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REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY

Neuroimaging of the Brain-Gut Axis: From Basic Understanding to Treatment of Functional GI Disorders

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We are enthusiastic in the introduction of a new monthly review article series, entitled "Reviews in Basic and Clinical Gastroenterology." Written by authorities in their respective fields, the objective of each review article is to provide an overview of a particular theme or topic for the broad scientific and clinical readership. Within a given topic, both basic and clinical aspects will be covered, accompanied by key figures and relevant references. The reader will also appreciate that topics will be interwoven from month to month as well. We hope you enjoy this section.—David C. Metz, MD, Wafik El-Deiry, MD, PhD, and Anil K. Rustgi, MD

Altered reflex and perceptual responses within the brain-gut axis have emerged as a generally accepted model to explain the cardinal symptoms of functional gastrointestinal (GI) syndromes. The ability to image the living human brain with various neuroimaging modalities has greatly enhanced our ability to study these brain gut interactions in health and disease. Reflex responses within the brain-gut axis, mediated by lamina I and vagal afferents, and efferents of the autonomic nervous system, play a crucial role in the maintenance of homeostasis during physiological perturbations caused by food intake, contractile activity, and metabolic products of the enteric flora. The insular cortex plays an important role in the conscious perception of all sensations arising from the body, while the dorsal anterior cingulate cortex (dACC), with its connection to effector systems, mediates the affective response and motivational drive. The magnitude and gain of these processes is highly influenced by central arousal systems and top-down corticolimbic modulation, mediating the effect of environmental context, emotions, cognitions, and memories on perception and gut function. The majority of neuroimaging studies of the brain gut axis in humans are consistent with the model of parallel processing of afferent information in insula and dACC. Newer hypothesis driven studies, studying the differential contributions of afferent input, central arousal systems, and cortico-limbic pontine interactions have greatly contributed to our understanding of brain gut interactions in health and disease. fMRI–mediated detection of changes in the activity and connectivity of brain regions involved in these different processes by pharmacological and behavioral therapies holds great promise for the development of novel approaches to functional GI disorders.

Glossary

Homeostatic Afferents

The term refers to small-diameter sensory afferent fibers terminating in lamina I of the spinal cord that innervate all of the tissues and organs of the body, including the viscera, skin, muscle, joint, and teeth. All of these fibers signal changes in the physiological condition of the body and provide the essential sensory input that is crucial for the autonomic responses that maintain homeostasis.[1]

Homeostatic Afferent Processing Network

The term refers to a brain network that is consistently activated in response to homeostatic afferent fiber activation. This network includes the insular and dACC, thalamic nuclei (MDvc, VMb, VMpo), and the parabrachial nucleus (PBN). Since non-painful and painful visceral and somatic stimuli, as well as emotional stimuli, can activate this network, the term "pain matrix" commonly used to describe these regions in the literature no longer seems appropriate.

Feelings

Several specific meanings are used for this word in common usage. First, we experience different feelings from our bodies—including satiety, abdominal pain, and discomfort which represent afferent sensory input from receptors and can be regarded as sensations (eg, visceral sensations). Second, we experience feelings associated with our ongoing emotional condition, otherwise known as mood or affective state, such as anxiety, contentment, or irascibility. We include also what we

Abbreviations used in this paper: dACC, dorsal anterior cingulate cortex; DNIC, diffuse noxious inhibitory control; FD, functional dyspepsia; fMRI, functional magnetic resonance imaging; IGLEs, intraganglionic laminar endings; LCC, locus coeruleus complex; MDvc, ventral caudal portion of the medial dorsal nucleus (of the thalamus); NCF, nucleus cuneiformis; NTS, nucleus tractus solitarius; pACC, perigenual cingulate cortex; PAG, periaqueductal gray; PBN, parabrachial nucleus; PET, positron emission tomography; PFC, prefrontal cortex; VMb, basal part of the ventral medial nucleus; VMpo, posterior part of the ventral medial nucleus (of the thalamus).

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regard as homeostatic feelings, such as chilliness, achiness, or burning pain, that represent our physical condition. Third, we experience feelings associated with strong emotions elicited by social or environmental conditions, such as anger, sadness, happiness, and so on, and the evaluation of such conditions. These feelings in particular represent the awareness of our behavioral condition. The subjective experience of all of these types of feelings is completely dependent on self-awareness in humans.[2,3]

Emotion

The term is used to describe a neurobehavioral state adapted for the attainment of a particular goal or the resolution of particular conditions as described by Rolls.[4] It is characterized in humans as a motivation accompanied by a characteristic feeling and autonomic sequelae. Emotional behavior may occur without awareness or without a concomitant feeling, as during unconscious emotional actions, or as in animals that do not display self-awareness. Emotions are viewed as ongoing and continuously varying events.

