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EDITORIAL

Gut Inflammation: More Than a Peripheral Annoyance

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More than 15% of the adult population of the Western world suffers from functional gastrointestinal disorders (FGID); in tertiary hospitals in Australia ~20% of referrals are due to FGID. Disease mechanisms involved in FGID include alterations of visceral sensory and gastrointestinal motor function, minimal mucosal inflammation, alterations of the gut microbiome, and altered central processing of visceral afferent neural inputs. In recent years, the Rome Committee has developed and refined symptom-based diagnostic criteria such as functional dyspepsia (FD) and irritable bowel syndrome (IBS) [1]. FD is defined by symptoms referred to the epigastric region and upper gastrointestinal tract with the two principal categories: postprandial distress syndrome (PDS) defined by postprandial fullness and/or early satiation and epigastric pain syndrome (EPS) with epigastric pain or burning. IBS in contrast is defined by symptoms referred to the abdominal cavity such as pain or bloating associated with an alteration of bowel movements. However, FD and IBS occur in the absence of conventionally diagnosed organic disease. In the clinical setting, the majority of patients with severe or very severe symptoms report overlapping FD and IBS symptoms. In both conditions, gastrointestinal hypersensitivity to routine inputs is a central hallmark believed to substantially contribute to symptom manifestations [2]. Subsequently, animal models have been developed to support detailed investigation of altered gastrointestinal viscerosensory function.

Anxiety and depression is diagnosed in up to 75% of FGID patients [3] and may in many cases precede the onset of FGID [4]. Psychiatric comorbidities such as anxiety and depression are likely to amplify the disease burden of FGID and may also contribute to GI disturbances through altered central regulation of GI functions. Since clinical diagnosis of functional GI disorders is simply based on the exclusion of potential organic causes of symptoms combined with adherence to set clinical criteria, disease-modifying comorbidities are not routinely assessed, and treatment decisions are based solely on GI symptoms using a trial-and-error approach. A better understanding of how sensitization within the gastrointestinal viscerosensory afferent system interacts with psychiatric symptoms and acute inflammatory challenges to the GI tract is urgently needed.

In this issue of *Digestive Diseases and Sciences*, Winston et al. [5] utilize a preclinical model of neonatal colon inflammation to examine symptoms or functions central to FD, specifically early satiety, discomfort, delayed gastric empting, and anxiety- and depression-like behaviors. This model induces long-term sensitization of GI afferents by inducing acute colonic inflammation at a key period in rat neonatal development [6]. Previously, Winston and Sarna reported that acute neonatal colonic inflammation induces long-term dysregulation of the sympatho-adrenal medullary axis in adult rats [7]. As adults, increased baseline circulating norepinephrine is linked to increased nerve growth factor expression in the gastric fundus and increased brain-derived neurotrophic factor in cells of the thoracic dorsal root ganglia. Importantly, these cells were

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specifically identified via retrograde CTB-488 labeling as being gastrointestinal afferents. Each of these features represents an alteration in the viscerosensory system underlying normal gastrointestinal interoception, and each potentially correlates with gastric hypersensitivity in adult FD-like rats. In previous studies with these rats, gastric hypersensitivity was typically demonstrated by responses to robust gastric or colonic stimuli, for example, balloon distension. Here, these authors convincingly demonstrate gastric hypersensitivity to a considerably more subtle and plausibly naturalistic stimuli, ad libitum consumption of a liquid nutrient meal after an overnight fast. Importantly, unlike balloon distension that primarily activates sympathetic (spinal) gastrointestinal afferents, a normal meal significantly activates spinal and vagal gastrointestinal afferents, providing high construct validity for investigating postprandial distress. More importantly, with this animal model of postprandial distress Winston et al. [5] demonstrated early satiety characteristic of postprandial distress, reduced gastric emptying, and behavior consistent with discomfort and anxiety and depression.

The integration of afferent information with conscious cognitive and emotional processing is an area of growing scientific interest. Motivational urge and subjective experience are closely tied to afferent information reflecting the current physiological state of the body [8]. Both interoception and nociception are important components of this system, alerting the organism to injury, illness, and infection in order to promote avoidance of current, anticipated, or remembered noxious stimuli. Interoceptive influences on behavior range from consciously experienced physiological drives such as hunger or nausea to less pronounced motivational urges which may subtly interact with and color subjective experience. Central to interoceptive influences on behavior are responses within the limbic nuclei such as the anterior cingulate and amygdala, which flag stimuli with autonomic salience. The paraventricular nucleus of the hypothalamus is a major organizer of patterned autonomic responses, which when combined with the dorsal vagal complex encompasses the primary projection site for peripheral vagal afferents. Human neuroimaging studies of functional dyspepsia have implicated alterations in the viscerosensory interoceptive network. As an example, experimental studies have investigated the reorganization of resting functional networks and the functional responses to gastrointestinal afferent information, typically evoked via balloon distension. Furthermore, neuroimaging experiments have examined structural brain differences in people with functional dyspepsia, including localized changes in the volume of gray and/or white matter, and altered microstructural organization, typically of white matter axonal tracts via diffusion-weighted magnetic resonance imaging (MRI). Together, these studies have identified alterations within principal nodes of the viscerosensory interoceptive network which appear to be altered in patients with functional dyspepsia [9]. These include the primary and secondary somatosensory cortices, which underpin topographic mappings of sensation and nociception, the insula and anterior cingulate cortices sometimes referred to as viscerosensory and visceromotor regions, respectively, the amygdala and hippocampus limbic regions, and diencephalon and brainstem nuclei. Human neuroimaging studies are important in the examination of how sensitization in the gastrointestinal

