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

b. Chronic homotypic stress and OXT
Repeated experience with the same stressor produces habituation, or diminution of behavioral responses and HPA axis responses. GI dysmotility (delayed gastric emptying and accelerated colonic transit) observed in acute restraint stress was completely restored to normal levels 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 OXT antagonists. Increased OXT mRNA expression and reduced CRF mRNA expression at the PVN were observed following chronic homotypic stress.

To further study the involvement of OXT in mediating the adaptation mechanism following chronic homotypic stress, we utilized OXT knockout (KO) mice. We showed that OXT-KO mice failed to restore GI motility following chronic homotypic stress. These suggest that central OXT is involved in mediating the adaptation mechanism in response to chronic homotypic stress.

c. Chronic heterotypic stress and OXT
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.

d. Social interaction and OXT
OXT plays an important role in regulating social behavior and positive social interactions. The social interaction of daily life as well as a positive environment continuously activates OXT system in both males and females. We have recently shown that social buffering (paired housing) restored GI dysmotility following chronic heterotypic stress in rats. We also showed that paired housing decreased CRF mRNA and increased OXT mRNA expression at the PVN following chronic heterotypic stress.

A positive social interaction is bidirectional, involving both giving and receiving empathy/care. It is reasonable that receiving empathy from others may promote OXT expression, resulting in coping with chronic heterotypic stress. In addition, our recent study suggests that giving affiliation towards others upregulates hypothalamic OXT expression, which in turn attenuates
stress responses. We propose that giving compassion toward others is beneficial for well-being of the givers.

d. Early life stress and OXT
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. GI dydmotility (delayed gastric emptying and accelerated colonic transit) was still observed following chronic homotypic stress in MS rats. The mechanism of impaired adaptation involves down-regulation of OXT and up-regulation of CRF in the hypothalamus in MS rats. We showed the possibility that lack of physical and emotional contact with mothers attenuates gene expression of OXT in MS pups.

We studied whether social interaction can improve GI dysmotility and OXT expression in MS rats. After weaning, 3 MS rats were housed together (pure MS). In another group, 1 MS rat was housed with 2 control rats (mixed MS). Pure MS rats demonstrated increased anxiety-like behaviors, which were significantly reduced in mixed MS rats. GI dydmotility observed in pure MS rats were restored in mixed MS rats following chronic homotypic stress. OXT expression was upregulated, while CRF expression was downregulated in mixed MS rats, compared to pure MS rats. Our study may contribute to the treatment strategies for GI motility disorders associated with early 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.

Reference


