut hormones are elaborated. The central role of the autonomic nervous system is also discussed. It is concluded that the concept of the brain–gut axis indeed enables the development of novel dietary intervention strategies in functional gastrointestinal disorders, but results directly transferable to daily practice are not immediately anticipated.

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Introduction

It is well accepted that the most common disturbances of gut health, except for those caused directly by a gastrointestinal infection, are associated with aberrations of intestinal function rather than intestinal anatomy or substantial changes in intestinal morphology. Irritable bowel syndrome (IBS) is the most encountered functional gastrointestinal (GI) disorder, characterized by abdominal pain or discomfort associated with alterations in defecation, in the absence of structural or biochemical abnormalities that can be identified using currently available tests (1). As much as 10–20% of the Western population suffers from symptoms consistent with the diagnosis of IBS according to the Rome criteria (2).

The pathophysiology of functional GI disorders is still not fully understood. Initially these disorders were attributed to a motor dysfunction. By the late 1980s it became apparent that a sensory dysfunction specific for visceral stimuli was a key feature in patients with functional GI disorders (3). It is now generally accepted that visceral hypersensitivity, characterized by the experience of pain in case of a normally non-painful visceral stimulus (allodynia) or a decreased threshold for the perception of a painful stimulus (hyperalgesia), is the hallmark of functional GI disorders, especially IBS (4, 5). This change in paradigm enabled the invention of a new multicomponent conceptual model of functional GI disorders, involving physiological, affective, cognitive and behavioural factors (1) (Fig. 1). The brain–gut axis is a theoretical model describing the bidirectional neural pathways linking cognitive and emotional centres in the brain to neuroendocrine centres, the enteric nervous system and the immune system (7). The visceral hypersensitivity as well as the high occurrence of psychiatric symptoms, in particular those of affective dysregulation, fit well into this concept (4, 8, 9). In addition, psychosocial stressors play a prominent role in symptom generation (10–13). The high rates of affective dysregulation in patients with functional GI disorders (up to 90% in IBS patients consulting a gastroenterologist) may be a specific and integral part of IBS, rather than a non-specific co-morbid

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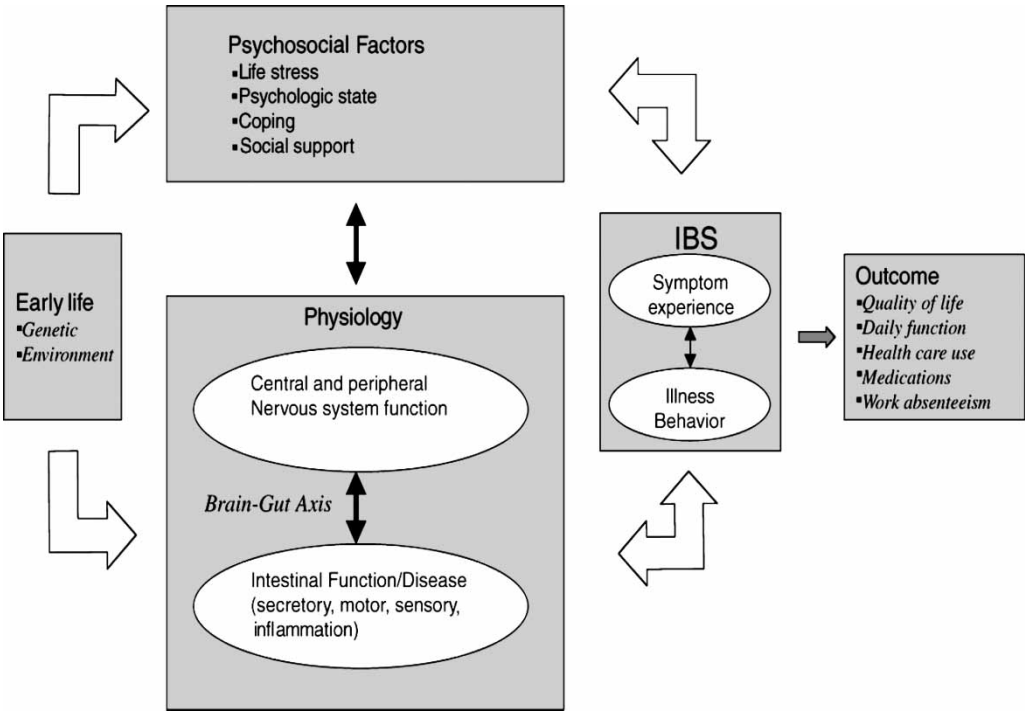

Fig. 1. The "brain–gut axis" as an integrated part of a comprehensive conceptual model of irritable bowel syndrome (IBS). [Adapted from Ringel et al. (6).]

syndrome related to a chronic GI disorder (14). It should be mentioned that such a holistic pathophysiological concept is rare in the traditionally dichotomic medical society (somatic versus psychiatric explanatory models).

