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Editorial

Interactions of Little-brain and Big-brain in explaining abdominal symptoms.

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For a long time, the role of an extensive neurological network in the gut (the little-brain) has been under-recognized because the enteric nervous system (ENS) is thought to have little impact beyond digestion. More recently, there has been a paradigm shift in understanding interactions between the gut and brain, i.e., the gut-brain axis, especially in clinical disorders termed functional gastrointestinal disorders (FGIDs). In a global epidemiology study commissioned by the Rome Foundation, among 70,000 adults, at least one FGID was diagnosed in 40.3% of internet surveys and 20.7% of household survey[1]. FGIDs are perhaps the second most common consults in gastroenterology practice in Asia (the first being chronic liver disorders largely due to a high burden of viral hepatitis). These disorders include functional dyspepsia (FD) and irritable bowel syndrome (IBS). During the recent fourth iteration of the Rome diagnostic criteria, FGIDs have been relabeled as disorders of gut-brain interactions (DGBIs)[2].

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There are many possible mechanisms that underlie FGIDs, but peripheral and central sensitization (hypersensitivity) are probably the most recognised[3]. With peripheral sensitization, inflammatory mediators activate and modulate the abundance of mucosal receptors in the gut, including TRPV1, TRPA1, and NAV1.8, which results in allodynia, i.e., stimuli that normally are physiological cause pain or hyperalgesia, i.e., responses that are painful become exaggerated. With central sensitization, underlying psychological or cognitive dysfunction would modify the central expression of genes, receptors, or mediators (central neuroplasticity) and resulted in abnormal signaling downstream in the spinal cord, especially through decreased modulation of the descending inhibitory pathway. Due to the above-mentioned neuroplastic changes in the gut-brain axis, symptoms in FGIDs are sometimes refractory, persistent, and difficult to treat. Such types of patients may benefit from neuromodulators that allow neurogenesis to occur, and the more receptors (e.g., acetylcholine, dopamine, serotonin, and norepinephrine) a neuromodulator can act on, the efficacy is better (e.g., amitriptyline), but the adverse events may be more too[4].

It is equally important to understand the factors that trigger the neuroplastic changes in the gut-brain axis. These factors would be food antigens and gut microbiota. There is a growing interest in gut microbiota, which interact closely with the immune system beneath the gut barrier and the gut-brain axis. The growing interest in gut microbiota results from vast improvement in the technology of molecular sequencing, allowing detailed profiling of the composition and abundance of micro-organisms that exist in the gut[5]. Beneficial microbiota, including the more commonly known lactobacilli and bifidobacterium, produce small anti-inflammatory chain fatty acids (SCFAs) (e.g., butyrate) that can protect the gut against the more harmful bacteria, including Clostridium difficile and others. These beneficial microbes may be harmed through the

indiscriminate prescription of antibiotics[6]. Recent research on the COVID-19 pandemic also indicates harm in the balance of good vs. bad bacteria, and the use of proton-pump inhibitor might have tipped the balance by allowing COVID-19 to bypass the acidic environment of the stomach[7].

Food antigen is the other triggering factor, and the FODMAPs are probably the most studied in IBS. FODMAPs is the acronym for fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; essentially, these are short-chain carbohydrates commonly found in certain fruits and vegetables that are not easily digested or absorbed by the gut[8]. As these sugars are readily fermented by the bacteria, the produced gas would stretch the large bowel resulting in symptoms (e.g., bloating), especially in hypersensitive IBS. A low FODMAPs diet has been shown in clinical trials to benefit IBS[9].

The bigger picture will be the role of environmental factors being a trigger of gut-brain axis dysfunction. One such factor is climate change. In the 21st century, climate change is becoming the biggest global public health threat due to high concentrations of greenhouse gases as a result of global warming above 1ºC[10]. Large, unpredictable floods are among the manifestations of climate change. We have reported that new-onset FGIDs are not unsurprisingly common after a major flood, and a possible reason is that environmentally derived pathobionts have expanded in the bowels of flood victims due to poor water sanitation and hygiene practices[11]. In addition, we have reported a beneficial effect of a probiotic in improving the mental health of flood victims with IBS that developed following a major flood disaster[12].

The gut-brain axis is also influenced by systemic conditions such as diabetes mellitus, Parkinson's disease, paraneoplastic syndrome, endocrinopathies, connective tissue diseases, and infiltrative diseases. The mechanism and pathways of interactions in systemic conditions can be rather complex or unclear but may be fibroinflammatory with altered motility and disturbed neuro-hormonal-immune regulation of the gut-brain axis[13]. Treatment is symptom-based; however, early control at the active stage may improve and reduce disease progression.

As a conclusion, first, abnormal neuroplasticity of the gut-brain axis may explain abdominal symptoms. Second, gut microbiota and food antigens are important triggers, and more recently, climate change too. Third, understanding the mechanism of dysfunction of the gut-brain axis will allow targeted therapy.

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