The Brain-Gut Team

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Keywords

Brain-gut axis · Enteric nervous system · Gut autonomic control · Functional disorders · Irritable bowel syndrome

Abstract

Background: Interactions between brain and gut have been suspected for centuries but our understanding of the neural centers and neurohormonal links that establish bidirectional regulatory communication between these 2 body systems has advanced significantly in the last decades. The label “brain-gut axis” designates a useful but deceptively simple concept, since the mechanistic complexity of brain-gut interaction is enormous. **Summary:** The significance of the brain-gut axis is perhaps best conceived as “a team” since both systems are physiologically coordinated to ensure a healthy status. However, under pathophysiological conditions, the axis also contributes substantially to distort homeostasis. For instance, normal signals emanating from the gut may be inappropriately received and interpreted by the central nervous system that responds by inadequately recruiting other brain structures and generate both symptoms and commands that disturb normal gut activity. **Key Messages:** Thus, at each end and in the brain-gut connecting routes, there is the potential for altering perceived and unperceived sensations and further impinging on normal function.

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Introduction

The brain-gut axis is a bidirectional link between the enteric nervous system and the central nervous system and involves direct and indirect pathways between cognitive and emotional brain systems and peripheral intestinal functions [1].

Abnormal brain-gut axis activity may lead to clinical chronicity [2]. To understand digestive illness, the status and influence of the gut-brain axis must be taken into consideration. It constitutes a helpful or unhelpful tool depending on circumstances [3].

The central nervous system and the gut are physiologically undissociable. Neural structures present at and linking both anatomic sites, central and enteric, are quite similar. However, the enteric nervous system, unlike the brain, is embedded in structures or tissues of remarkable diversity: smooth muscle, stroma, immunologically active cellularity, and absorbing epithelium. These various gut components perform functions that are highly regulated by local neural nets and, at the same time, provide key information to be relayed from the gut to the central

Is part of the special issue “50th Anniversary of the EAGEN. Successes and Failures in Gastroenterology during the past 50 years with an Outlook to the Future.”

apparatus in spine and brain. Thus, local control of gut activity prevails but is supervised and regulated at higher neural centers.

Significant advances have recently occurred in our understanding of the complex mechanisms that operate in the enteric nervous system, both effector and sensorial. Furthermore, although it is well established that the enteric and central nervous systems are tightly linked, but much remains to be learned about the operational processes that allow these relatively far away anatomic sites to integrate their regulatory activity on the gut.

The concept of a brain-gut axis was originally put forward as a hypothesis model to describe the bidirectional neural link between the enteric and central nervous systems. However, the brain-gut axis concept has been considerably expanded in recent years to include not only the classical autonomic nervous system pathways, that is, sympathetic and parasympathic, but also the hormonal pathway (hypothalamic-pituitary-adrenal [HPA] axis) and the intracerebral connections that exist between cognitive and emotional functions. The latter are part of the receptor and regulatory systems that determine gut physiological activity and, if perturbed, may also evolve into pathophysiological disturbances.

The HPA coordinates the adaptive responses to stress. It activates memory and emotional centers in the limbic system of the brain. Therefore, we must contemplate the existence of a multinodal brain-gut axis with interacting brain and spinal mechanisms that greatly increase the complexity of the system and constantly force researchers to redimension the model and reformulate its operational concept [4].

At a peripheral level, the brain-gut axis model has also been greatly expanded by the recognition of the important participation of the gut microbiota in the regulation of gut and brain physiological activity. The cells in various tissues of the gastrointestinal tract, chiefly epithelial, neural, and immune tissues, are under the influence of certain species that integrate the human microbiome. Current knowledge about the microbial species that specifically participate in the cross talk with gut-brain axis structures is still rudimentary but rapidly developing. Altogether the neuro-immune-endocrine-microbiome mediators of the gut-brain axis constitute the scaffolding of central regulation of intestinal function. A smooth and homeostatic operation of the axis is probably critical to healthy digestive function and well-being.

