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ROME IV, FOOD ALLERGY AND BRAIN-GUT CONECTION

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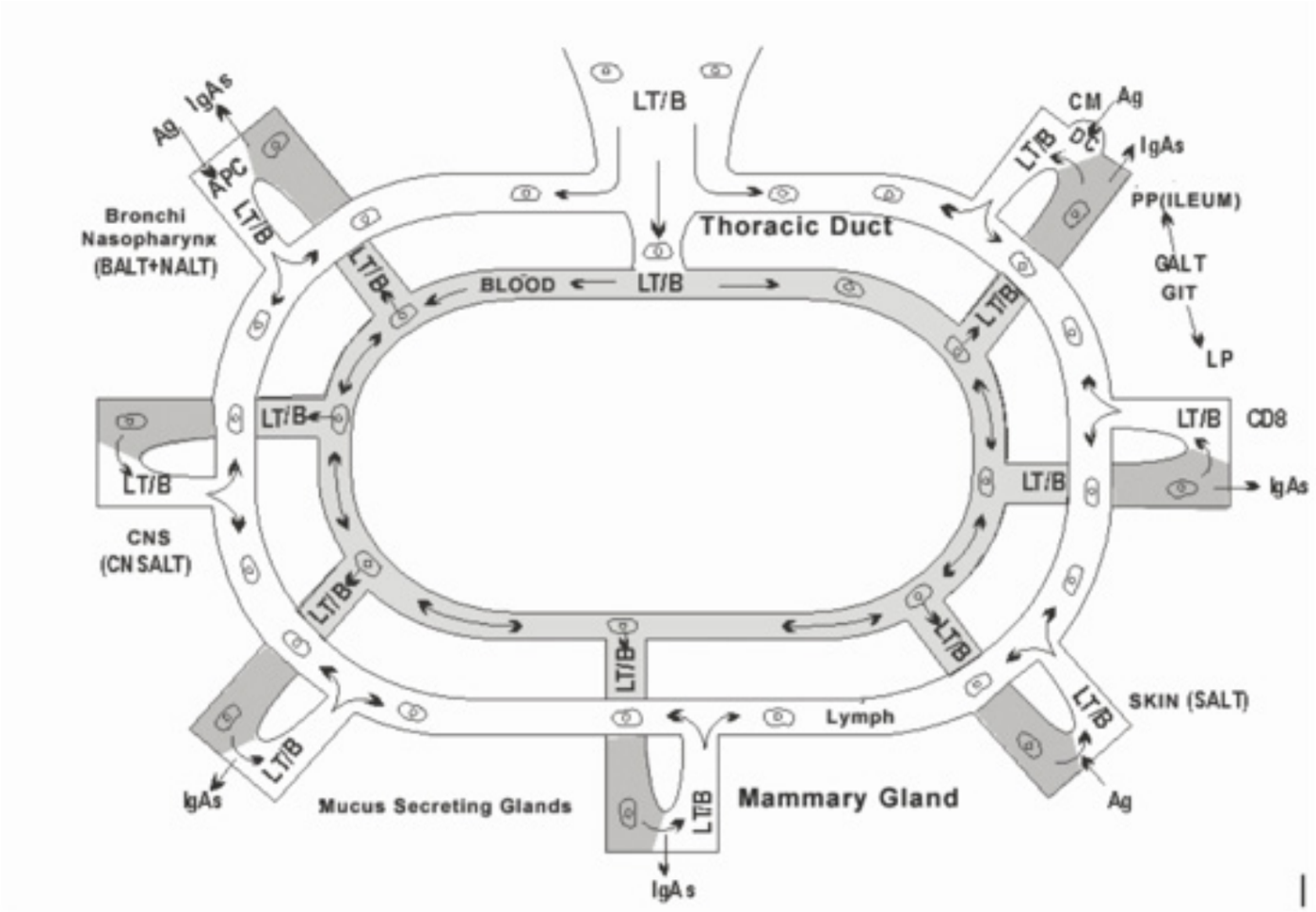

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CONTEÚDO

ABSTRACT

Neste volume 7 número 3 fizemos uma síntese do que foi o ROMA IV, com foco na interação cérebro-intestinos.

Um tema fascinante e sempre muito negligenciado pelos gastroenterologistas de adultos, que nomeavam como "Síndrome do Cólon Irritável" (SCI) ou "Síndrome dos Intestinos Irritados (SII), a toda e qualquer entidade clínica, sem diagnóstico, que apresentassem diarreia e constipação, de longa duração e que não respondiam aos tratamentos convencionais.

Dentro destas falsas entidades (SCI ou SII) sempre reconhecíamos e diagnosticávamos pacientes com alergia alimentar do tipo colite alérgica ou procto-colite alérgica. Fazíamos o tratamento e curávamos os pacientes.

Surge finalmente uma luz no fim do túnel no ROMA IV. Pela primeira vez é colocada de forma racional e com bases fisiopatológicas as "desordens funcionais dos intestinos" ou "functional gastrointestinal disorders" (FGID), embora ainda se desconheça na gastroenterologia dos adultos o papel da alergia alimentar nestas patologias. Como fica patente no ROMA IV, estas doenças são diagnosticadas apenas pelos seus sinais e sintomas, sendo logo informado na introdução do tema que existe uma total ausência de intendimento de seu mecanismo.

Pasmem meus colegas estudiosos, como ainda o ROMA IV passa longe da Alergia Alimentar, como causa de parte destas doenças estudadas como FGID. Cabe realçar entretanto que no ROMA IV merece destaque o parte que relaciona o Sistema Nervoso Entérico com o Sistema Nervoso Central. A seguir apresentamos uma síntese do ROMA IV com ênfase na "Brain-Gut Conection".

Original Article

ROME IV, FOOD ALLERGY AND BRAIN-GUT CONECTION

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Definition
Functional gastrointestinal disorders (FGIDs) are a highly prevalent group of disorders diagnosed solely by symptomatology as there is a lack of understanding of the underlying structural or chemical abnormalities.

Functional GI disorders (FGID) are disorders of gut–brain interaction. It is a group of disorders classified by GI symptoms related to any combination of the following disorders: motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, and altered central nervous system (CNS) processing. The bidirectional communication pathways between the gut and the brain, involved in the pathogenesis of FGIDs, are collectively known as the gut-brain axis.

The main symptoms described by patients with FGIDs include abdominal pain, dyspepsia, regurgitation, bloating, constipation, diarrhea, incontinence, problems in the passage of food or stool, or any combination of these symptoms. Common FGIDs include gastroesophageal reflux disease (GERD), functional dysphagia, functional dyspepsia, gastroparesis, irritable bowel syndrome (IBS), functional constipation, diarrhea, and fecal Incontinence. It has been well established that patients with FGIDs, along with having symptoms related to the gastrointestinal tract, have co-existing psychosocial symptoms such as stress, anxiety and depression and thus a biopsychosocial model has been proposed for FGIDs.

