Stress-induced GI motility disorders

Stress is one of the most important contributing factors in the pathogenesis of functional GI disorders. Patients with serious stress frequently complain of GI symptoms and these symptoms are, at least in part, due to GI motility disorders. Restraint stress delays solid gastric emptying in rats. The inhibitory effect of restraint stress on gastric emptying is mediated via central corticotropin releasing factor (CRF), CRF₂ receptors and peripheral sympathetic neurons. Restraint stress augments postprandial gastric motility and impairs the coordination between the antrum and pylorus in rats.

In contrast to gastric emptying, restrain stress accelerates colonic transit in rats. The stimulatory effect of restraint stress on colonic transit is mediated via central CRF₁ receptors, peripheral parasympathetic neurons and 5-HT₃ receptors.

Anti-stress effect of central oxytocin

Functional GI disorders are common in the general population and stress is widely believed to play a major role in the development of functional GI disorders. Patients with serious stress frequently complain of GI symptoms and these symptoms are, at least in part, due to GI motility disorders. In modern society, individuals encounter various types of physical, mental and social stress on a daily basis. GI symptoms may develop when we fail to adapt to various stressors of our daily life (chronic stress).

A growing body of evidence suggests that stress stimuli, both acute and chronic, import different physiological mechanisms and neuroendocrine responses. Oxytocin is mainly synthesized in the paraventricular nucleus (PVN) and supraoptic nucleus (SON) of the hypothalamus. Central oxytocin has an anxiolytic effect and attenuates the hypothalamic–pituitary–adrenal (HPA) axis in response to stress. Anti-stress effect of oxytocin is due to its inhibitory effect on CRF mRNA expression at the PVN. The inhibitory effect of oxytocin on CRF mRNA expression is mediated via GABA receptors.

Repeated experience with the same stressor produces habituation, or diminution of behavioral responses and HPA axis responses. We have recently demonstrated that GI dysmotility (delayed gastric emptying and accelerated colonic transit) observed in acute restraint stress was completely restored to normal following repeated stress loading for 5 consecutive days (chronic homotypic stress) in rats and mice. Restored gastric emptying and colonic transit following chronic homotypic stress was antagonized by icv-injection of oxytocin antagonists. Increased oxytocin mRNA expression and reduced CRF mRNA expression at the PVN were observed following chronic homotypic stress.

To further study the involvement of oxytocin in mediating the adaptation mechanism following chronic homotypic stress, we utilized oxytocin knockout (KO) mice. We showed that oxytocin KO mice failed to restore gastric emptying and colonic transit following chronic homotypic stress. These suggest that central oxytocin is involved in mediating the adaptation mechanism in response to chronic homotypic stress in rodents.

In contrast to chronic homotypic stress, delayed gastric emptying and accelerated colonic transit were still observed, when rats received different types of stress (chronic heterotypic stress) for 7 days. Increased CRF expression and reduced OXT expression at the PVN were observed following chronic heterotypic stress.

The social interaction of daily life as well as a positive environment continuously activates the system of oxytocin release in both males and females. We have recently shown that social buffering (paired housing) restored delayed gastric emptying following chronic heterotypic stress.

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stress in rats. We also showed that paired housing decreased CRF mRNA and increased oxytocin mRNA expression at the PVN following chronic heterotypic stress in rats.

Exposure to early life stress causes increased stress responsiveness and permanent changes in central nervous system. Once neonatal rats receive maternal separation (MS), the rats failed to adapt to chronic homotypic stress. The mechanism of the impaired adaptation involves down-regulation of OXT and up-regulation of CRF in the hypothalamus in MS rats. It is highly likely that lack of physical and emotional contact between young pups and their mothers attenuates gene expression of OXT. Our study will provide the scientific benefit of social attachment to overcome our daily life stress.

Epidemiological studies suggest considerable overlap between FD and IBS. About half of the FD patients fulfill the Rome II criteria for IBS. We propose that the restoration of gastric and colonic dysmotility in both chronic homotypic and heterotypic stress occurs through the mechanisms of upregulation of oxytocin and attenuation of CRF expression. Our study will contribute to a better understanding of the mechanism and treatment of functional GI disorders, both of FD and IBS, associated with stress.

論文報告


講義

1. 鹿児島大学 Stress and GI motility “Invited lecture at Kogoshima University, Kagoshima, Japan” March 16, 2006.


3. 兵庫医科大学 Stress and GI motility “Invited lecture at Hyogo College of Medicine, Nishinomiya, Japan” July 10, 2006.


8. ウィスコンシン医科大学 Stress and GI motility “Invited lecture at Digestive Disease Center, Medical College of Wisconsin, Milwaukee” April 21, 2008.
9. ウィスコンシン医科大学 Effects of acute and chronic stress on gastric motor function “Invited lecture at Dept. of Physiology, Medical College of Wisconsin, Milwaukee” November 18, 2008.
10. 藤田学園大学 Love and oxytocin “Invited lecture at the Dept. of Internal Medicine, Fujita Gakuen University, Nagoya, Japan “ November 12, 2009.
12. 岐阜大学 Oxytocin and love “Invited lecture at Dept. of Veterinary Physiology, Gifu University, Gifu, Japan” April 15, 2011.
13. AMDA 岡山 Physiology of love “Seminar at Association of Medical Doctors of Asia (AMDA), Okayama Japan” July 7, 2011.