Anti-stress effect of central oxytocin on GI motility

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 [58]. Anti-stress effect of oxytocin is due to its inhibitory effect on CRF mRNA expression at the PVN [59]. The inhibitory effect of oxytocin on CRF mRNA expression is mediated via $GABA_A$ receptors [60].

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 is completely restored to normal following repeated stress loading for 5 consecutive days (chronic homotypic stress) in rats [53,61] and mice [62]. Restored gastric emptying and colonic transit following chronic homotypic stress are antagonized by ICV injection of oxytocin antagonists [59,62]. Increased oxytocin mRNA expression and reduced CRF mRNA expression at the PVN are observed following chronic homotypic stress [59,62]. 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 fails to restore gastric emptying and colonic transit following chronic homotypic stress [63,64]. 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 are still observed, when rats receives different types of stress (chronic heterotypic stress) for 7 days [59,65]. Increased CRF expression and reduced oxytocin expression at the PVN were observed following chronic heterotypic stress [59,65].

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) restores delayed gastric emptying following chronic heterotypic stress in rats [66]. Paired housing decreased CRF mRNA and increased oxytocin mRNA expression at the PVN following chronic heterotypic stress in rats [66]. We also showed that affiliative behaviors upregulates hypothalamic oxytocin expression, which in turn attenuates stress responses [67]. 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.

58. Bulbul M, Babygirija R, Ludwig K, Takahashi T. Central oxytocin attenuates augmented gastric postprandial motility induced by restraint stress in rats. Neurosci Lett 2010;479:302-6.
59. Zheng J, Babygirija R, Bulbul M, Cerjak D, Ludwig K, Takahashi T. Hypothalamic oxytocin mediates adaptation mechanism against chronic stress in rats. Am J Physiol Gastrointest Liver Physiol 2010;G946-53.
60. Bulbul M, Babygirija R, Cerjak D, Yoshimoto S, Ludwig K, Takahashi T. Hypothalamic oxytocin attenuates CRF expression via GABA(A) receptors in rats. Brain Res 2011;1387:39-45.
61. Zheng J, Dobner A, Babygirija R, Ludwig K, Takahashi T. Effects of repeated restraint stress on gastric motility in rats. Am J Physiol Regul Integr Comp Physiol 2009;R1358-65.
62. Babygirija R, Zheng J, Ludwig K, Takahashi T. Central oxytocin is involved in restoring impaired gastric motility following chronic repeated stress in mice. Am J Physiol Regul Integr Comp Physiol 2010;298:R157-65.
63. Babygirija R, Zheng J, Bulbul M, Cerjak D, Ludwig K, Takahashi T. Sustained delayed gastric emptying during repeated restraint stress in oxytocin knockout mice. J Neuroendocrinol 2010;22:1181-6.
64. Babygirija R, Bülbül M, Cerjak D, Ludwig K, Takahashi T. Sustained acceleration of colonic transit following chronic homotypic stress in oxytocin knockout mice. Neurosci Lett 2011;495:77-81.
65. Yoshimoto S, Cerjak D, Babygirija R, Bulbul M, Ludwig K, Takahashi T. Hypothalamic circuit regulating colonic transit following chronic stress in rats. Stress 2012;15:227-36.
66. Babygirija R, Zheng J, Bulbul M, Ludwig K, Takahashi T. Beneficial effects of social attachment to overcome daily stress. Brain Res 2010;1352:43-9.
67. Babygirija R, Cerjak D, Yoshimoto S, Gribovskaja-Rupp I, Bulbul M, Ludwig K, Takahashi T. Affiliative behavior attenuates stress responses of GI tract via up-regulating hypothalamic oxytocin expression. Auton Neurosci 2012;169:28-33.