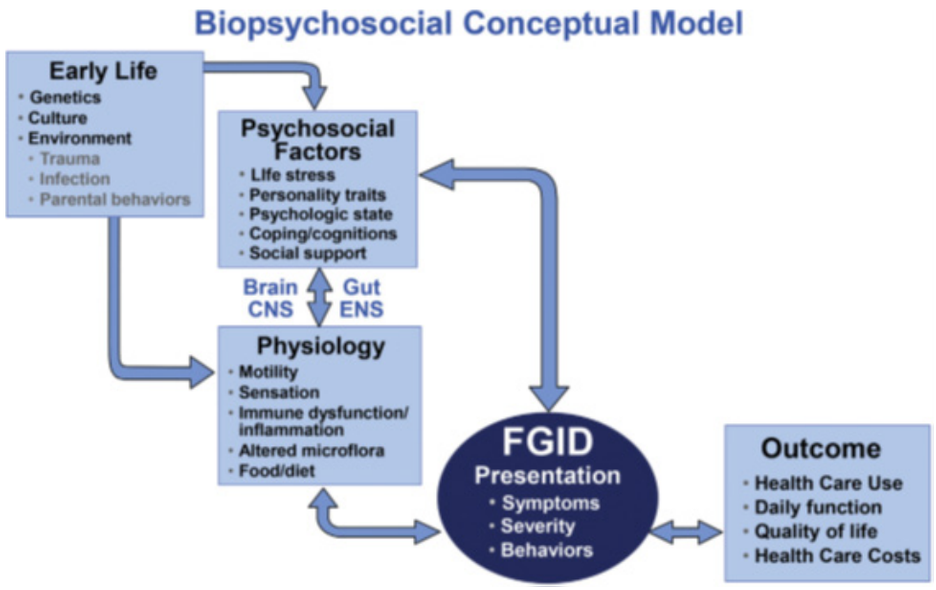
Concepts of Gastrointestinal Disease, Motility, and Functional GI Disorders.

1-The organic (structural) disorders (eg, esophagitis, inflammatory bowel disease) are classified in terms of organ morphology and the criterion for a disease is pathology at a macro- or microlevel.

2. A motility disorder (eg, gastroparesis, intestinal pseudo-obstruction), is classified in terms of organ function and specifically altered motility. Although dysmotility relates to abnormal visceral muscle activity (ie, slow bowel transit, delayed gastric emptying), a motility disorder is presumed to be persistent or recurrent dysmotility recognized as a clinical entity, and variably associated with symptoms. We also recognize that dysmotility may come and go with repeated physiological testing.

3. A functional GI disorder (eg, IBS, functional dyspepsia) relates to the patient's interpretation and reporting of an illness experience, and it is classified primarily in terms of symptoms. A symptom is a noticeable experiential change in the body or its parts that is reported by the patient as being different from normal and may or may not be interpreted as meaningful. However, a syndrome relates to the association of several clinically recognizable symptoms or signs that occur together to define a clinical entity. A functional GI disorder is a syndrome based on symptoms that cluster together and are diagnosed by Rome criteria.

However, IBS appears to be more complex and may result from a combination of factors relating to motility, visceral hypersensitivity, mucosal immune dysregulation, alterations of bacterial flora, and CNS–enteric nervous system dysregulation.



Pain in the Gut: pathways from Gut to Brain

Afferent fibers from the colon and rectum may converge with fibers from other pelvic organs, contributing to cross-organ sensitization between gut, bladder, and reproductive organs that often complicates the clinical diagnosis of pelvic pain. The low density of innervation, convergence with somatic inputs, and viscerovisceral convergence in the spinal cord can explain why gut pain generally is localized poorly.
Stretch or distension is effective for stimulating endings in the muscle layers, ganglia, and serosa.Different populations of afferents respond over a range of distension volumes from innocuous (physiological) to noxious levels that cause pain. Powerful contractions, especially against an obstruction, cause traction on the mesentery and is especially painful. In some cases, stimuli that normally are innocuous can cause pain (allodynia), whereas responses that are painful can become exaggerated (hyperalgesia).
A universal perception of the enteric nervous system (ENS) as a brain-in-the-gut implies that, similar to the brain and spinal cord, the ENS is assembled in a hierarchy of neural organization.
Cells participating in neuroimmune interactions: intestinal epithelial cells (enterocytes and colonocytes), intraepithelial lymphocytes, innate lymphoid cells, dendritic cells, T lymphocytes, B lymphocytes, mast cells, and macrophages.

The epithelial cells of the intestinal wall have distinct denominations: those of the small intestine are called enterocytes and those of the large intestine are called colonocytes. With their brush edge they separate the inner medium from the intestinal lumen. Among its innumerable functions are the digestion, absorption, secretion, transport of water and nutrients from the intestinal lumen to the internal environment and the interaction with our microbiome.

Among the enterocytes, the epithelial cells located in the terminal ileum, called M-cells, are prominent. In this region of the intestines, this double layer of cells that make up the M-cell membrane constitute the only obstacle between the internal environment and the intestinal lumen. Among the functions of this cell are the transport and absorption of macro molecules from the intestinal lumen to the internal environment, such as proteins, viruses and bacteria.

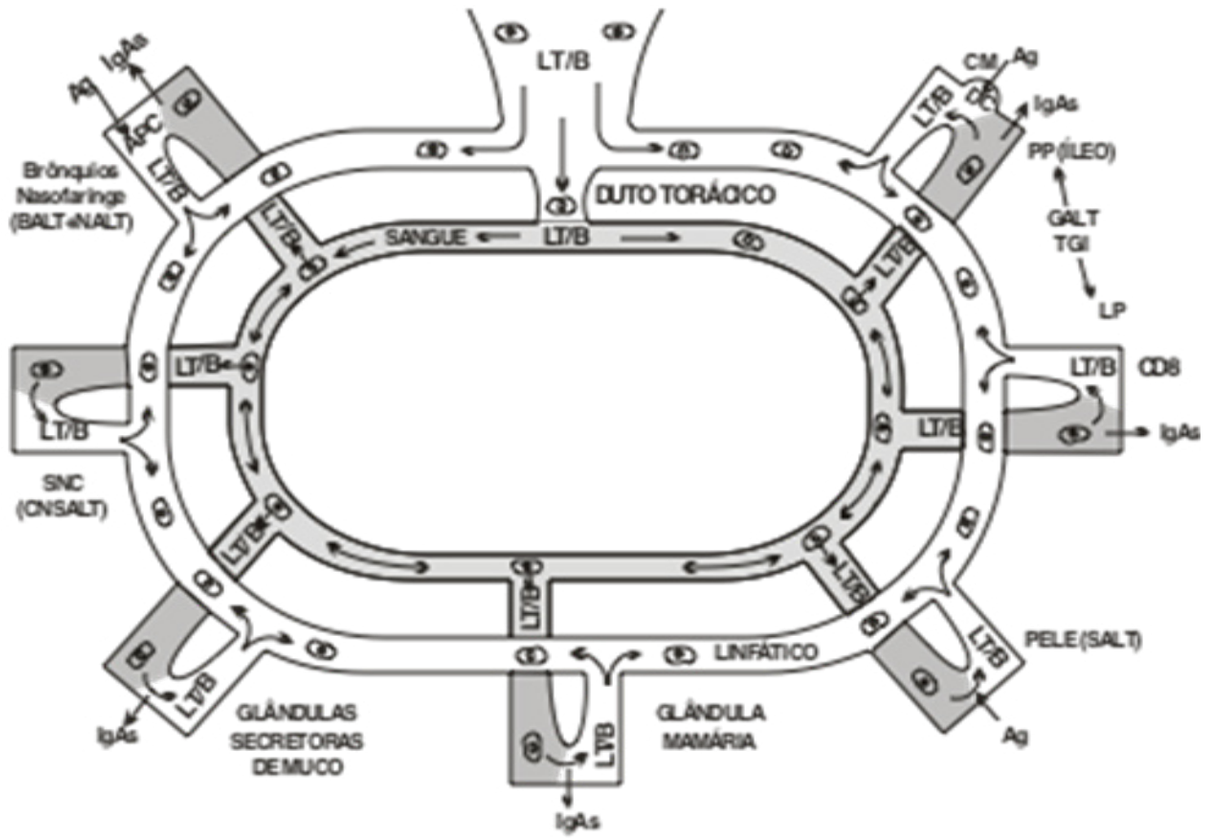
Neuroimmune interaction occurs when the macro molecule crosses the membrane of the M cell and enters the internal environment. In this site there are large concentrations of Dendritic Cells, which act as the most perfect macrophages in the presentation of this macro molecule the Lymphocytes T.

