

## Journal Club

**Editor's Note:** These short, critical reviews of recent papers in the *Journal*, written exclusively by graduate students or postdoctoral fellows, are intended to summarize the important findings of the paper and provide additional insight and commentary. For more information on the format and purpose of the Journal Club, please see [http://www.jneurosci.org/misc/ifa\\_features.shtml](http://www.jneurosci.org/misc/ifa_features.shtml).

## Oxytocin Influence on the Nucleus of the Solitary Tract: Beyond Homeostatic Regulation

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Review of Peters et al. (<http://www.jneurosci.org/cgi/content/full/28/45/11731>)

Oxytocin is a neuropeptide that until recently was perhaps best known for its role in parturition, lactation, and maternal care. It is now well documented that oxytocin also influences a wide range of social and affective behaviors and is a powerful modulator of physiological and behavioral responses to stress. Indeed, exposure to a variety of stressors triggers paraventricular nucleus secretion of oxytocin to limbic brain regions, brainstem, and spinal cord, as well as pituitary release into the blood. Numerous studies in humans and rodents have demonstrated that oxytocin suppresses the “classic” stress hormones of the hypothalamic–pituitary–adrenal (HPA) axis, and as such, oxytocin is an important regulator of both the physiological and behavioral aspects of the stress response and anxiety-like behavior. Furthermore, the anxiolytic function of elevated oxytocin release has been observed both after endogenous elevations in oxytocin during parturition and lactation and after exogenous oxytocin administration, resulting in a blunted HPA axis-mediated stress response (for review, see Neumann, 2008).

The nucleus of the solitary tract (NTS) contains oxytocin receptors and receives oxytocinergic input from the paraventricular nucleus, and recent work has expanded on the modulatory role for oxytocin projections onto the NTS (Higa et al., 2002). Because the NTS is an important relay center for incoming central and peripheral visceral sensory inputs, second-order NTS neurons are ideally located to integrate peripheral inputs (i.e., cardiovascular reflexes) with centrally mediated responses such as stress. This has led to a push for the identification of a role for oxytocin in mediating cardiopulmonary inputs onto the NTS (Higa et al., 2002). However, the cellular mechanisms by which oxytocin mediates incoming peripheral and central afferents into the NTS have remained unknown. The analysis of a role for oxytocin in the NTS may provide a better understanding of the significance of oxytocin-mediated visceral sensory inputs in the context of stress and anxiety.

In a recent study published in *The Journal of Neuroscience*, Peters et al. (2008) elucidated the cellular mechanisms by which hypothalamic oxytocin projections enhance visceral afferent transmission to the NTS. The authors first identified a population of second-order NTS neurons in the medial subnucleus of the caudal NTS in brainstem slices and assessed mEPSC frequency after application of oxytocin. High concentrations of oxytocin increased the

frequency of mEPSCs twofold [Peters et al. (2008), their Fig. 2], an effect that was attenuated by coadministration of a selective oxytocin receptor antagonist [Peters et al. (2008), their Fig. 4]. Importantly, this effect was selective to approximately half of the second-order NTS neurons identified within a mixed distribution of oxytocin-sensitive and oxytocin-resistant neurons. This divergence in neuronal responses to oxytocin suggests varied distribution of oxytocin receptors on NTS neurons, which in turn suggests that only a subset of second-order NTS neurons may be selectively influenced by the paraventricular nucleus via this mechanism.

To better understand the site of oxytocin action, the authors assessed the synaptic transmission properties of the oxytocin-sensitive NTS neurons. Although oxytocin application increased the frequency of mEPSCs in a concentration-dependent manner, the amplitude and decay kinetics of the mEPSCs remained unaltered relative to the control condition. Because oxytocin did not influence postsynaptic event properties, the authors concluded that the oxytocin actions were presynaptic. Additionally, neuronal excitability was increased in oxytocin-sensitive neurons via inhibition of a  $K^+$  conductance, thereby suggesting that oxytocin acts to enhance afferent transmission to selective NTS neurons via both presynaptic (increased frequency of EPSCs) and postsynaptic (depolarization)