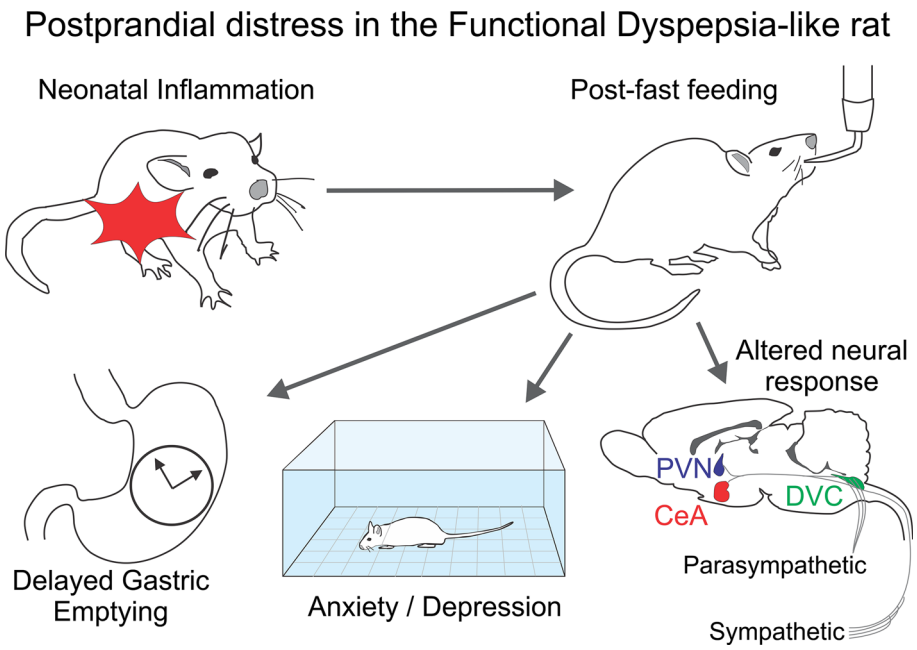

Fig. 1 Schematic representation of the neonatal gastrointestinal inflammation and subsequent alterations of the brain–gut axis

viscerosensory afferent system interacts with psychiatric symptoms. Yet human studies are also often limited in their ability to examine alterations within this network at a cellular level. The findings reported by Winston et al. [5] are of importance in that they clearly demonstrate symptoms associated with alterations in CNS responses. Neonatally sensitized rats, which were fed to satiety after fasting, displayed delayed gastric emptying and behaviors consistent with anxiety and depression. These rats also demonstrated postprandial activation of the central nucleus of the amygdala (CeA), dorsal vagal complex (DVC), and the periventricular nucleus (PVN). The control group of neonatally sensitized rats, which were fed to satiety but not fasted prior, did not show postprandial cFOS activation in either the CeA, DVC, or PVN. Thus, acute neonatal colonic inflammation initiated long-term gastric hypersensitivity, which when challenged by ad libitum feeding after a fast was associated with the hallmark features of postprandial distress: early satiety, delayed gastric emptying, activation of the central viscerosensory interoceptive networks, and behavioral changes consistent with psychiatric comorbidities. These findings fit very nicely into the concept that gut inflammation does not only alter gut function and cause symptoms, but also has a sustained effect on the central processing of afferents and the manifestation of behavioral patterns consistent with psychiatric disorders such as anxiety or depression (Fig. 1). In this context, emerging information in relation to the gut microbiome becomes relevant. Bacteria colonizing the gut mucosa can alter mucosal inflammation and sensory function and can impair quality of life [10]. On the basis of these and similar data, unraveling the mechanisms that cause functional gastrointestinal disorders and developing the therapies that will specifically target the underlying pathological mechanisms appears to be closer to fruition. The work done by Winston and colleagues nicely complements related clinical and translational research that promises to revolutionize the field. There is an urgent need to revisit current categorizations of functional gastrointestinal disorders. We need to move away from the still poorly validated symptom-based categorization of functional gastrointestinal disorders to a categorization that is based upon the underlying pathophysiologies and takes into consideration co-morbidities such as anxiety and depression which may point towards inflammation-mediated disturbances of the brain-gut axis.

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