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Editorial

Irritable Bowel Syndrome: Is It Really a Functional Disorder? A New Perspective on Alteration of Enteric Nervous System

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Article: Changes in enteric neurons of small intestine in a rat model of irritable bowel syndrome with diarrhea
Li S, Fei G, Fang X, et al
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In recent decades, we have regarded irritable bowel syndrome (IBS) as a functional disorder which means symptoms of IBS are not explained by identifiable structural or biochemical abnormalities.[1] Under the premise that the symptom of IBS originated from disturbance of function, multi-factorial etiologies have been suggested, including abnormal motility, visceral hypersensitivity, genetic predisposition, and psycho-social influences. Of these, the role of the central nervous system in terms of brain-gut interaction has been considered as an important factor for abnormal motility and visceral hypersensitivity, and has been intensively studied. For example, the corticotrophin-releasing factor, a key modulator of stress response in the brain, has been extensively investigated and the present role in the gastrointestinal tract such as decreasing gastric emptying, increasing colonic motility, and inducing visceral hypersensitivity are established.[2-4] Psychological comorbidities such as depression and anxiety are also more prevalent in patients with IBS compared to healthy controls and is thought to play an important role in IBS.[1]

However, latest medical and scientific developments have led to further investigation of organic changes in patients with IBS such as inflammatory cell infiltration, increased permeability, and changes in neuroendocrine system in the gut.[5,6] The enteric nervous system (ENS) is one of the candidates for a possible organic cause of underlying IBS pathophysiology. The ENS regulates muscular, neuro-hormonal, and secretory systems of the gastrointestinal tract to generate functionally effective patterns of various digestive states.[7] The ENS can be divided into 2 major regions, the submucosal plexus (SMP) and the myenteric plexus (MP). The SMP controls absorptive and secretory functions of the mucosal epithelium, intramural blood flow, and neuroimmune interactions, while the MP regulates intestinal motility for specific digestive states.[7]

In this issue of the *Journal of Neurogastroenterology and Motility*, Li et al[8] nicely and diligently described changes in the ENS using a diarrhea dominant IBS (IBS-D) rat model induced by heterotypic chronic and acute stress (CAS). Rats exposed to CAS exhibited accelerated intestinal transit, increased number of secretomotor neurons such as choline acetyltransferase (ChAT), vasoactive intestinal peptide (VIP)—immunoreactive neurons in SMP, and

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decreased inhibitory musculomotor neurons such as nitric oxide synthase (NOS)-immunoreactive neurons in MP. The previous study from the authors on the CAS rats had shown that changes secreto- and musculomotor neurons were not limited to the small intestine but to the colon as well.[9] Altogether, the increase of ChAT and VIP neurons in the intestinal SMP of rats could promote intestinal secretion leading to secretory diarrhea in the IBS-D rat model.

Nitric oxide is an inhibitory transmitter released by enteric inhibitory musculomotor neurons.[10] In rats exposed to CAS in this study, NOS positive neurons in the MP were decreased while the number of cholinergic neurons was unchanged. In other words, attenuated inhibitory capacity in musculomotor neurons may be responsible for the enhanced propulsive motility found in CAS model of IBS-D.

This study suggested some possibility of structural change in the ENS as an underlying pathophysiology in stress related IBS-D symptoms. However, we have to be cautious before translating this finding into human IBS.

First, because it is difficult to obtain full-thickness biopsy specimens, scientifically reliable evidence of the changes in ENS in human IBS patient has been hard to come by these days. Early in this century, a study with laparoscopic full-thickness jejunal biopsies from 10 IBS patients reported low grade peri- and intra-ganglionic lymphocyte infiltration and neuronal degeneration in the MP, while the SMP was rarely affected.[11] However, patients in this study were recruited from a tertiary referral center and had very severe symptoms. In addition, mast cells infiltration, which is a well known pathophysiology of IBS, was not found in these patients. Therefore, these findings could not be representative for all IBS patients. Some authors suggest that the presence of anti-enteric neuronal antibodies in IBS patients indicate some form of an autoimmune degenerative neuropathy in the ENS.[12] However, a relatively high percentage of anti-enteric neuronal antibodies in the normal population also suggests that it may be a consequence of complex intestinal pathophysiology, rather than the cause of it.

Second, we should consider the difference between human and animal models because the evidence regarding ENS abnormalities in IBS usually came from animal studies. Although the authors did not state the exact age of the rats in this study, the weight 160-180 g is roughly equivalent to 6-7 weeks old. In rats, young adulthood begins from postnatal 70 days.[13] So the rats used in this study were in the relatively adolescent period, and 10.5 days of rat age in this stage is equivalent to 1 human year. If we roughly translate the experimental condition of this study to human life, it would be a teenager who has been exposed to severe, unpredictable and chronic stress (such as water and food deprivation, experience of physical pain, exposure to hot weather, swimming in cold water, and inversion of day and night) for several years until early adulthood. Therefore, the experimental condition in this study represents only very specific situation of human life, and the results of this study cannot be considered for all patients with IBS.

However, few human and several animal studies undoubtedly points to the possibility of disturbance of ENS in some portion of patients with IBS, so efforts to explore the changes in the ENS in patients with IBS should be continued. As a practical matter, it would be helpful to see if CAS rats could recover from neuronal alterations caused by stress after a certain period of "relaxing" time, since we would like to believe that ENS, like other complex nervous systems, could have restoring or adaptive plasticity over outside stimuli and stress.

In conclusion, we should strongly deliberate if we can really expand these findings to human IBS intestinal physiology and pathophysiology for the reasons mentioned above. Does increase or decrease in immune reactive secretomotor neurons or musculomotor neurons can really account for actual alterations in intestinal secretions or muscular contractions? And if so, are they reversible or redeemable with specific target drugs in which we hope to use for the treatment of IBS? The question still remains to be answered desperately, while we struggle to manage IBS patients in our daily practice.

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