Sharpening the Focus: Acupuncture Interrupts the Brain–Gut Vicious Cycle Underlying Functional Dyspepsia

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Functional dyspepsia (FD), characterized by recurrent or chronic epigastric symptoms including early satiety, postprandial fullness, epigastric pain, and epigastric burning in the absence of apparent organic disease, is considered to be related etiopathologically to gastric motor dysfunction [1]. The Rome IV consensus recommended that the diagnosis of FD should fulfill the following criteria: (1) history of symptoms at least 3-days/week over the last 3 months of early satiety and postprandial fullness, of severity sufficient to interfere with routine daily activities, and (2) at least a 6-month history of epigastric pain or burning occurring 1 day per week [1]. Approximately 10% of the adult population have chronic symptoms that match the above diagnostic criteria according to an Internet-based cross-sectional health survey in the USA, Canada, and the UK [2].

FD is a major clinical challenge with regard to both diagnosis and management. It is a multifactorial and complex disease with treatment based primarily on poorly understood pathogenetic mechanisms and empirical pharmacological treatment [3]. In many guidelines, eradication of *Helicobacter pylori* is the first-line treatment for infection-positive patients [3]. With regard to patients negative for *H. pylori*, antisecretory drugs such as proton pump inhibitors (PPIs) are considered the first-line treatment option, followed by the use of psychotropic agents and prokinetics [3]. When conventional treatment is not satisfactory, refractory symptoms can be managed with acupuncture [1]. Acupuncture has been used as an alternative and supplementary treatment in China, Japan, and other East Asian countries for hundreds of years [1]. Currently, acupuncture treatment of FD is increasingly accepted worldwide [1]. This form of treatment can also be used as an add-on therapy, mostly combined with

prokinetic agents or PPIs, depending on the type and severity of FD symptoms [1].

There is a growing interest in the effects and mechanisms of acupuncture or electroacupuncture (EA) on gastrointestinal motility as a safe alternative treatment for FD [1, 3]. The reported symptomatic improvement could be related to acupuncture-induced acceleration of gastric emptying and normalization of the brain–gut interactions [3]. Ma et al. [4] investigated the effect of acupuncture in relieving FD symptoms and improving quality of life in a randomized, double-blind, placebo (sham acupuncture)-controlled protocol, confirming the efficacy of acupuncture conducted on traditional acupoints in the treatment of FD. Nevertheless, the majority of such clinical studies did not accurately evaluate the effectiveness of acupuncture due to methodologic shortcomings, such as problems related to the open-label study designs, and the inclusion of small population samples, thus calling for more rigorous clinical studies [1]. Although many animal models of FD have improved gastrointestinal motility following acupuncture or EA treatment, the reason(s) by which these treatments are effective have not been adequately addressed.

The pathophysiological features of FD include: (1) delayed gastric emptying, (2) impaired gastric fundic accommodation, (3) visceral hypersensitivity, and (4) psychological distress including anxiety and depression [5]. Animal experimental models, in which these four mechanisms can be modulated, have been extensively used to determine the pathological mechanisms of FD and to facilitate the development of new therapies [5]. In the Rome IV consensus, FD is defined as a disorder of the gut–brain interaction with contributions of altered brain processing and luminal alterations, including microbial dysbiosis [6]. A systematic review of functional neuroimaging studies in FD documented reproducible anomalies in several brain regions, including the frontal and somatosensory cortex [6]. Abnormal efferent modulation from the brain to the gut and overactive visceral sensory afferent signaling from the gut to the brain are

