Effect of electro-acupuncture on substance P, its receptor and corticotropin-releasing hormone in rats with irritable bowel syndrome.

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AIM: To investigate the effect and mechanism of electro-acupuncture (EA) at ST25 and ST37 on irritable bowel syndrome (IBS) of rats.

METHODS: A total of 21 male Sprague-Dawley rats were randomly divided into normal group, model group and EA group. A rat model of IBS was established by constraining the limbs and distending the colorectum of rats. Rats in EA group received bilateral EA at ST25 and ST37 with a sparse and intense waveform at a frequency of 2/50 Hz for 15 min, once a day for 7 d as a course. Rats in normal and model groups were stimulated by distending colorectum (CR). An abdominal withdrawal reflex (AWR) scoring system was used to evaluate improvements in visceral hypersensitivity. Toluidine blue-improved method, immunohistochemistry and radioimmunoassay were used to observe mucosal mast cells (MC), changes of substance P (SP) and substance P receptor (SPR) in colon and change of corticotropin-releasing hormone (CRH) in hypothalamus.

RESULTS: The threshold of visceral sense was significantly lower in model group than in normal group, and significantly higher in EA group than in model group. The number of mucosal MC was greater in model group than in normal group and significantly smaller in EA group than in model group. The CRH level in hypothalamus of rats was significantly higher in model group than in normal group, which was remarkably decreased after electro-acupuncture treatment. The SP and SPR expression in colon of rats in model group was decreased after electro-acupuncture treatment.

CONCLUSION: EA at ST25 and ST37 can decrease the number of mucosal MC and down-regulate the expression of CRH in hypothalamus, and the expression of SP and SPR in colon of rats with IBS.
Regulatory mechanism of electroacupuncture in irritable bowel syndrome: preventing MC activation and decreasing SP VIP secretion.

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The efficacy of electroacupuncture (EA) for treating patients with diarrhea-predominant IBS has been confirmed in the authors' former research, but the regulatory mechanism of EA in IBS is still unknown. The aim of this study was to explore the relationship between the effect of EA on treating IBS rats and the activation and proliferation of mast cell (MC), the secretion of substance P(SP), and vasoactive intestinal polypeptide (VIP). The IBS rat model was set up with stress of binding limbs and colorectal distention. All rats were randomly assigned to four groups (Normal, Model, Tegaserod and EA). Hematoxylin and eosin staining has been used to observe the pathological change in the rats' colonic mucosa and an AWR scoring system has been applied to evaluate improvement of viscer al hypersensitivity in various methods of the different groups. Toluidine blue improved method (TBI) and immunohistochemistry have also been involved in observations of mucous mast cells in the colon, change of c-fos positive cells, and secretion of SP, SPR, VIP, VIPR in the local colon. Firstly, the threshold of visceral sensitivity in the rats model with IBS was remarkably reduced (P < 0.01). The MC count in colonic mucosa and c-fos positive cells count increased significantly (P < 0.01) with positive correlation within each. Secondly, EA on ST-25 and Tegaserod pouring into the stomach can inhibit the proliferation and activation of MC in the colon and regulate secretion of SP, SPR, VIP, VIPR (P < 0.01, P < 0.05), while the effect of EA is obviously superior to Tegaserod. We concluded, firstly, that the abnormal proliferation and activation of mucous mast cells in the colon, and oversecretion of neuropeptides such as SP, VIP and their receptors could be one of key mechanisms of etiology of IBS. Secondly, the inhibition of activation and proliferation and the secretion of SP, VIP could be major effects of EA when treating rats with IBS.

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Physiology and pathophysiology of the 5-HT3 receptor.

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The 5-HT3 receptor is a ligand-gated cation channel located in the central and peripheral nervous system; it has also been detected on a variety of other cells.

In the periphery, it is found on autonomic neurons and on neurons of the sensory and enteric nervous system. In the CNS, the 5-HT3 receptor has been localized in the area postrema, nucleus tractus solitarii, nucleus vaudatus, nucleus accumbens, amygdala, hippocampus, entorhinal, frontal, cingulate cortex, and in the dorsal horn ganglia. Further extraneuronal locations include among others lymphocytes, monocytes, and foetal tissue. 5-HT3 receptors modulate the release of neurotransmitters and neuropeptides like dopamine, cholecystokinin, acetylcholine, GABA, substance P, and serotonin itself. They have been demonstrated to be involved in sensory transmission, regulation of autonomic functions, integration of the vomiting reflex, pain processing and control of anxiety. While the physiologic functions of the 5-HT3 receptor are discrete and difficult to detect, it plays a key role in certain pathologic situations related to increased serotonin release. Clinical development of 5-HT3 receptor antagonists revealed a remarkable range of activities. 5-HT3 receptor antagonists do not modify any aspect of normal behaviour in animals or induce pronounced changes of physiological functions in healthy subjects. Clinical efficacy was shown for various forms of emesis like chemotherapy-induced, radiotherapy-induced, and postoperative emesis, diarrhoea-predominant irritable bowel syndrome, anxiety, chronic fatigue syndrome, alcohol abuse, and in pain syndromes such as fibromyalgia and migraine. Most recent data also suggest that 5-HT3 receptor antagonists are effective for the treatment of other rheumatic diseases such as rheumatoid arthritis, tendinopathies, periarthropathies, and myofascial pain. Other possible indications under discussion are chronic heart pain and bulimia. Unfortunately, experimental findings do not yet provide a homogenous conception of the significance of 5-HT3 receptors in all investigated fields; in nociception, for example, contradictory observations are still inadequately explained and complicated by bell-shaped dose-response curves. Further elucidation and better understanding of the serotonergic neuronal network remains a task for the next decade.

