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BASIC SCIENCE

Fundamentals of Neurogastroenterology: Basic Science

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This review examines the fundamentals of neurogastroenterology that may underlie the pathophysiology of functional GI disorders (FGIDs). It was prepared by an invited committee of international experts and represents an abbreviated version of their consensus document that will be published in its entirety in the forthcoming book and online version entitled *Rome IV*. It emphasizes recent advances in our understanding of the enteric nervous system, sensory physiology underlying pain, and stress signaling pathways. There is also a focus on neuroimmune signaling and intestinal barrier function, given the recent evidence implicating the microbiome, diet, and mucosal immune activation in FGIDs. Together, these advances provide a host of exciting new targets to identify and treat FGIDs, and new areas for future research into their pathophysiology.

Keywords: Sensory Physiology; Enteric Nervous System; Neuroimmune Signaling; Mucosal Barrier Function.

In the 8 years since the publication of Rome III there has been rapid expansion in our understanding of the fundamentals of neurogastroenterology. What has fueled this advance is the desire to integrate basic science research with clinical gastroenterology to better diagnose and treat functional gastrointestinal disorders (FGIDs). This research continues to shed light on the complex hierarchy of neural, molecular, and cellular interactions that control gut function. However, what recent research also has shown is the complex interaction between the host gut wall and the luminal microbial environment that is responsible for balancing immune tolerance with protection against pathogenic and antigenic material. Neuroimmune function and the mechanisms that regulate mucosal barrier function, immune surveillance, innate and adaptive immunity, sensory signaling, and central nervous system (CNS) adaptation consequently are the major themes for this review.

The Basis of Brain–Gut Interactions

The GI tract has important barrier and immune functions that interface with the luminal microbiota and protect against potential pathogenic and antigenic material. Integral to these ostensibly conflicting functions is the ability to monitor events in the gut wall and within the gut lumen to orchestrate reflexes that bring about appropriate patterns of motility, secretion, and blood flow to digest and absorb or to dilute and expel. GI sensory mechanisms play a pivotal role in triggering these reflexes by conveying sensory information to the enteric reflex circuits that provide local control and through afferent pathways to the CNS.

Pathways From Gut to Brain

Sensory information is conveyed from the GI tract to the brainstem and spinal cord via vagal and spinal (splanchnic and pelvic) afferents, respectively. Most dorsal root ganglion neurons innervate somatic structures. It is estimated that the proportion of dorsal root ganglion neurons innervating the GI tract range between 3% and ~7%. The dominance of somatic afferent input to the spinal cord and the convergence of visceral and somatic afferents on ascending spinal pathways accounts for the phenomenon of referred pain. In addition, 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.[1] 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.

Subtypes of Visceral Afferents

GI afferent fibers terminate within the gut wall mainly as bare nerve endings and are classified according to their

Abbreviations used in this paper: **CNS, central nervous system; CRF, corticotrophin-releasing factor; DC, dendritic cell; EC, enterochromaffin; ELA, early life adversity; ENS, enteric nervous system; FGID, functional gastrointestinal disorder; HPA, hypothalamic-pituitary-adrenal; 5-HT, 5-hydroxytryptamine; IBS, irritable bowel syndrome; ICC, interstitial cells of Cajal; IEC, intestinal epithelial cells; IEL, intraepithelial lymphocytes; IL, interleukin; ILC, innate lymphoid cells; PAG, periaqueductal gray; PFC, prefrontal cortex; PRR, pattern recognition receptor; SERT, serotonin-selective reuptake transporter; TLR, Toll-like receptor; TRP, transient receptor potential; VIP, vasoactive intestinal polypeptide.**

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terminal distribution as mesenteric, serosal, muscular, ganglionic (intraganglionic laminar endings), or mucosal endings.[2] The location of these endings plays an important role in determining the functional properties of the afferent. Mucosal afferents respond to distortion of the mucosal epithelium and to luminal chemicals. Stretch or distension is effective for stimulating endings in the muscle layers, ganglia, and serosa. These endings express an array of membrane receptors and ion channels that determine neuronal excitability, mechanosensitivity, and modulation by a host of chemical mediators within the GI milieu. 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.