Once activated by this immunological synapse, T-cell

TCRs recognize the macro molecular antigen and command this information from the non-self molecule known as B-lymphocytes to produce antigen-specific immunoglobulins, such as specific antibodies of the IgA, IgE, IgG and IgM type thus produced for the elimination of the then recognized antigens.

Depending on the nature of this response, when the Th2 humoral pathway is activated, circulating antibodies attach to mast cells, particularly IgE, and when they find their specific antigen, they promote the antigen-antibody reaction, degranulate the mast cells, and elicit the histamine response in the shock organ .

Among these antibodies IgA has the specific function of protecting the intestinal wall of the already recognized antigens, to avoid a second presentation of this antigen in the internal environment. In this way IgA crosses the enterocytes and picks up its secretory part, transforming it into secretory IgA, migrating to the intestinal lumen, where it acts as an antibody of first defense against already recognized antigens that occur in the intestinal lumen.



STRESS

Although the etiology of FGIDs is unknown, there is compelling evidence that psychological and physical stressors play an important role. It is a generally accepted hypothesis that dysfunction of the bidirectional communication between the brain and the gut, in part through activation of the principal neuroendocrine stress system, namely the hypothalamic–pituitary–adrenal (HPA) axis, plays a role in the symptomatology of IBS.

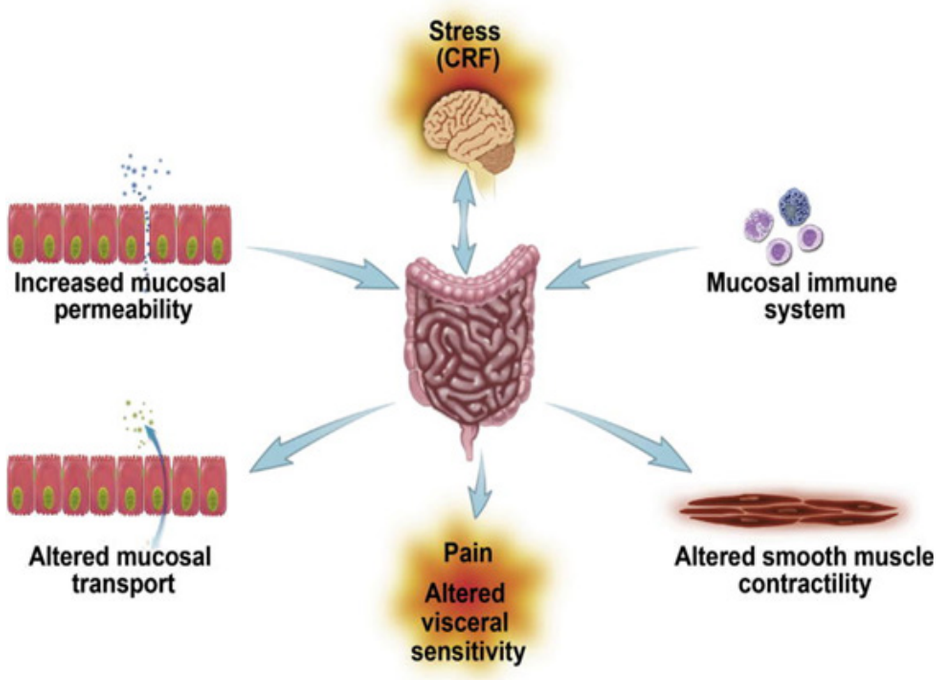
The HPA axis is activated by stress, causing the release of corticotropin releasing factor (CRF). Adrenocorticotropic hormone then is released from the pituitary into the systemic circulation to cause the synthesis and release of the glucocorticoid cortisol from the adrenal cortex.

The amygdala is sensitive to corticosteroids and facilitates behavioral, neuroendocrine, and autonomic res-

ponses to stress. The amygdala facilitates behavioral, neuroendocrine, and autonomic responses to stress. The altered balance in stress modulation induced by amygdala hyperactivity may represent an essential aspect of alterations in GI motor function, colonic permeability, and colorectal sensitivity apparent in IBS. These findings suggest that in IBS patients exposed to chronic stress, increased amygdala activation dysregulates the HPA axis.

Chronic psychological stress plays a significant role in the pathophysiology of IBS.

Psychological stress and negative life experiences are recognized as exacerbating psychosocial factors in IBS. Stress often exacerbates symptoms of cramping abdominal pain, diarrhea and urgency in IBS patients. These stress-exacerbated symptoms in IBS are similar, if not identical, to the abdominal pain, diarrhea and urgency associated with enteric allergic responses, infectious enteritis, radiation-induced enteritis and noxious mucosal irritation (e.g. senna laxatives). Recent advances in the basic science of brain-to-gut and immune cells-to-ENS signaling have introduced fresh insight into mechanisms underlying the effects of psychological stress on the intestinal tract.



The Brain-Gut Conection: Enteric motor neurons

Motor neurons in the ENS are excitatory or inhibitory motor neurons. The excitatory motor neurons release neurotransmitters, which evoke contraction of the musculature and secretion from mucosal glands. Acetylcholine and substance P are the main excitatory neurotransmitters released at neuromuscular junctions to stimulate muscle contraction. Acetylcholine, vaso-active intestinal polypeptide and ATP are excitatory neurotransmitters responsible for evoking secretion from the intestinal glands.

Neurogenic Secretion: Diarrhea and Constipation

Disordered defecation in IBS is related directly to the physiology of enteric secretomotor neurons. Secretomotor neurons are excitatory motor neurons in the submucosal plexus of the ENS, which innervate and stimulate secretion from the intestinal crypts of Lieberkühn, Brunner's glands and goblet cells.