Brain–gut axis communication routes and nutritional intervention

The question arises as to whether nutrition may play a role in the (patho)physiology of the brain–gut axis and, consequently, whether diet can positively affect gut health by modifying physiological processes within the brain–gut concept. To expand our knowledge about this issue not only is more insight into the role of the brain–gut axis in dysregulation of GI function important, but the development of relevant biomarkers of brain–gut axis physiology and GI function is also of pivotal importance.

Based on the existing knowledge on the physiology of the brain–gut axis and the available hypotheses about how diet may interact with interorgan signalling routes, the following communication routes and modulators of the brain–gut axis were selected as the primary points of action for nutritional intervention, as well as for the development of relevant biomarkers of brain–gut function:

- bioamines, especially serotonin (5-hydroxytryptamine, 5-HT)
- the hypothalamic–pituitary–adrenal (HPA) axis
- long-chain polyunsaturated fatty acids (LC-PUFAs) and associated inflammatory cytokines
- gut hormones.
- Autonomic nervous system (especially with regard to the development of biomarkers).

Serotonin

Serotonin (5-HT) is a biogenic amine that acts as a neurotransmitter and paracrine signalling molecule. It is peripherally involved, along with other factors, in the regulation of GI secretion, motility and perception, whereas it plays a role in the regulation of mood, appetite, sleep, cognition and sexual behaviour in the central nervous system (CNS). Most of the total body 5-HT is located in the GI tract (80%). The remainder is located in the CNS and blood platelets. Serotonin is synthesized from the essential amino acid tryptophan by two enzymic steps (15). Nearly all of the 5-HT in the blood is derived from the GI tract (16), and blood platelets avidly accumulate 5-HT from the plasma (17). The metabolism of 5-HT is rather complex and differs between the CNS and the periphery. Manipulation of serotonergic activity using 5-HT modulators,

such as antidepressants, has been used in the treatment of both affective disorders and IBS (14, 18–20). Hence, 5-HT should be regarded as a key denominator of the brain–gut axis (14, 21). Disturbed serotonergic metabolism seems especially prevalent in the diarrhoea-associated alterations of intestinal function, as well as in visceral hypersensitivity, the key feature of IBS.

As tryptophan is the substrate for 5-HT, the question arises as to whether serotonergic metabolism and activity can be modulated by dietary means. It was recently demonstrated that acute lowering of 5-HT synthesis, using acute tryptophan depletion, was associated with altered brain–gut responses, i.e. enhanced visceral perception and impaired memory performance in diarrhoea-predominant IBS patients and healthy controls (22) (Fig. 2). This result could be regarded as a proof of principle that 5-HT activity can be modulated by nutritional means. However, increased central serotonergic activity, rather than tryptophan depletion, is regarded as advantageous with regard to brain–gut regulation, and could result in improved mood, cognition and visceral sensitivity. A simple increase in tryptophan intake will not result in the desired modulation of the brain–gut axis, because of the complex metabolic route of tryptophan and 5-HT and the regulation of its transport through the blood–brain barrier (23–25). In general, a systemically high tryptophan concentration in the presence of a low concentration of long-neutral amino acids (LNAAs) is regarded as beneficial to stimulate tryptophan transfer over the blood–brain barrier and consequently promote 5-HT synthesis. The blood concentration of LNAAs can be decreased by the anabolic action of insulin. In relation to

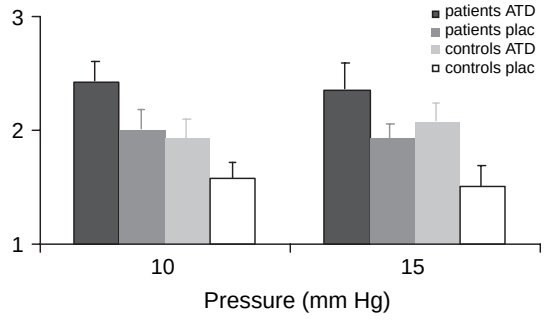

Fig. 2. Pressure-urge scores (mean ± SEM) during intermittent pressure distension of the rectum in diarrhoea-predominant irritable bowel syndrome patients and control subjects, during acute tryptophan depletion (ATD) and placebo. ATD was significantly associated with increased urge scores compared with placebo ($p < 0.0001$) (22).

