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.

Specialized Networks for Social Cognition: A Defining Role for the Oxytocin Receptor

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Review of Mitre et al.

Oxytocin is a member of a neuropeptide family with a well established role modulating reproductive and social behaviors (Donaldson and Young, 2008). Oxytocin is expressed in conserved populations of neurons that release oxytocin broadly throughout the brain (Venkatesh et al., 1997; Ross and Young, 2009). Unlike oxytocin, the expression of oxytocin receptor (OXTR) is remarkably variable, and further, associates with species-specific behaviors. For example, differences in expression of an OXTR homolog in the lateral septum are associated with variation in group size preference between bird species (Goodson et al., 2009). In another case, monogamous prairie voles express more OXTR in the nucleus accumbens compared with promiscuous vole species (Young and Wang, 2004). Prairie vole pair-bonding requires OXTR activation in the nucleus accumbens, and higher individual levels of OXTR in this region facilitate prairie vole bonding (Ross et al., 2009b; Keebaugh et al., 2015; King et al., 2016). Such comparative studies revealed a critical aspect of oxytocin signaling: the peptide acts on specialized neural networks within a given species. Marlin et al. (2015) recently investigated the effects of oxytocin in the context of mouse maternal behavior. Dams respond to pup distress calls with retrieval behavior. Virgin females do not initially respond to pups, but can be trained to respond as if they had pups of their own. Oxytocin facilitates the acquisition of this behavior. In an article recently published in *The Journal of Neuroscience*, Mitre et al. (2016) extend these findings and detail the cellular distribution of OXTR and the neurophysiological response to oxytocin. These types of studies have been hindered by a lack of reliable OXTR antibodies (Yoshida et al., 2009). Overcoming this limitation, Mitre et al. (2016) designed a specific antibody for the mouse OXTR, OXTR-2. Mitre et al. (2016) compared OXTR-2 distributions between sexes and reproductive states, to identify regions where oxytocin may act to influence maternal behavior. Females differed from males in only one region, having more OXTR-2-positive cells in the piriform cortex. Mothers did not differ from virgins, suggesting the naive-to-maternal transition may not require a change in OXTR expression. Within females, the left auditory cortex contained more OXTR-2-positive cells than the right, and the CA2 region more than other hippocampal regions. Therefore, the authors proposed that piriform cortex, left auditory cortex, and hippocampal CA2 may be particularly important for oxytocin-mediated maternal behavior. The left but not right auditory cortex is required for retrieval of isolated pups (Marlin et al., 2015). Neither the piriform cortex nor hippocampus have yet been studied in the context of oxytocin-dependent pup retrieval.

For the most part, the OXTR-2-positive distribution reported by Mitre et al. (2016) agrees with OXTR distributions in the mouse obtained with receptor autoradiography; the most commonly used method to examine OXTR expression. Two recent studies performed detailed analyses with autoradiography and are amenable for a cursory comparison (Hammock and Levitt, 2013; Gigliucci et al., 2014). There are some small discrepancies worth noting. For example, the CA3 region is the only area of the hippocampus reported to contain noteworthy levels of OXTR in the two autoradiography studies. The medial amygdala and paraventricular thalamus are two regions with high OXTR binding density but no OXTR-2 labeling. It is not clear why the discrepancies between labeling techniques occur but future studies could benefit from a consideration of all potential sites of oxytocin modulation.

Using the specific OXTR-2 antibody to perform electron microscopy, Mitre et al. (2016) next characterized the subcellular location of OXTR in the left auditory cortex. In neurons, OXTR-2 immunolabeling appeared at synapses and axons of passage. Presynaptic and postsynaptic sites were enriched for OXTR, at both excitatory and inhibitory synapses. Inhibitory synapses were labeled at both dendrites and the soma.