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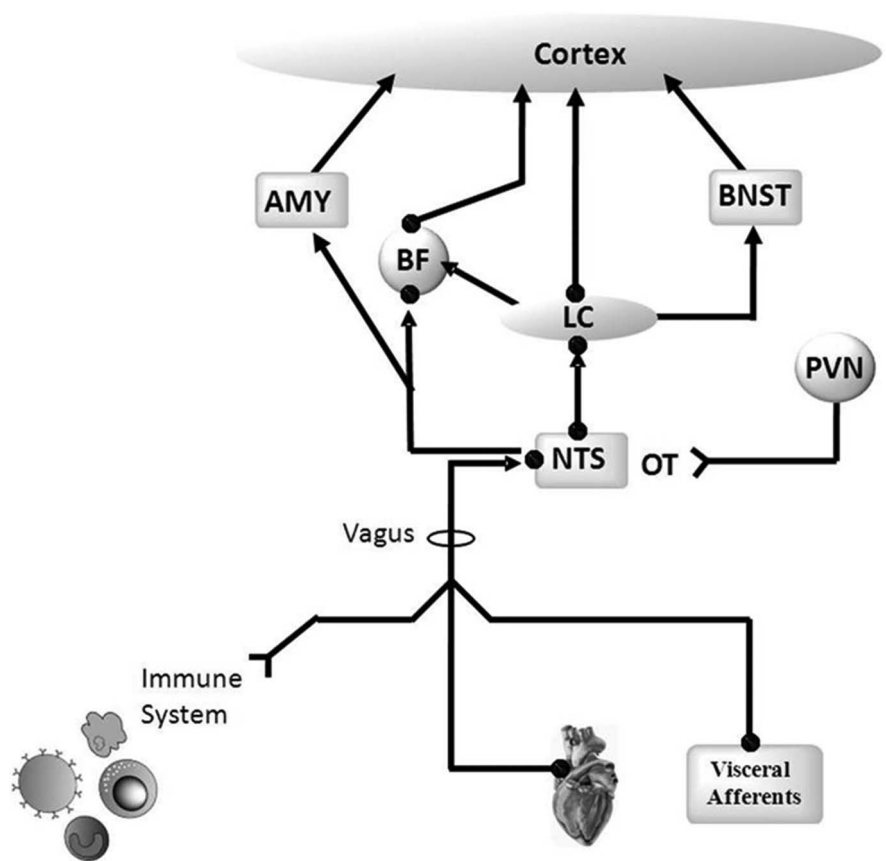
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mechanisms [Peters et al. (2008), their Figs. 3, 7].

Finally, Peters et al. (2008) identified NTS neurons that were responsive to electrical stimulation of the vagus nerve and activation of cardiopulmonary afferents. They further measured oxytocin immunoreactivity of nearby axons. Among the doubly responsive NTS neurons, half appeared to receive inputs from oxytocin-immunoreactive terminals [Peters et al. (2008), their Fig. 8]. Notably, some oxytocin-resistant neurons were in close proximity to oxytocin-sensitive neurons but remained resistant to oxytocin actions. Thus, selective modulation of the NTS is achieved via variation in the oxytocin responsiveness of the second order NTS neurons and heterogeneous innervation by oxytocin-containing axons projecting from the paraventricular nucleus.

The study includes a brief, but interesting, discussion of how innervation of the NTS by oxytocin-synthesizing paraventricular nucleus neurons may modulate homeostatic reflexes; we propose that the data from this study may have much broader behavioral implications, including alterations in affective and cognitive processes. Specifically, we will focus on converging evidence suggesting that oxytocin modulation of NTS function could influence the development of stress and anxiety-like behavior.

In addition to providing homeostatic information, somatic afferents can bias limbic and cortical information processing (Berntson et al., 1998). Indeed, several hypotheses suggest that aberrant signaling from the viscera to CNS may play an important predisposing role in anxiety disorders (Watkins et al., 1998). The NTS receives afferent signals from viscera and immune system and transmits them to forebrain regions, such as the basal forebrain, a structure involved in regulating cortical processing of anxiogenic stimuli (Berntson et al., 1998). Similarly, NTS projections to the locus coeruleus, the bed nucleus of the stria terminalis and amygdaloid structures, serve as additional conduits through which NTS activity is able to influence the processing of anxiogenic stimuli (Fig. 1). Thus, NTS neurons are ideally situated to coordinate afferent signaling to multiple brain regions associated with emotion. For example, blocking central afferent neurotransmission, through inactivation of NTS transmission, inhibits the stress-induced potentiation of emotional memories (Wil-