5-HT and stress resistance, it has been shown that dietary intervention can modify 5-HT metabolism and activity (26).

There is an important interindividual variation in the response to alterations of serotonergic metabolism in subjects with affective disorders. It has been assumed that these differences are predominantly of genetic origin and determined by gene polymorphisms. Such polymorphisms encoding for serotonin reuptake transporters (SERT) are selected as potential candidates (27, 28). Recently, a polymorphism encoding for the enzyme tryptophan hydroxylase-2 (Tph-2), which controls 5-HT production in the brain, has been identified. The mutated gene variant, changing the enzyme by a single amino acid, is associated with a very poor response to antidepressive treatment (29). Studies related to dietary intervention of serotonergic metabolism and action should take genetic heterogeneity into account.

It can be concluded that dietary intervention directed towards improvements in 5-HT regulation and abdominal comfort is feasible. However, initial efforts should investigate the question of how diet can induce a prolonged alteration in serotonergic activity at both CNS and peripheral level and how this affects GI function according to the brain–gut paradigm.

Dietary modulation of the metabolism and action of other biogenic amines, such as dopamine and norepinephrine, has not yet been systematically studied with regard to the brain–gut axis. Dopamine receptors are present in both the brain and the gut, and further studies with respect to dietary modulation and GI function are awaited.

Hypothalamic–pituitary–adrenal axis

The HPA axis is the primary regulatory system of the body that copes with stress in a comprehensive sense, including physical, mental and metabolic (e.g. inflammation-related) stress (30). This (neuro)endocrine system regulates numerous metabolic routes and processes and is intimately connected with other regulatory mechanisms such as the autonomic nervous system (Fig. 3). Stimulation of serotonergic neurotransmission induces HPA axis-mediated neuroendocrine responses, which also offer the possibility for the development of biomarkers of serotonergic response. Furthermore, the HPA axis itself is important in brain–gut interaction. It has been shown that physiological and psychological stress-induced release of corticotropin-releasing