Knowledge of the neurobiology of submucosal secret-omotor neurons is necessary for understanding the patho-physiology of secretory diarrhea, as well as constipation. In general, secretomotor hyperactivity is associated with neurogenic secretory diarrhea;

hypoactivity is associated with decreased secretion and a constipated state. Suppression of secretomotor firing by antidiarrheal agents (e.g. opiates, clonidine and somatostatin analogs) is manifest as harder-drier stools. Stimulation by chemical mediators, such as vasoactive intestinal peptide (VIP), serotonin and histamine, is manifest as more liquid stools.

Abdominal Pain and Disconfort

Primary causes of abdominal pain of digestive tract origin are distension and excessively strong muscular contractions. Hypersensitivity of the sensory mechanoreceptors for stretch (distension) and contractile force are implicated as pain factors in IBS. Hypersensitivity to distension is present in a substantial subset of IBS patients. Hypersensitivity of this nature to distension is not restricted to the distal bowel. Patients, who are diagnosed with functional dyspepsia, also experience more discomfort and pain at lower distending volumes in the stomach than normal subjects and hypersensitivity to distension is present in the esophagus of patients with non-cardiac chest pain.

Postinfectious IBS

A significant percentage of patients develop IBS-like symptoms following an acute bout of infectious enteritis. Hypochondriasis and adverse life events during the infectious episode are reported to double the risk for development of postinfective IBS. Nevertheless, the question of whether the association between acute infectious enteritis and IBS reflects low-level inflammation (e.g. microscopic enteritis) and chronic exposure of the neural and glial elements of the ENS to elevated levels of serotonin, histamine or other inflammatory mediators remains to be fully resolved.

Intestinal motility and abdominal pain

Strong contractions of the intestinal circular muscle coat during intestinal power propulsion underlie the sensation of cramping abdominal pain. Power propulsion, which is one of the patterns of motility stored in the program library of the ENS, occurs more frequently in IBS patients than in normal subjects and the circular muscle contractions are significantly stronger than normal in IBS patients. Postprandial power propulsion is more prevalent in the colon of IBS patients than in normal individuals and power propulsion in the colon is often associated with their diarrhea.

The pain and discomfort in IBS patients during the powerful contractions of power propulsion may be explained in three ways, either separately or in combin-ation. One explanation is for the exceptionally powerful circular muscle contractions to activate high-threshold mechanoreceptors that transmit the information centrally where it is processed and projected to consciousness as the perception of pain and discomfort. A second is for the mechanoreceptors to become sensitized in the IBS patients (e.g. by inflammatory mediators or other paracrine signals) and send erroneously coded information to processing centers in the spinal cord and brain. A third explanation is for accurately coded sensory information carried by spinal afferents to be mis-interpreted as it is decoded in the spinal cord and central processing centers of the brain.

Neuro-immunophysiological paradigm for IBS-Like symptoms

The human enteric immune system is developed at birth and is colonized by populations of immune/inflammatory cells that will change continuously in response to luminal conditions and pathophysiological states throughout the individual's lifetime.

The enteric immune system is positioned to provide security at one of the most contaminated borders between the interior of the body and the outside world. It deals continuously with dietary antigens, parasites, bacteria, viruses, and toxins as they appear in the warm-dark-moist-anaerobic environment of the intestinal lumen. The system is continuously challenged because physical and chemical barriers at the epithelial interface never exclude the large antigenic load in its entirety.

Sources of immuno-neural signals

Lymphoid and myeloid cells colonize the gastrointestinal tract in numbers that continuously fluctuate with changing luminal conditions and pathophysiological states. Cell types including polymorphonuclear leukocytes, lymphocytes, macrophages, dendrocytes and mast cells are present in continuously varying numbers in the intestinal mucosa, lamina propria and smooth muscle and are potential sources of immuno--neural signals. Each of these cell types can be situated in close histoanatomical association with the neuro-

nal elements of the ENS, vagal nerve fibers and spinal sensory nerves.

Signaling from the cells of the enteric immune/inflammatory system to the ENS establishes a first line of defense against foreign invasion at the vulnerable interface of a single epithelial cell barrier between the body and the outside environment.

In inflammatory states, close histoanatomical proximity of elevated numbers of lymphocytes and polymorphonuclear leukocytes to enteric nerve elements suggests that inflammatory mediators released by these cells might access and influence the ENS. Electrophysiological studies in enteric neurons confirm that inflammatory mediators released in paracrine fashion alter electrical and synaptic behavior of enteric neurons.

Enteric mast cells

Enteric mast cells are packed with granules that are sites of storage for a broad mix of preformed chemical mediators. Antigens stimulate the mast cells to release the mediators, which then diffuse into the extracellular space inside the ENS.

Enteric mast cells express high affinity receptors for IgE antibodies or other immunoglobulins on their surfaces. A deluge of multiple mediators is released from the mast cells when antibodies to a sensitizing antigen occupy the receptors and cross-linking occurs by interaction of the sensitizing antigen with the bound antibody.

Mast cells and the brain-gut connection

Aside from their sensing function, enteric mast cells provide a connection node between the CNS and ENS. This is a brain-gut interaction in which central psychological status can be linked to irritable states of the digestive tract by way of mast cell degranulation and release of mediators. Mast cell degranulation evoked by psychological stress activates the ENS "defense program" to produce the same symptoms of diarrhea and abdominal distress as antigen-evoked degranulation.

The brain-mast cell connection is significant because the gastrointestinal symptoms associated with mast cell degranulation are expected to be the same whether the mast cells are degranulated by antigen-antibody cross-linking in allergies or input from the brain during stress.

Mast cell signal substances

Several mast cell-derived mediators have neuropharmacological actions on electrical and synaptic behavior of neurons in the ENS. Some important mediators known to act at their receptors on neural elements in the ENS are: (1) Histamine; (2) Interleukin-6; (3) Leukotrienes; (4) 5-hydroxytryptamine; (5) Platelet activating factor; (6) Mast cell proteases; (7) Adenosine; (8) Interleukin-1β; (9) Prostaglandins.

Histamine

Histamine is not synthesized by enteric neurons and is not considered to be a neurotransmitter in the ENS. Mast cells and neutrophils are sources of histamine in the intestine. Knowledge of histaminergic actions on ENS neurons comes from results obtained from electrophysiological and immunohistochemical studies on single enteric neurons in animals. Mast cells in colonic mucosal biopsies from patients with diarrhea-predominant IBS release more histamine than normal subjects and might enhance intestinal secretion leading to secretory diarrheal symptoms like those associated with infectious agents and food allergies.

Serotonin

5-Hydroxytryptamine is another preformed mediator that is known to be released during degranulation of enteric mast cells and mucosal enterochromaffin cells to form a neuromodulatory overlay on the ENS in humans.