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OXTR is poised to modulate both excitatory and inhibitory synapses. Some of the OXTR-2-positive synapses certainly belong to inhibitory interneurons. In cortical areas, some inhibitory interneuron cell bodies are OXTR-positive (Nakajima et al., 2014; Marlin et al., 2015). In the hippocampus, fast-spiking interneurons respond to an OXTR agonist (Owen et al., 2013). Some other synapses may consist of terminals projecting from other brain regions. For example, OXTR in serotonergic terminals projecting from the dorsal raphe nucleus modulates nucleus accumbens activity in mice (Dölen et al., 2013). Further work is required to clarify whether specific cell types account for any particular subcellular OXTR-2 labeling patterns.

Several recent studies have shown that oxytocin modulates inhibitory transmission (Owen et al., 2013; Marlin et al., 2015; Oettl et al., 2016). Mitre et al. (2016) confirmed this effect in the left auditory cortex. The authors measured IPSCs in pyramidal neurons after providing local electrical stimulation *in vitro*. Oxytocin caused a rapid (within 3–6 min) decrease in IPSC amplitude, after either a bath application or optogenetic release of endogenous oxytocin. Similar levels of disinhibition were seen in pyramidal neurons in the piriform cortex and neurons in the paraventricular nucleus of the hypothalamus. Evoked excitatory currents did not change after oxytocin treatment in all three regions. Oxytocin-induced disinhibition is a functional outcome for local circuits in multiple brain regions.

Oxytocin release in the left auditory cortex during exposure to pups facilitates virgin retrieval behavior (Marlin et al., 2015). Hypothesizing that oxytocin produces plasticity that could mediate this behavioral shift, Mitre et al. (2016) tested whether oxytocin induces long-term potentiation (LTP). In left auditory cortex slices, the authors measured EPSPs in response to local stimulation. Within 20 min of oxytocin application, both the initial slope of the EPSP and probability of spiking had significantly increased. In an *in vivo* preparation, the authors made single, multiunit, and whole-cell current-clamp recordings in response to pure tones. Pairing oxytocin with these artificial stimuli for 3 min increased spiking frequency or EPSP amplitude. This result extends a previous finding that oxytocin induces plasticity in response to pup calls (Marlin et al., 2015).

Mitre et al. (2016) suggest that cortical disinhibition may account for the oxytocin-dependent LTP they observed in the left auditory cortex. Indeed, disinhibition generally influences learning and sensory processing in the context of many circuits, behaviors, and modulatory systems (Letzkus et al., 2015). Application of a GABA receptor antagonist in the left auditory cortex produced similar LTP as oxytocin, demonstrating that disinhibition is sufficient for plasticity independently of oxytocin (Mitre et al., 2016). Essentially, disinhibition allows local circuits to respond more strongly, or with higher fidelity, to incoming information without additional activation that could interfere with the processing of that information (i.e., without generating noise). These short-term changes in circuit behavior can then promote longer-term plasticity in regions like the cortex through mechanisms such as spike-timing-dependent plasticity (Mitre et al., 2016).

Oxytocin induces long-term changes in the left auditory cortex when paired with either a social (Marlin et al., 2015), or nonsocial auditory stimulus (Mitre et al., 2016). Oxytocin release therefore determines coincidence between auditory input and the priming of the cortex for plasticity. Mammalian parturition results in a large release of oxytocin, so OXTR is active in a mother's brain when her pups arrive and emit their first calls. This timing is important because oxytocin signaling is required for even mothers to acquire appropriate retrieval behavior (Rich et al., 2014). Extracellular oxytocin occurs at small concentrations that are difficult to measure (Ross et al., 2009a), and thus little is known about when and how much oxytocin is released during innocuous social interactions.

OXTR has been proposed as a therapeutic target for psychiatric disorders involving social behavior, such as autism spectrum disorder (Penagarikano et al., 2015; Young and Barrett, 2015). Clinical strategies should consider that a major function of oxytocin is a short-term enhancement of sensory information processing, as shown by Mitre et al. (2016) and others. For example, Modi and Young (2012) proposed that OXTR stimulation could be used in structured programs to enhance the acquisition of social skills.

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