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OBJECTIVE: To investigate the changes of the mast cells (MCs) and substance P (SP), and to elucidate their possible roles in visceral hypersensitivity in patients with irritable bowel syndrome (IBS).

METHODS: In 22 diarrhea-predominant IBS, 20 constipation-predominant IBS and 19 controls, the biopsies were carried out from the terminal ileum, the ileocecal junction, the ascending colon, and the sigmoid colon. The MCs and the SP-ergic nerve terminals, SP receptor (SPR) cells were stained by histochemistry and immunohistochemistry respectively, and the results were investigated qualitatively and quantitatively by color image analyzer. The biopsies of the ICJ and the sigmoid colon were measured by radioimmunoassay. The structure relation between the MCs and SP-ergic terminals, SPR-ergic cells were studied through an ultramicroscopy using in situ embedding technique and a light microscopic study in serial sections respectively.

RESULTS: The number of MCs in the terminal ileum, the ileocecal junction, and the ascending colon were significantly elevated in IBS patients (P < 0.01), and the MCs in IBS have great variations. Significantly increased the SP-ergic nerve terminals were found in patients with IBS of intestine compared with the control. The correlation between mucosal MC and the SP-ergic nerve terminals was found, and MCs were close to these terminals in lamina propria, which were demonstrated SP-ergic nerve terminals. Some MCs were demonstrated to be SPR-positive cells.

CONCLUSIONS: The MCs and SP of intestinal mucosa may play a central role in the gut hypersensitivity in both motor response and visceral perception in IBS.

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Involvement of tachykinins in intestinal inflammation.

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The tachykinins, substance P, neurokinin A and neurokinin B are small peptides expressed in the extrinsic primary afferent nerve fibers and enteric neurons of the gut. Tachykinins exert a variety of biological actions mediated by three distinct receptors, termed NK1, NK2 and NK3, and at the gastrointestinal level these peptides influence motility, electrolyte and fluid secretion and tissue homeostasis. Several intestinal disorders are associated with changes in the expression of the tachykinin system. Thanks to biological studies and receptor cloning, new selective tachykinins antagonists are now available and have been shown to be active in experimental gut disorders. Some of them are now under clinical trial in inflammatory bowel diseases and the irritable bowel syndrome. The body of preclinical data so far available seems to indicate that tachykinin antagonists might be a new therapeutic tool in the treatment of gut disorders.

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Tachykinins: receptor to effector.

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Tachykinins belong to an evolutionarily conserved family of peptide neurotransmitters. The mammalian tachykinins include substance P, neurokinin A and neurokinin B, which exert their effects by binding to specific receptors. These tachykinin receptors are divided into three types, designated NK1, NK2 and NK3, respectively. Tachykinin receptors have been cloned and contain seven segments spanning the cell membrane, indicating their inclusion in the G-protein-linked receptor family. The continued development of selective agonists and antagonists for each receptor has helped elucidate roles for these mediators, ranging from effects in the central nervous system to the perpetuation of the inflammatory response in the periphery. Various selective ligands have shown both inter- and intraspecies differences in binding potencies, indicating distinct binding sites in the tachykinin receptor. The interaction of tachykinin with its
receptor activates Gq, which in turn activates phospholipase C to break down phosphatidylinositol bisphosphate into inositol trisphosphate (IP3) and diacylglycerol (DAG). IP3 acts on specific receptors in the sarcoplasmic reticulum to release intracellular stores of Ca2+, while DAG acts via protein kinase C to open L-type calcium channels in the plasma membrane. The rise in intracellular [Ca2+] induces the tissue response. With an array of actions as diverse as that seen with tachykinins, there is scope for numerous therapeutic possibilities. With the development of potent, selective non-peptide antagonists, there could be potential benefits in the treatment of a variety of clinical conditions, including chronic pain, Parkinson's disease, Alzheimer's disease, depression, rheumatoid arthritis, irritable bowel syndrome and asthma.

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Plasma substance P in the irritable bowel syndrome.
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