Histamine and 5-HT both act at presynaptic inhi-bitory receptors on cholinergic axons to suppress fast neurotransmission at nicotinic synapses in the enteric neural networks. Presynaptic inhibition by both neuromodulators is mediated by a different receptor subtype than the one that evokes excitatory responses in the neuronal cell bodies.

Serotonin and functional disorders

Infusion of 5-HT either intravenously or into the intestinal lumen evokes copious secretion of H2O, electrolytes and mucus from the intestinal secretory glands. The stimulatory action of 5-HT underlies its action as a diarrheagenic agent and its involvement in diarrheagenic syndromes in humans.

The IBS symptoms of cramping abdominal pain, diarrhea and fecal urgency are exacerbated in the postprandial state. Elevated appearance of 5-HT in the hepatic portal circulation in the postprandial state

reflects stimulated release from mucosal enterochromaffin cells. The normal postprandial release of 5-HT is reported to be augmented in IBS patients and this contributes to the suspicion that overactive release of serotonin might be an underlying factor in the symptoms of IBS in diarrhea-predominant patients. This suspicion is reinforced by findings of elevated numbers of mast cells and enterochromaffin cells, both of which contain 5-HT, in colonic mucosal biopsies from IBS patients.

Brain-to-mast cell connection: Implications for functional disorders

A brain-to-mast cell connection is currently the most plausible mechanism for explanation of the well-known relationship between stress and IBS-like bowel symptoms. A brain-to-mast cell connection implies a mechanism that links central psycho-emotional status to irritable states of the digestive tract.

The irritable state of the bowel (i.e. abdominal discomfort, cramping lower abdominal pain, diarrhea and urgency), known to result from degranulation of intestinal mast cells and release of signals to the ENS, is expected to occur irrespective of the mode of stimulation of the mast cells. This most likely explains the similarity of bowel symptoms between those associated with noxious insults in the lumen and those associated with psychogenic stress in susceptible individuals.

The immuno-neurophysiological evidence reinforces the hypothesis that moment-to-moment behavior of the gut, whether normal or pathological, is determined primarily by integrative functions of the ENS. The enteric minibrain processes input signals derived from immune/inflammatory cells (e.g. mast cells), sensory receptors and the CNS. The immuno-neurophysiology in this respect is suggestive of mechanisms with susceptibility to malfunctions that could result in symptoms resembling diarrhea-predominant IBS.

FGID : effects of pharmacologic agents on sensation and motility

Some of the disappointing results of the past decade in the development of new drugs can be attributed to the heterogeneity of functional disorders, lack of understanding of pathophysiology, and lack of short-term mechanistic studies that can predict clinical outcome. New drugs should target the entire pathophysiologic mechanism(s) contributing to the functional disorder rather than only an individual part or a specific receptor. Thus, nonselective agents designed to modulate multiple targets of the whole pathophysiologic process (eg, dysmotility, sensory disorder, inflammation) would be advantageous over highly selective medications addressing a single mechanism.

Risk zero: low risk is not acceptable for drugs that target pathophysiologic mechanisms and provide relief of nonfatal diseases such as FGIDs, and the drug development process should identify such undesired effects as early as possible.

Serotonergic Agents

Serotonin, or 5-hydroxytryptamine (5-HT), plays a key role in the control of gastrointestinal motility, sensitivity, and secretion, but to date no convincing beneficial therapeutic effects have been reported in FGIDs. 5-HT3 receptor antagonists, such as alosetron, delay orocecal and colonic transit times and reduce colonic compliance but not sensitivity to isobaric distention. Several clinical studies confirmed the efficacy of alosetron in diarrhea-predominant irritable bowel syndrome (IBS). Shortly after its introduction, alosetron was withdrawn due to suspected side effects of ischemic colitis/colonic ischemia and is now available for restricted use in the United States only.

5-HT4 receptor agonists, such as tegaserod or prucalopride, act on intrinsic neurons to stimulate gastric, small bowel, and colonic transit in health, in constipation, and in constipation-predominant IBS. Tegaserod improves constipation, provides relief of pain/discomfort and bloating, and is approved for women with constipation-predominant IBS and for men and women younger than 65 years with chronic constipation. Prucalopride and tegaserod were shown to be effective in the treatment of constipation.

Activation of 5-HT1A receptors on enteric neurons inhibits the release of acetylcholine. In humans, 5-HT1A receptor agonists such as buspirone inhibit motility and decrease gastric tone, but therapeutic usefulness has not been established.

Motilides

Activation of motilin receptors on smooth muscle and on cholinergic nerves enhances gastric contractility and gastric emptying in health and in gastroparesis, as seen in erythromycin or the macrolide prokinetic ABT-229.

The symptomatic impact of enhanced emptying by erythromycin in gastroparesis has been questioned, and no symptomatic benefit (but rather some symptom aggravation) was found in studies with ABT-229.

Tachykinin Receptor Antagonists

The biological effects of endogenous tachykinins substance P, neurokinin A, and neurokinin B in the gastrointestinal tract, has the potential to inhibit motility, sensitivity, secretion, and inflammation in the gastrointestinal tract. Neurokinin 1 receptor antagonists also have antiemetic properties. Several tachykinin receptor antagonists are currently under evaluation for treatment of FGIDs.

Adrenoceptor Agonists

The α2-adrenoceptor agonist clonidine was shown to reduce colonic tone and pain sensation in response to distention. A preliminary study of clonidine in diarrhea-predominant IBS suggested therapeutic potential for clonidine, but clinical application is hampered by dose-limiting side effects such as somnolence or hypotension.

Opioid Receptor Ligands

Opioid receptor activation located in the enteric nervous system and on nociceptive pathways reduces visceral pain through peripheral (spinal afferents) and central mechanisms and inhibits motility through decreased acetylcholine release.

Fedotozine and asimadoline, κ-opioid receptor agonists have been proposed as a pharmacologic approach to the treatment of hypersensitivity in FGIDs. Studies showed decreased sensitivity to gastric or colonic distention. However, therapeutic studies in IBS and functional dyspepsia with fedotozine have been disappointing.

Loperamide the μ-opioid receptor agonist, used in the treatment of diarrhea, inhibits secretion, reduces colonic transit, and increases resting anal sphincter tone. Peripherally restricted μ-opioid receptor antagonists, such as N-methylnaltrexone and alvimopan, normalize bowel function in opiate-treated patients without compromising central opioid analgesia. The use of these agents in constipation and in constipation-predominant IBS is under investigation.

Miscellaneous Agents

Cholecystokinin drugs as loxiglumide and dexloxiglumide, enhance gastric emptying in health and in constipation-predominant IBS, although effects on colonic motility are unclear. So far, clinical usefulness has not been established.

The transient receptor potential ion channel of the vanilloid type 1 (TRPV1), expressed by primary afferent neurons, is viewed as a trigger for chemonociception and may be up-regulated in some FGIDs. Capsaicin long-term administration, which is believed to desensitize TRPV1, was more effective than placebo in decreasing symptoms in functional dyspepsia. So far, clinical usefulness has not been established.