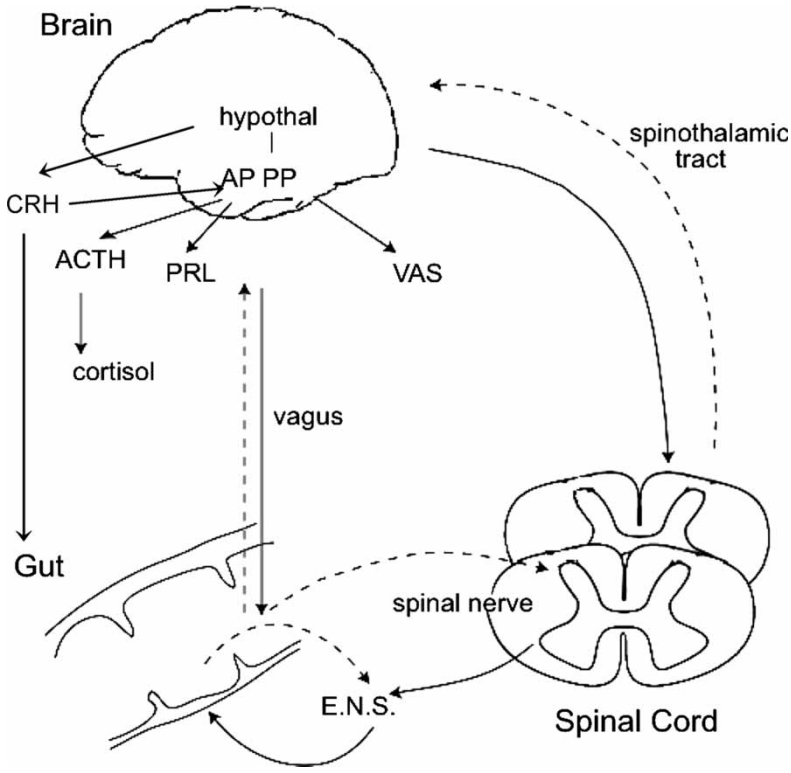

Fig. 3. The hypothalamic–pituitary–adrenal axis integrated in the brain–gut axis concept. Neural control of visceral perception (gut sensation) and motility occurs at three primary levels: (a) the enteric nervous system (ENS) (local) of the gut, (b) the spinal cord and (c) the brain, integrated by the autonomic nervous system. Dysregulation at any level could explain the hypersensitivity and abnormal motor patterns seen in irritable bowel syndrome. [Adapted after Mertz (5).] Release of the hormones cortisol [mediated via the release of adrenocorticotropic hormone (ACTH)] and prolactin (PRL) is partly under the control of 5-hydroxytryptamine innervation from nerve terminals originating in the raphe nuclei that innervate the hypothalamus (31). Stress-induced secretion of CRH directly affects the gut by destabilizing mast cells. Hypothal: hypothalamus; AP: anterior pituitary; PP: posterior pituitary; VAS: vasopressin; CRH: corticotropin-releasing hormone.

hormone (CRH) from the hypothalamus is a main contributor to the stress-associated alterations in intestinal function, such as enhanced GI motility, decreased mucosal integrity resulting in impaired intestinal barrier function, and visceral hypersensitivity (32–35). The CRH release triggers, among other things, mast cell degranulation, with the release of histamine, tryptase, serotonin and substance P. This causes inflammatory reactions involving a complex cross-talk between mast cells and nerves with tryptase, substance P and nerve growth factor (NGF) as dominant players (neurogenic inflammation) (36–38). Recently, this CRH-associated mast cell release has been considered to be an important feature in the pathophysiology of IBS (39, 40) and offers another lead in the understanding of the co-morbidity of GI dysfunction and disorders of mood and anxiety regulation. Furthermore, this concept enables additional understanding of the pathophysiology of postinfectious IBS and the connection between IBS and inflammatory bowel disease (IBD).

Attenuation of stress-associated CRH release, increasing the stability of mast cells, or attenuating the effect of mast cell degranulation would be the preferable option with respect to functional bowel disorders. So far, it has not been shown that CRH release can be modified by dietary intervention. However, dietary modulation of HPA responses in general may be achieved by amino acids, peptides or proteins (41). Nutrition-induced stabilization of mast cells and attenuation of the effect of degranulation are under investigation by the present group and seem conceivable. However, implementation of this research from the bench into dietary practice is not expected within the next couple of years.

Long-chain polyunsaturated fatty acids

The involvement of LC-PUFAs, especially the n-3 and n-6 fatty acids, is based on the fact that these fatty acids and their metabolites are involved in local and systemic inflammatory responses, as well as in brain development and function.

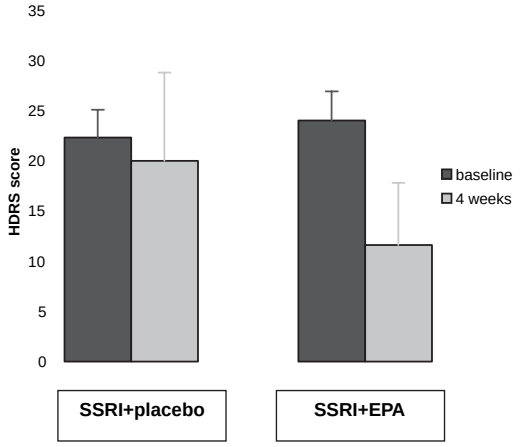

Fig. 4. Oral supplementation with eicosapentaenoic acid (EPA) (20:5 n-3) (right) enhances the effect of treatment with selective serotonergic reuptake inhibitors (SSRI) compared with placebo supplementation (left) in patients with recurrent unipolar depression. [Adapted after Nemets et al. (49).] HDRS: Hamilton Depression Rating Scale.