In one of his plays, Shakespeare wrote “unquiet meals make ill digestions” reflecting on popular knowledge of the importance of sensory and emotional environment to normal gut function. Indeed, stressful life events can im-

pact upon gut-brain signaling and cause alterations of meal tolerance and intestinal dysfunction but also cognition and task performance. Recent research indicates that nucleotide binding oligomerization domain (Nod)-like receptors, Nod 1 and Nod 2, have a key role as regulators for gut-brain signaling [5]. Nod-like receptors are innate immune pattern recognition receptors expressed in the gut and in the brain. Intestinal epithelial cell-specific deletion of Nod 1 in mice increased susceptibility to stress-induced anxiety-like behavior and cognitive impairment. Thus, Nod-like receptors in intestinal epithelium appear to perform an important role as modulators of gut-brain communication.

The Role of Gut Microbiota

It represents an ecosystem susceptible to environmental influences and in constant interaction with the human host. In this regard, both commensal and pathogenic bacteria are capable of generating innate immune responses that modify gut epithelial permeability, activate nociceptive sensory/pathways, dysregulate the enteric nervous system, and probably influence brain activity [6, 7].

Bioactive xenobiotic products are produced in the gut by the biotransformational capabilities encoded in the microbiome. Some of these metabolites participate in the gut-brain axis activity with potential to modulate central physiological and pathologic processes. Mechanisms potentially include binding to host receptors in the brain, stimulation of vagus nerve in the gut, alteration of central neurotransmission, and modulation of neuroinflammation [8, 9]. Microbiota-gut-brain axis signaling can occur via several pathways including the immune system, recruitment of host neurochemical signaling, direct enteric nervous system routes and the vagus nerve, and the production of bacterial metabolite such as short-chain fatty acids, branched-chain amino acids, and peptide glycans [10, 11].

Neuroimaging techniques, chiefly functional MRI and magnetic resonance spectroscopy, have been applied to detect putative changes in brain activity related to gut microbiota features or effects of probiotics, but the results are still fairly preliminary [12].

There is substantial preclinical and clinical evidence for an autoinflammatory effect of the vagus on local intestinal level acting via acetylcholine receptors on multiple cell types in innate and adaptive immunity and the enteric nervous system. This vagal activity appears to have protective properties on the intestinal barrier, inflammatory mechanisms, and the microbiome. This potentially useful pathway deserves to be explored therapeutically [8, 13].

Pathophysiological Implications of Gut-Brain Interaction

Gut Sensory Pathways

The main pathways connecting the gut with the central nervous system are the vagal afferent pathway that mediates upper gut nausea and satiety, the splanchnic pathway that involves mechanosensitive high-threshold sensorial afferents responding to intense stretch and compression, and the pelvic pathway that involves high- and medium/low-threshold sensorial afferents plus mucosal and circular muscular afferents responding to stroking and stretch.

These sensory channels may be sensitized by inflammation that may activate silent visceral afferents, high-threshold fibers encoding for pain at noxious range, low-threshold fibers that continue encoding for pain at noxious range, and spinal visceroreceptive neurons. It is unlikely that a single nociceptive pathway would be activated by inflammation. Furthermore, local inflammatory activity may lead to damage and remodeling of enteric nerves as well as implicate enteric neuroplasticity and neurogenesis.

The Role of the Brain

Under repeat stimulation from peripheral signaling, the brain is susceptible to undergo a number of structural and functional changes that impinge upon pain perception at central level [14]. Some of these changes may be predisposing, that is, already existing, and other changes may be secondary to chronic abnormal inputs. Whatever their origin, existing or secondary, these changes may increase the susceptibility to peripheral signals. Observed brain changes include thinning of the AMC and insular cortex that may modify perception of internal body states; regional variations in gray matter density in areas involved in emotion, attention, and pain modulation and activation of regions associated with emotional arousal and pain modulation as well as brain regions processing visceral information. There is also evidence of lesser recruitment of the dorsolateral prefrontal cortex suggesting decreased descending pain modulation at central level.