Dopamine2 receptor antagonists have gastroprokinetic effects and central antiemetic properties resulting in suppression of nausea and vomiting. Although clinically used in the treatment of FGIDs and gastroparesis, efficacy has not been established by high-quality studies.

Muscarinic receptor antagonists and smooth muscle relaxants are used in some countries for the treatment of IBS. Meta-analysis suggests they are superior to placebo in IBS-related pain, although the quality of trials has been questioned.

Somatostatin and its stable analogues such as octreotide inhibit rapid gastric and small bowel transit as well as sensitivity to rectal or colonic distention in humans. The need for multiple subcutaneous injections, high cost, and potential side effects limit its present use in FGIDs.

Cannabinoid CB1 receptors are expressed on nociceptive afferents and enteric nervous system neurons, whereas cannabinoid CB2 receptors are expressed on immune cells. Activation of CB1 receptors slows gastrointestinal transit in animals through inhibition of acetylcholine release. The nonspecific agonist δ-9-tetrahydrocannabinol has strong antiemetic properties and delays gastric emptying in humans.

It is unclear whether the potential for abuse of CB1

agonists would preclude their regulatory approval. Inverse CB1 agonists (which function as antagonists at constitutively active CB1 receptors) are being developed for treatment of obesity, because they may induce nausea and vomiting. The effects on stomach function are unclear.
On the other hand, agonists at the nonneuronal CB2 receptors have no abuse potential and exert antinociceptive effects in pain associated with inflammation.
Principles of Pharmacogenomics in FGIDs

Pharmacogenetics refers to the study of individual variations in DNA sequence related to drug response. Pharmacogenomics is the study of the variability of the expression of individual genes relevant to disease susceptibility and drug response at cellular, tissue, individual, or population levels.
Polymorphisms may be markers associated with predisposition to FGIDs. Examples in the literature include patients with IBS having significantly reduced frequencies of the high producer genotype for interleukin-10 than controls, suggesting that at least some patients with IBS may be genetically predisposed to produce lower amounts of this anti-inflammatory cytokine. This lends some support to the hypothesis that there may be an inflammatory or genetic component in some cases of IBS.
A second aspect is genetic variations influencing response to medications. There may be genetic polymorphism in drug metabolism. Genetic polymorphism may also involve transporters that may influence drug response.
Other observation is that drug response in patients with functional dyspepsia may be influenced by genetic variation in GNβ3 translation. These results require confirmation, but they suggest that pharmacogenetics may affect drug response and need to be considered in drug development programs and in clinical therapeutics. Pharmacogenetics may also provide new insights on the mechanism or pathophysiology of FGIDs.
Psychopharmacology of FGIDs

5-HT1A receptors and α2 adrenoceptors are both presynaptic and postsynaptic receptors and heteroreceptors (ie, they modulate norepinephrine and 5-HT neurotransmission, respectively, via presynaptic somatodendritic receptors).
When administered long-term, all antidepressants also enhance glucocorticoid signaling and inhibit overactivity of corticotrophin-releasing factor in the brain and presumably in the periphery. Each class affects several transmitters via reciprocal actions between amine and neuropeptide systems and reduces excessive cytokine release associated with various conditions in which inflammatory cytokines play a role. Long-term treatment with any antidepressant alters receptor sensitivity, which in all cases is believed to result in enhanced 5-HT neurotransmission.
Tricyclic antidepressants, increase the sensitivity of postsynaptic 5-HT receptors and down-regulate α2 presynaptic receptors and heteroreceptors. The analgesic effect of tricyclic antidepressants is also mediated by blockage of a class of voltage-dependent sodium channels in extrinsic sensory neurons.
Buspirone, an anxiolytic, down-regulates 5-HT1A somatodendritic autoreceptors to produce anxiolysis. Down-regulation of 5-HT1Areceptors is believed to play the most important role in antidepressant, anxiolytic, and analgesic effects of antidepressants.
Benzodiazepines enhance the inhibitory effects of γ-aminobutyric acid via potentiation at the GABAA receptors, indirectly enhance 5-HT, and diminish norepinephrine neurotransmission and antagonize the effects of cholecystokinin in brain and gut. This results in immediate anxiolytic activity.

Evidence for Efficacy of Psychotropic Treatments in FGIDs

Psychotropic agents are commonly used to treat patients with FGIDs:
Tricyclic antidepressants: desipramine
Drossman et al compared the efficacy of the tricyclic antidepressant desipramine (on average 100 mg/day) with placebo in women with moderate to severe IBS. In the intention-to-treat analysis, treatment with desipramine failed to reach statistical superiority over placebo in the overall sample. It was concluded that because most of the patients who dropped out did so due to side effects and a significant portion had nondetectable desipramine levels, tolerability of desipramine treatment ultimately limited the statistical po-

wer of this study.
SSRIs (selective serotonin reuptake inhibitor): fluoxetine, citalopram, paroxetine
Clinically, SSRIs appear to be useful for some patients with FGIDs. Kuiken et al reported that 6 weeks of treatment with fluoxetine 20 mg daily was not superior to placebo overall but did reduce abdominal pain in the subgroup with rectal hypersensitivity.
Citalopram: In a pediatric population with recurrent abdominal pain, a response was reported in 21 of 24 subjects (ages 7–18 years) after 12 weeks of treatment with flexible-dose citalopram.
In the only placebo-controlled, randomized, controlled trial of the SSRI paroxetine to date, Tabas et al compared 12 weeks of flexible-dose treatment with paroxetine (10–40 mg/day) with placebo in 81 patients with IBS. Treatment with paroxetine was associated with significantly higher improvement of overall well--being and patient preference compared with placebo. Abdominal pain and bloating were not significantly better after treatment with paroxetine.
Indication and Choice of Psychotropic Agents in FGIDs: tricyclic agent (desipramina), benzodiazepínicos, buspirone.

Psychotropic agents are indicated in the presence of significant psychiatric symptoms. The goal of therapy is to achieve relief of gastrointestinal and psychosocial distress. Patients with prior mania, prominent suicidal ideation, or a history of worrisome or unstable behavior should be referred promptly for assessment by a mental health specialist.

Desipramina: the SNRIs and SSRIs are generally considered to be equivalent in efficacy and tolerability, and either class is a reasonable first-line approach. They are broadly efficacious as antidepressants and anxiolytics and are safer and more tolerable than the traditional antidepressants. Obtaining tricyclic agent plasma levels (8–12 hours after the last dose) after initiating therapy can assure continued patient safety.
Benzodiazepínicos: if patients are intolerant of antidepressants and have prominent anxiety, they can be treated with benzodiazepine monotherapy. However, long-term use in patients with FGIDs is discouraged due to a number of factors. Treatment with benzodiazepines may be associated with the development of tolerance, physical dependence, abuse, sedation, cognitive impairment, and, in particular, inability to discontinue benzodiazepines when their use is no longer clinically indicated.
Buspirone: is a partial 5-HT1A receptor agonist that is efficacious in general anxiety disorder, but efficacy in FGIDs needs to be studied.
Starting psychotropic drugs for FGIDs at a low dosage may help reduce exacerbation of preexisting gastrointestinal and other symptoms. Achieving full remission is not a reasonable goal for the initial 6- to 8-week treatment and may require 4–6 months or even longer. For some patients, the use of concomitant benzodiazepines for anxiety control may help with compliance and allow more optimal control of symptoms.
In summary, the presence of clinically significant psychiatric symptoms in patients with FGIDs is an indication for psychotropic agents, especially when stress reactivity is observed. Enthusiasm for newer antidepressants for FGIDs is based on their broad efficacy in the psychiatric conditions and potential efficacy on core IBS symptoms. Confirmation of existing practice with randomized controlled trials is still needed.