**Figure 1.** Vagal afferents convey visceral information to the NTS, the major visceral relay nucleus of the brainstem. The NTS issues a direct projection to forebrain areas such as the amygdala and basal forebrain and can also activate the ascending noradrenergic system arising in the locus coeruleus noradrenergic system (LC). The LC, in turn, projects to the basal forebrain cholinergic system as well as to the amygdala and the cortex. There are thus several routes by which oxytocin acting on ascending visceral information can impact cortical/cognitive processing. Reciprocal interactions between the amygdala and basal forebrain, together with their overlapping targets in the medial prefrontal cortex, constitute important processing substrates for the processing of anxiogenic stimuli. AMY, Amygdala; OT, oxytocin; PVN, paraventricular nucleus; BF, basal forebrain cholinergic system; BNST, bed nucleus of the stria terminalis.

liams and McGaugh, 1993) and inhibits anxiety in rats (Miller et al., 2002).

Whereas Peters et al. (2008) primarily focused on the role of NTS in afferent signaling, this structure also is an essential regulator of cardiovascular reactivity in the context of anxiety and fear. Direct descending projections from the central amygdala and medial prefrontal cortex, two brain regions associated with the processing of anxiogenic stimuli to the NTS, represents a pathway for the regulation of cardiovascular reactivity states by telencephalic structures (Berntson et al., 1998). Together with the data put forth by Peters et al. (2008), it is reasonable to propose that oxytocin may alter anxiety-induced cardiovascular reactivity via its actions in the NTS, in addition to its influences within the limbic system.

As established by Peters et al. (2008), oxytocin acts on a select group of neurons within the NTS to increase afferent

visceral synaptic transmission. In addition to the homeostatic processes previously suggested, oxytocin signaling in the NTS is well positioned to inform various structures associated with emotion of peripheral processes. Linking emotions to homeostatic mechanisms is a salient way for peripheral processes, such as infection or sympathetic arousal, to influence behavior.

In summary, the data presented in Peters et al. (2008) have broad implications and are likely to spark new interest in the NTS among behavioral neuroscientists. Whereas numerous reports have demonstrated anxiolytic effects of oxytocin (for review, see Neumann, 2008), the findings of Peters et al. (2008) suggest a novel pathway through which oxytocin may influence anxiety and other complex behaviors. Given that the NTS can alter activity at nearly all levels of the CNS, and that oxytocin has been implicated in a wide spectrum of behav-

iors, it is unlikely that its effects on the NTS are limited to homeostatic reflexes.

## References

- Berntson GG, Sarter M, Cacioppo JT (1998) Anxiety and cardiovascular reactivity: the basal forebrain cholinergic link. *Behav Brain Res* 94:225–248.
- Higa KT, Mori E, Viana FF, Morris M, Michelini LC (2002) Baroreflex control of heart rate by oxytocin in the solitary-vagal complex. *Am J Physiol Regul Integr Comp Physiol* 282:R537–R545.
- Miller CC, Holmes PV, Edwards GL (2002) Area postrema lesions elevate NPY levels and decrease anxiety-related behavior in rats. *Physiol Behav* 77:135–140.
- Neumann ID (2008) Brain oxytocin: a key regulator of emotional and social behaviours in both females and males. *J Neuroendocrinol* 20:858–865.
- Peters JH, McDougall SJ, Kellett DO, Jordan D, Llewellyn-Smith IJ, Andresen MC (2008) Oxytocin enhances cranial visceral afferent synaptic transmission to the solitary tract nucleus. *J Neurosci* 28:11731–11740.
- Watkins LL, Grossman P, Krishnan R, Sherwood A (1998) Anxiety and vagal control of heart rate. *Psychosom Med* 60:498–502.
- Williams CL, McGaugh JL (1993) Reversible lesions of the nucleus of the solitary tract attenuate the memory-modulating effects of posttraining epinephrine. *Behav Neurosci* 107:955–962.