Visceral Hypersensitivity

This appears to be a key mechanism for explaining symptomatology in the presence of minimal or no apparent changes in intra-abdominal morphology or measurable digestive physiological activity. Visceral hypersensitivity may derive from enhanced afferent pain signaling through some of the mechanisms modifying gut sensory pathway activity, as described earlier. Visceral hypersen-

sitivity may also be due to decreased descending pain modulation than may implicate central mechanisms susceptible to be recruited in stress/anxiety situations. There is also evidence that the autonomic nervous system plays a role influencing reflex activity, perception, and extra intestinal manifestations via serotonergic and endocannabinoid systems.

Relevance of the HPA Axis

The humoral arm of the brain-gut axis is highly relevant in the modulation of gut sensations and brain-commanded peripheral function responses. Activation of the HPA axis by corticotrophin releasing factor may originate or involve the amygdala center in the brain that would operate as a link between emotional arousal and the humoral effector mechanism. Indeed, in rodents, corticotrophin-releasing factor and Urocortin I appear to induce both anxiety-like behavior and increased visceral sensitivity. All these pathways are part of the stress response system that includes brain and hormone-releasing neuro-endocrine structures.

In a clinical context, the answer to the obvious question: where does the pain come from? implies both disturbed peripheral pain signaling and disturbed emotional and cognitive pain modulation. The impact of psychosocial factors is substantial, as attested by a considerable body of research. Psychosocial factors may alter visceral nociceptive pathways and physiological gut function. Stress is increasingly recognized as an important epidemiological and pathophysiological element in functional and organic digestive disorders. Early adverse events may produce permanent epigenetic changes in the central and enteric nervous systems as well as sensitize the HPA axis. Abuse may impact upon central mechanisms including pain modulation, affect, and attention that are probably relevant to the genesis of abdominal symptoms. Chronic stress may modulate the immune response to infection in the gut. In summary, dysregulation of mind-body interactions may produce clinical manifestations.

Clinical Implications

Elucidating Central versus Peripheral Contribution to Clinical Presentation

In gastroenterology, it is not always possible to distinguish between illness (the personal experience of a medical condition) and disease (abnormalities in structure and function of organs or tissues). Even in the presence of ob-

vious organic gut disease such as ulcer or Crohn's, central mechanisms modulating pain perception, affect, and attention modify individually the clinical picture. In functional disorders, there may be no obvious morphological changes in the gut but deeper investigation of gastrointestinal tissues or brain structures may reveal pathological changes. Thus, as stated by Drossman [15], in attempting to explain functional disorders Cartesian dualism is to be rejected. Rather, clinical manifestations may be elicited within the full spectrum from illness to disease. It follows that symptom criteria, as established by observation and consensus, are insufficient to establish the precise location within such wide spectrum in a given patient.

However, in clinical practice it may be appropriate to attempt distinguishing a predominantly peripheral gut disturbance from a central processing disturbance, particularly in patients with apparent functional-type pain and other symptomatology. This is so for several reasons. First, there are specific disorders such as gastrointestinal neuromuscular disease that may be firmly established only by applying special diagnostic tests, particularly when presenting early in the evolution of the condition. Failing to diagnose such an entity in patients with unclear symptomatology may prevent the application of specific treatment and the elucidation of an accurate prognosis. Another important reason for establishing as early as possible the relative pathogenetic contribution of either end of the gut-brain axis is to facilitate introduction of pharmacological tools that serve to modulate central and peripheral neural processes impinging on symptoms expression and hence facilitate an early restoration of a satisfactory quality of life. Further to this point, it has been shown that in functional painful conditions, high severity may point toward amplified central perception of normal peripheral input and hence greater efficacy of brain-directed therapies [15].

The Role of Gut Microbiota

There are well-established examples of gut-host bacterial interactions playing a pathogenetic role in clinical gut disorders. A particularly well-studied example is the post-infectious IBS-like syndrome, but the SIBO (small intestinal bacterial overgrowth syndrome) may be another putative example. Unfortunately, the lack of good biomarkers of healthy microbiota hampers our present capability to predict disease based on microbiota analysis.