Twelve Steps to Enhance the Therapeutic Relationship

1-Improve patient satisfaction and engage with the patient.
2. Obtain the history through a nondirective, nonjudgmental, patient-centered interview.
3. Determine the immediate reason for the patient's visit (eg, What led you to see me at this time?) and evaluate the patient's verbal and nonverbal communication.
4. Conduct a careful physical examination and costefficient investigation. A well-conducted physical examination has therapeutic value.
5. Determine what the patient understands of the illness and his or her concerns (eg, What do you think is causing your symptoms? or What concerns or worries do you have about your condition?).
6. Elicit the patient's understanding of the symptoms (illness schema) and provide a thorough explanation of the disorder that takes into consideration the patient's beliefs.

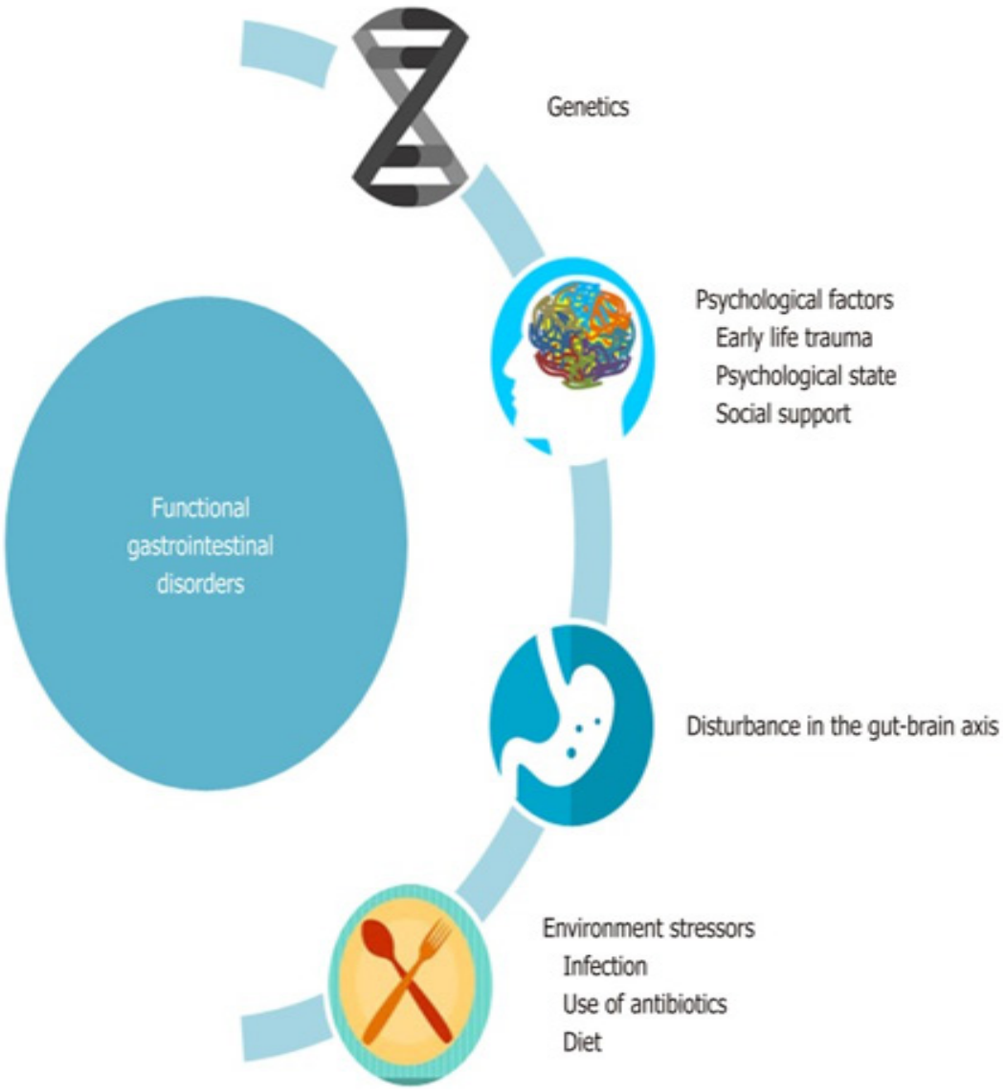
7. Identify and respond realistically to the patient's expectations for improvement (eg, How do you feel I can be helpful to you?).
8. When possible, provide a link between stressors and symptoms that are consistent with the patient's beliefs.
9. Set consistent limits (eg, I appreciate how bad the pain must be, but narcotic medication is not indicated because it can be harmful).
10. Involve the patient in the treatment (eg, Let me suggest some treatments for you to consider).
11. Make recommendations consistent with patient interests.
12. Help establish an ongoing relationship with you or in association with a primary care provider.

In Severe symptoms in patients with FGID:

1-(a)perform diagnostic and therapeutic measures based on objective findings rather than in response to patient demands; (b) set realistic treatment goals, such as improved quality of life rather than complete pain relief or cure; (c) shift the responsibility for treatment to the patient by giving therapeutic options; and (d) change the focus of care from treatment of disease to adjustment to and management of chronic illness.
2-antidepressant treatment. If pain is a dominant feature, tricyclic antidepressants (eg, desipramine, amitriptyline) or the serotonin-norepinephrine reuptake inhibitors (eg, duloxetine, milnacipran) help control pain via central analgesia as well as provide relief of associated depressive symptoms.
3-Functional GI or pain treatment center referral