The following propositions illustrate this involvement in the brain–gut axis and offer leads for the development of dietary intervention strategies:

- There is a high prevalence of mood disorders in functional bowel disorders (14).
- Mood disorders are bilaterally associated with a proinflammatory cytokine profile (42–44).
- There is increasing evidence that several functional GI disorders are associated with chronic low-grade inflammation (45, 46).
- Inflammatory cytokine profiles can be modified by LC-PUFA intake (47).
- LC-PUFA intake is associated with the incidence and prevalence of mood disorders (48).
- Oral administration of specific LC-PUFAs may have additional value in the treatment of depression (48, 49) (Fig. 4).
- Chronic stress has a strong pathophysiological similarity with depression (50, 51) and is associated with a proinflammatory cytokine profile (52).
- Chronic stress is associated with impaired mucosal integrity and intestinal barrier function in animal models (34).
- Impaired intestinal barrier function may be causally related to postinfectious functional GI disorders and even Crohn's disease (45, 53, 54).

Hence, it can be postulated that a specific LC-PUFA intake, through its possible synergistic mood-enhancing effects and anti-inflammatory properties, may beneficially affect intestinal function. However, many issues remain to be solved. The systemic and brain bioavailability of fatty acids is of pivotal importance for their bioactivity. The specific fatty acid composition of dietary intervention should be determined against the background that eicosapentaenoic acid (EPA) (20:5 n-3) is generally considered a potent anti-inflammatory agent, while docosahexaenoic acid (DHA) (22:6 n-3) has specific effects on brain development and function (personal communication). Recently, it became apparent that the interaction between LC-PUFAs and cytokines is associated with a number of gene polymorphisms, which also may explain the variation in anti-inflammatory response in various intervention trials (47, 55). This knowledge offers the development of personalized dietary advice with regard to anti-inflammatory action. However, this comprises only one pathway of the possible beneficial bioactivity of LC-PUFAs on GI function.

The metabolism of LC-PUFAs is also related to immunological responses and to alterations in monoaminergic neurotransmission in the CNS, underlining the complexity of the brain–gut axis (56, 57).

Gut hormones

The physiological effect of a number of gut hormones is not restricted to the GI tract in a strict sense. Examples are ghrelin, cholecystokinin (CCK), neuropeptide Y (NPY) and peptide YY (PYY), which contribute to brain–gut signalling, but predominantly are considered to be associated with the regulation of food intake (58–60). It is well known that the intraluminal composition of the various segments of the gut and, hence, dietary composition heavily affect the secretion of these hormones. Whether this also affects brain–gut function with regard to functional GI disorders is largely unresolved. Interesting in this respect are observations that intraduodenal lipid infusion was able to modify visceral perception from colonic stimuli (61). These changes were more pronounced in IBS patients than in healthy controls, which may contribute to the explanation of the postprandial symptoms in IBS patients. One could speculate that separate influences on brain function may modify the central responses to the release of gut hormones. More research is needed to elucidate the role of gut

hormones in brain–gut signalling and how this can be modified by diet. The example of ghrelin has shown that gut hormones may use an unexpected route (i.e. the somatotrophic axis) to achieve their biological effect.

Autonomic nervous system

The autonomic nervous system offers a major route in brain–gut communication and hence may yield important biomarkers of brain–gut signalling, especially in efferent pathways. Together with the CNS and the enteric nervous system it forms a highly integrated and complex regulatory system, as illustrated by the aberrations in GI function caused by the various neuropathies (62). The autonomic nervous system is intimately connected to other regulatory pathways within the brain–gut axis, such as the HPA axis and the serotonergic system.

The non-invasive and minimally invasive measurement of autonomic nervous system parameters has progressed substantially in recent years, and is applied most often in cardiovascular and metabolic research (63–65). The determination of autonomic nervous system parameters should be seen in relation to biomarkers of brain function and brain–gut interaction offering pathophysiological knowledge of the brain–gut axis. It is unlikely that the autonomic nervous response itself – separate from alterations in brain or intestinal stimuli – could be affected by dietary intervention in the near future.

Conclusion

The concept of the brain–gut axis offers a novel approach for the development of dietary intervention strategies with regard to functional GI disorders. Such a holistic approach necessitates a transdisciplinary approach involving, among others, nutritionists, gastroenterologists, neuroscientists and psychologists. Although results directly transferable to daily practice are not yet expected, this review substantiates the view that the novel approach may yield important breakthroughs in the dietary treatment of functional bowel disorders contributing to an improved quality of life in this large group of people. Progress may be hampered by the lack of availability of validated and applicable biomarkers of brain and gut function, as well as interindividual variation in brain–gut responses to dietary intervention.

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