The gut mucosal barrier is particularly susceptible to interact with luminal and mucosal adhering bacteria. In post-infectious disorders, it has been shown that there is increased apical junction complex permeability, mucosal immune activation, and increased mast cell abundance

and proximity to nerve endings. It has also been shown that proinflammatory cytokines are able to sensitize colonic afferent nerve endings.

The relation between gut microbiota and chronic pain is beginning to be elucidated. Action on gut receptors by microbiota-derived mediators may regulate peripheral and central sensitization and in turn mediate the development of chronic pain via direct or indirect action on the excitability of primary nociceptive neurons [16].

Probiotic bacteria in experimental animals seem capable of modulating behavior and brain biochemistry via, for instance, the vagus nerve. Thus, probiotics derived from natural strains selection or genetically modified organisms may be a potentially useful instrument to modulate bacterial-gut interaction for therapeutic purposes but this is still evolving. Therefore, this tantalizing and attractive possibility remains to be proven effective and useful in clinical practice.

The Role of Food

Food is another important element to activate and induce responses via the gut-brain axis. Stress and sadness modulate hunger and food preferences. Reciprocally, calorically dense food, even without visual, taste, or olfactory awareness, may modulate mood [17, 18]. Indeed, patients may spontaneously utilize such calorically rich foods to self-induce well-being and calm down. Ghrelin and CCK stimulate food intake and gastrointestinal motility decreasing gastric accommodation and enhancing gastric emptying. These hormones may play a putative role in coping with stress and tempering gut inflammation. Food is also an important factor to modulate the gut microbiome, and with this objective, prebiotic foods are being utilized, as well as probiotic, in attempting to correct gut symptoms and enhance quality of life.

Distorted Operation of the Brain-Gut Axis under Pathological Conditions

Functional gut disorders, in a broad sense, constitute a paradigm of distorted brain-gut axis operative activity. Hypersensitivity of sensory afferent neural fibers is a frequent, although admittedly not an invariable finding among patients with painful functional gut disorders. Hypervigilance and stress act at a central level to sensitize healthy individuals to gut distension, and functional imaging techniques have, indeed, shown differences between healthy volunteers and functional patients in cortical activation induced by rectal stimulation.

Gas is the intraluminal element inside the gut with the highest probability of acting as a trigger for afferent sen-

sory stimulation via intestinal distension. Co-existing visceral hypersensitivity amplifies the discomfort produced by abnormal gas retention and may also be responsible for symptoms in patients with gas retention volumes below the normal threshold for discomfort (allodynia). Combined therapeutic interventions at both central and peripheral levels may be required to alleviate symptoms in such situations [19].

Stress is associated with bowel disturbance in some healthy individuals and in a substantial proportion of patients with functional type disorders. In addition, many such patients exhibit psychological disturbances including major depression and anxiety [20]. It has been pointed out that emotional and mood instability may also stimulate these patients to seek medical advice. Thus, patients evaluated at medical clinics and hospital facilities may represent a subgroup of individuals in whom psychological problems, including mood disturbances, inability to “cope” adequately with stress and life challenges, and catastrophizing tendencies, exacerbate the “severity” of the abdominal clinical picture [21]. These “patients” may represent a highly selected sample of many community individuals experiencing similar annoying symptoms but staying away from the medical system [22].

Epidemiology of the Brain-Gut Axis

A “meme” is an idea that prospers and expands as an infectious agent because it looks attractive and convincing. Ross [23] has pointed that anguished individu-

als may be particularly prone to accept medical diagnoses (“syndromes”) that gradually consolidate and become self-fulfilling prophecies. This would be an example of the brain-gut team being pathophysiologically expanded and reinforced by influences transmitted in the form of “memes” by family members, friends, and doctors. These infection-like packages may include symptoms induced inadvertently, contradictory changes in eating habits and psychological inputs. Thus, the brain-gut axis may operate pathophysiologically not only within the patient but also through contact with other individuals, patients or not, and even health providers and the media [24]. This concept of “contagious” functional illness is to be taken into account, particularly in the current over informed and over connected society.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Acknowledgments

The authors thank Gloria Santaliestra for secretarial assistance.

Disclosure Statement

No competing interests declared.

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