Biopsychosocial aspects of the functional gastrointestinal disorders

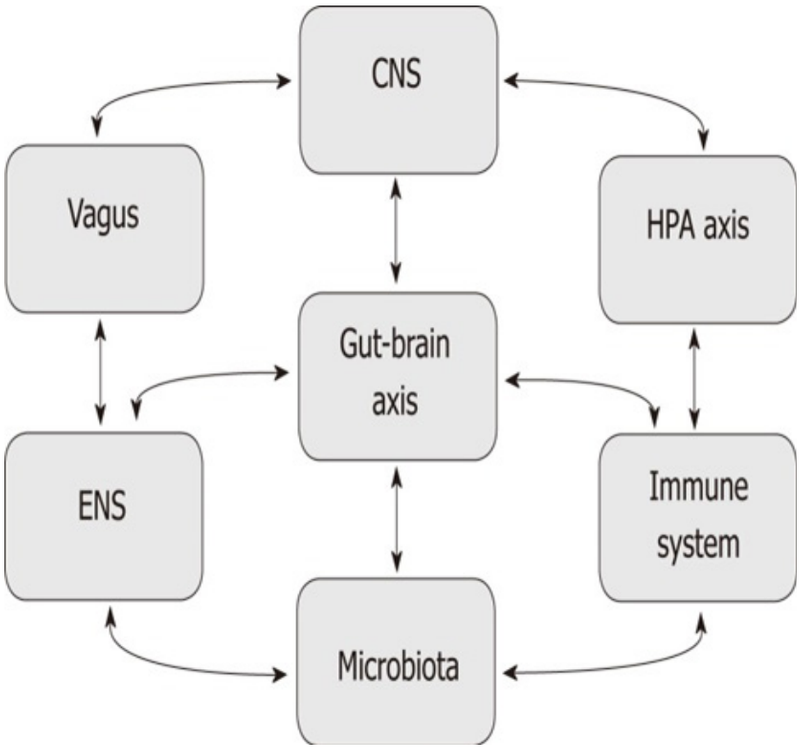
The functional gastrointestinal disorders (FGID) are the most frequent conditions seen in gastroenterology practice and comprise a major portion of primary care. Psychosocial factors are important in these disorders with regard to: (1) their effects on gut physiology; (2) their modulation of the symptom experience; (3) their influence on illness behavior; (4) their impact on outcome; and (5) the choice of the therapeutic approach. This paper provides a review and consensus of the existing literature by gastroenterologists, psychiatrists, psychologists, physiologists, and health services investigators.
Evidence is provided to support the biopsychosocial model as a basis for understanding and treating these disorders, and epidemiological and clinical information on the relations of psychosocial factors to gut physiology, symptom presentation, health behavior, and outcome is offered. Features of motility, personality,
abuse history, health concerns, and treatment-seeking differ between patients with FGID and healthy controls,
but they are not specific to FGID. They occur in other patients with chronic medical conditions and/or psychiatric disorders.
Review of treatment trials indicates clear support for psychotherapeutic treatments, especially in the long term, as well as some evidence for the benefit of antidepressants in FGID, even in the absence of
improvements in mood.



The biopsychosocial model for functional gastrointestinal disorder. The figure illustrates the interaction of psychosocial factors, environmental factors and disturbances in gut-brain axis with functional GI disorders. Early life stress events combined with psychosocial state of an individual determines the symptomatology and quality of life of individuals.

Role of Microbiota-Gut-Brain Axis in FGIDs

The microbiota and central nervous system interact in a bidirectional relationship bridged by the gut-brain axis. This axis is also influenced by Immune system, enteric nervous system, hypothalamic-pituitary axis, and vagus nerve.



CNS: Central nervous system; ENS: Enteric nervous system; HPA: Hypothalamic-pituitary.

Although it has been a widely held belief that human cells are outnumbered by microorganisms by a ratio of 1:10 recent literature shows that the ratio is closer to1:1. This, however, does not diminish the important role of microbiota in our bodies.

The microbiota, living in harmony with the human tissues, has a number of synergistic roles. Although the exact composition of the microbiota may differ among individuals as each individual has their own microbiome signature, its functional role in homeostasis and development is ubiquitous to all humans.

From helping in digestion, to protecting against pathogenic microorganisms, the gut microbiota has played an important role in maintaining immunity and homeostasis. Recently, studies have shown that one of the main inputs to the gut-brain axis comes from microbiota, leading to the coining of the term 'microbiome-gut-brain axis'

This interaction is bidirectional, meaning that the disturbance in the complex community of microbiota (dysbiosis) can affect the brain and vice-versa. The underlying signaling mechanisms for these communicating networks between gut flora and the gut-brain axis have been of special interest to researchers and pharmacists who are seeking potential therapeutic interventions.

The evidence for bidirectional communication comes from studies that have shown that early life stress can alter the composition of gut microbiota, highlighting the role of the brain as an influencer on the gut through the gut-brain axis.

Dysbiosis

Every human has a unique and subject specific community of microorganisms. This fingerprint of microorganisms, which is an ecosystem in homeostasis, develops early in life and may undergo some modifications but by and large, it remains stable throughout life. The modifications may be due to

competition from other microorganisms or pressure from the host.

Microbiota participates in the modulation of intestinal motility, blood flow, secretions, immunity and perception of visceral signals. Other mechanisms that have been suggested include gut distention and alterations in secretion and motility of the GI tract. These changes seem to arise from the production of gas and fatty acids by the bacterial flora influencing the microbiota to host signaling.

Dysbiosis is seen in different GI diseases including celiac disease, IBS and IBD. Although dysbiosis seems to be an important denominator in patients with FGIDs, no specific symbiotic signature has been identified. Dysbiosis could be one of the causes of behavioral traits associated with anxiety disorders.

Neuroimmune interactions in FGIDs

The ENS, also called the 'second brain', is capable of independent functioning without intermediation from the ANS. It consists of an estimated 108 neurons arranged in two ganglionic plexuses. There is a complex interdependent relationship between the gut immune system and the ENS. Physiological functions of the gut such as motility, absorption and secretion are all very sensitive to subtle changes in this fine balance between the immune system and the nervous system. For example, immune activation due to local inflammation can have a diffuse effect on GI motility.

Patients with post-infectious IBS (PI-IBS) have been studied for understanding the role of the immune system in FGIDs. The incidence of PI-IBS is reported between 5% and 32%. The risk of developing PI-IBS increases many times if the presenting illness is predominantly diarrheal and lasts for more than 3 wk. Additionally, hypochondriasis and stressful life event at the initial illness doubles the risk of PI-IBS, providing further evidence for the involvement of the immune system.

Different factors that that modify gut-brain-axis and play a role in the pathophysiology of FGIDs.

Dysbiosis: Disturbance in the complex community of microbiota seems to influence gut-brain axis by modulating neuroendocrine, neuroimmunal and visceral sensory system.

Altered mucosal secretions: Secretion is modulated by complex interaction of intrinsic and extrinsic factors acting on gut mucosa. Dysregulation of the epithelial cells due to autonomic reactivity may lead to 5-HT release contributing to altered secretion.

Disturbance in motility : Products of metabolism of gut bacteria, such as short-chain fatty acids modulate enteric system and influence the rate of gut transit.

Visceral hypersensitivity: Patients with IBS have been found to have an increased concentration of pain-sensing receptors such as TPRV1 (Transient receptor potential vallinoid 1) compared to the controls.

Altered processing of visceral signals: There is increased activation of certain cerebral areas in IBS patients compared to the controls. Altered processing of the visceral pain in the central nervous system has been a recurring theme in many studies.

Immune dysfunction: Patients with prolonged Infectious diarrhea are much more prone to developing IBS. Also, biopsies of patients with IBS have shown increased immune cells in the mucosa.

Psychological disturbances: Patients with FGIDs have co-existing psychosocial symptoms such as stress, anxiety and depression and thus a biopsychosocial model has been proposed for FGIDs.

Early life stress: Early life-stress can alter the composition of gut microbiota.

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