Homeostatic Emotions

We define these as the motivations and feelings that are associated with changes in the body's physiological condition and with the autonomic responses and behaviors that occur in order to restore an optimal balance.[2] For example, if your body is hypoglycemic, you feel hunger and you are motivated to eat. Homeostatic emotions are the background emotions that affect our energy level, our mood, and our disposition. Spinal and vagal visceral afferent input to the central nervous system plays an important role in the generation of such emotions.

I. Introduction

Bidirectional brain-gut interactions play an important role in the regulation of many vital functions in health and disease. In health, brain-gut interactions play a crucial role in the regulation of digestive processes (including the regulation of food intake and bowel movements), in the modulation of the gut-associated immune system, and in the coordination of the overall physical and emotional state of the organism with digestive processes (reviewed in Mayer and Saper 2000[5]). Altered brain-gut interactions are likely to underlie symptom generation in several functional GI disorders, including irritable bowel syndrome (IBS), functional dyspepsia (FD), non-cardiac chest pain, and cyclical vomiting syndrome. Although less well characterized, alterations in brain-gut interactions may also be involved in the modulation of disease activity in inflammatory bowel disease (reviewed in Mayer 2000[6]) and in the pathophysiology of various eating disorders.[7]

Although the term brain-gut axis provides a general construct to explain how alterations in perception and in the autonomic regulation of the gut contribute to the cardinal symptoms of abdominal pain and discomfort reported by functional GI patients, the concept does not provide a comprehensive framework to understand other characteristic features of these disorders, such as the overlap between different functional GI syndromes,[8] and the overlap between functional GI syndromes with other visceral, somatic, and affective disorders (reviewed in Wesseley et al 1999[9]). A broader framework is also needed to interpret the consistent widespread activations seen in brain imaging studies of visceral pain (in particular insula, dACC, and prefrontal cortex [PFC] regions), regardless of experimental paradigm, as well as in studies using somatic or emotional stimuli. Finally, there is a need for more hypothesis driven experimental designs to deconstruct brain circuits activated by visceral afferent stimuli into afferent processing networks, as well as overlapping networks activated by cognitive, emotional, and arousal components of the experimental setting. Such identification of specific brain circuits is the prerequisite for evaluation of pharmacologic and behavioral therapies using imaging technologies (for details, see part II).

In the current review, we will discuss brain-gut interactions in health and disease based on the concept of homeostatic reflex regulation, the conscious perception of homeostatic responses, and the possible alteration of both processes in functional GI disorders. We will provide an overview of the functional neuroanatomical basis for this concept derived from preclinical research, and we will review published neuroimaging studies performed in humans which are consistent with many of the functional neuroanatomical concepts laid out in the first part of this review. Finally, we will discuss implications of this conceptualization for the development and evaluation of novel therapeutic approaches to functional GI disorders.

The Concept of Homeostatic Emotions

It has traditionally been taught that the gut and the skin differ starkly in their relationship with the brain.[10] This seems intuitively acceptable, because there are major differences: the gut and the skin certainly feel different; we can localize sensations on our skin, but we have difficulty pinpointing sensations from our viscera and generally refer them to somatic dermatomes; we have voluntary control over our limbs, but very little control over our gut. Nevertheless, recent neurobiological evidence suggests that there is a common pattern in the neural connections of all tissues of the body—gut, skin, muscle, joint, teeth, and so on—that is evolutionarily related to the primal need for the brain to maintain the integrity of the entire body. This process is called homeostasis. The pathways for homeostatic control of the body are evolutionarily ancient. Each of the various tissues of the body generates sensory inputs that signify changes in physiological conditions, and the brain integrates these signals to maintain a homeostatic balance of the entire body that optimizes the use of energy for survival.

We humans uniquely experience feelings from each of the tissues of our bodies because evolution has produced brain mechanisms for the conscious perception of an image of the physiological condition of our bodies (ie, "how you feel"). In the healthy person, and in the absence of arousal and attentional focus on a particular feeling (such focus does occur with painful stimulus intensities), these feelings and sensations contribute to background emotions[3] but do not distract from constant cognitive demands on the individual. In contrast, in the functional GI patients, there is an alteration in the attentional, perceptual, and affective response to such feelings from the digestive tract, typified by such expressions as "I feel constipated," "I feel bloated," "I don't feel right." The classical term interoception, formerly used only to refer to visceral sensation, has recently been redefined, based on these new findings, to refer to the sense of the physiological condition of the body. The new neuroanatomical findings indicate that all of the feelings from our bodies reflect its physiological condition and