There is a continuous barrage of information projecting from the gut to the CNS. Many afferent endings respond to levels of distension that occur as part of normal digestion and these usually go unperceived. Instead, this information is used in reflexes that control motility, secretion, blood flow, and other aspects of GI function. In contrast, there are other afferents that respond only at high levels of stimulus intensity and function as nociceptors that mediate pain. Some afferents (so-called silent or "sleeping" nociceptors) are mechanically insensitive under normal circumstances but can be awakened in response to inflammation or injury. In patients this process of sensitization can give rise to altered pain perception. In some cases, stimuli that normally are innocuous can cause pain (allodynia), whereas responses that are painful can become exaggerated (hyperalgesia).

Mechanotransduction

Mechanotransduction refers to the process by which stimulus energy is interpreted by sensory nerve endings, leading to the generation of action potentials. There are specific molecular mechanisms that underlie mechanotransduction. Moreover, the excitability of the afferent ending is determined by various voltage-gated and calcium-dependent ion channels[3] that set gain in the system, and that can change according to external influences leading to hypersensitivity.

Sensory endings contain a variety of mechanosensitive ion channels that can convert the stimulus energy into action potentials. They respond to membrane deformation, causing channels to open or close, carrying ionic currents into or out of the nerve terminal to cause depolarization. Three main ion channel families have been identified as mechanosensitive: (1) the DEG/ENaC family that includes the acid-sensing ion channels 1, 2, and 3; (2) the transient-receptor potential (TRP) channel family; and (3) the 2-pore potassium channel family that includes TREK-1 and TRAAK. Different combinations of these channels exist in different populations of vagal, pelvic, and splanchnic afferents, suggesting a complex heterogeneity in sensory signaling.[4]

Another mechanism of mechanotransduction occurs when a secondary sense cell releases mediators that act on ionotropic or metabotropic receptors to stimulate sensory endings. This indirect mechanism relies on close association between afferent endings in the gut wall and various other cell types that are a source of these chemical ligands. These include mast cells, epithelial cells, enteroendocrine cells, macrophages, interstitial cells of Cajal (ICC), and enteric neurons. Considerable attention has been paid to the role of 5-hydroxytryptamine (5-HT) and adenosine triphosphate in sensory signaling, especially in the context of post-inflammatory hypersensitivity.[5]

Luminal Sensing

Some vagal and pelvic afferent endings come into close proximity to the mucosal epithelium, but never penetrate through to the lumen. However, their proximity to the mucosa exposes them to chemicals absorbed across the mucosal epithelium or released from enteroendocrine cells whose apical membrane is exposed to luminal content. This is similar to the relationship seen between taste buds in the mouth and gustatory afferents and as such provides a mechanism by which mucosal afferents can taste luminal contents. This is important for controlling digestive function via reflex effects on motility and secretion. However, nutrient detection also influences metabolic activity and energy intake. The molecular basis for each modality of gustatory taste has been identified. Strikingly, many of these same G-protein–coupled receptors and ion channels are expressed within the GI tract. The cells expressing taste-receptor molecules in the GI mucosa have a characteristic morphology, which is typified by the enterochromaffin (EC) cell.[6] However, EC cells are just one of a diverse family of enteroendocrine cells that are scattered diffusely in the GI mucosa and whose mediators can act in a paracrine fashion on afferent fibers or diffuse into the blood stream for more distant endocrine actions. Each type of enteroendocrine cell has a characteristic distribution along the GI tract. Among the mediators released, cholecystokinin and glucagon-like peptide-1 play important roles in reflex control of GI function and in regulating food intake.

Peripheral Sensitization

Sensory neurons express a large array of receptors that are activated by mediators released from various cellular sources within the gut wall. Neurotrophins, for example, play a role in axon guidance and remodeling of the sensory innervation after inflammation and injury. Their receptors are expressed on different populations of GI sensory neurons. Both nerve growth factor and glial-derived neurotrophic factor are important in the adaptive response to nerve injury and inflammation. Both also are possible mediators underlying chronic pain. Increasing neurotrophin signaling causes increased TRP channel expression (eg, TRPV1 and TRPA1), an increase in sodium channel expression (NaV1.8[7]), and a decrease in potassium channels. Any, or all of these, could contribute to the development of hypersensitivity.[8]

Many other mediators are released during inflammation, injury, and ischemia, from platelets, leukocytes, lymphocytes,