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both involved in the pathophysiology of FD. Furthermore, these pathways can also be activated or modulated through psychological factors and the stress response involving the hypothalamic–pituitary–adrenal axis [6]. Based on this background, it seems that the stress stimulation model, such as a chronic restraint stress model, is suitable for simulating and studying the pathological mechanisms of FD. Interventions directed toward modifying brain–gut interaction should be tested in the stress stimulation model in order to identify a therapeutic target for FD. Recently, activation of the classical renin–angiotensin system in the intestine has been reported in a chronic restraint animal model, which evoked low-grade inflammation with accumulation of reactive oxygen species and production of pro-inflammatory cytokines, altering tryptophan metabolism with decreased expression of the intestinal amino acid transporter, ACE2/B⁰AT-1, and altered microbial composition [7]. Interestingly, administration of an angiotensin receptor blocker suppressed the stress-induced low-grade inflammation in the intestine and improved brain serotonin synthesis [7]. These results suggest that stress-induced low-grade intestinal inflammation can modulate the brain areas involved in depression and anxiety. Furthermore, since impaired duodenal mucosal integrity and low-grade inflammation are associated with altered neuronal signaling and systemic immune activation, it is likely that these changes can ultimately lead to dyspeptic symptoms [6]. Duodenal low-grade mucosal inflammation and increased numbers of small intestinal homing T cells (as markers of intestinal inflammation) correlate with delayed gastric emptying and the severity of dyspepsia [6]. Conversely, suppression of stress-induced low-grade inflammation of the gastrointestinal tract could probably be a therapeutically useful strategy in that targeting the pro-inflammatory signal pathway in the intestine might break the vicious circle in the gut–brain interaction.

A number of animal studies and a few clinical studies showed that although acupuncture and EA improve gastric and intestinal motility impairments [1, 5], their effects on the brain–gut interaction have not been investigated thoroughly. In this issue of *Digestive Diseases and Sciences*, Tang and colleagues [8] provide important new insight into the effects of EA in stimulating the “Zusanli” acupoint in the rat stress model of FD. In the stress-induced FD model, expression of ghrelin in the brain and gut was downregulated, suppressing ghrelin-related anti-inflammatory signaling [8]. The authors provided convincing evidence that EA treatment improved gastrointestinal function, suppressed stress-induced intestinal mucosal inflammation, and restored ghrelin expression with the effective activation of the AMPK/TSC2/Rheb/mTOR signaling pathway in the hypothalamus, gastric antrum, and intestine [8].

Ghrelin is a 28-amino acid peptide produced and released principally by the stomach, and also in small amounts by

the small intestine and brain, that regulates gastric motility and appetite via mTOR signal activation [9]. The ghrelin gene encodes three molecular forms: acyl ghrelin, desacyl ghrelin, and obestatin [9]. Among these three, acyl ghrelin acts as an endogenous ligand for growth hormone secretagogue receptor and is essential for the maintenance of normal gastrointestinal motility via the brain–gut axis [9]. Acyl ghrelin affects the growth hormone secretagogue receptor in vagal afferent nerve fibers in the stomach, which transmits the signal to the nucleus of the solitary tract (NST). The signal from the NTS is activated by neuropeptide Y neurons projected on the arcuate nucleus of the hypothalamus. This signal is finally transmitted to the dorsal vagal complex via vagal efferent fibers, accelerating gastric motility [9]. Since subnormal ghrelin and acyl ghrelin concentrations were observed particularly in patients with FD, stimulation of ghrelin receptors can be potentially effective in accelerating gastric emptying in patients with FD [1, 8]. Ghrelin and acyl ghrelin reduce stress-induced anxiety [10] and suppress several inflammatory responses [11]. EA-induced ghrelin production improved gastrointestinal motility while suppressing low-grade inflammation via anti-inflammatory ghrelin-AMPK signaling [12]. Thus, acupuncture can restore ghrelin expression in the rat stress model of FD, which in turn suppresses low-grade inflammation in the gastrointestinal tract and improves gastrointestinal motility through the modulation of the brain–gut axis.

Understanding the etiology of FD induced by derangement of the brain–gut interaction is key to facilitating the development of new FD therapies. Clinical and basic studies should provide evidence that acupuncture is an efficient alternative treatment for patients with FD.

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