

The Emerging Role of Nucleus Accumbens Oxytocin in Social Cognition

Gül Dölen and Robert C. Malenka

The nucleus accumbens (NAc), also known as the ventral striatum, is a key node of the mesocorticolimbic reward system. This circuit has received great attention because of its role in the pathophysiology of addiction and depression. However, it likely evolved to motivate behaviors that were important for survival, reproduction, and fitness. Increasing evidence suggests that adaptive social behaviors in a wide diversity of species are also reinforced by this system. The evolutionary persistence of these behaviors might require this reinforcement, particularly in cases where individual benefit and group benefit are in conflict. A particularly attractive idea is that the neuropeptide oxytocin (OT) functions as a reward signal in the NAc for affiliative interactions. Initially, the strongest experimental evidence in support of this hypothesis derived from classic work showing that oxytocin receptors (OTRs) in the NAc of the prairie vole were critical for its monogamous, highly affiliative behavior (1,2). More recently, we have demonstrated that OT induces plasticity at excitatory synapses in the mouse NAc and that pharmacologic blockade or molecular ablation of OTRs in the NAc impairs social reward processing (3). In this issue of *Biological Psychiatry*, Loth *et al.* (4) demonstrate that polymorphisms in the *OXTR* gene, which encodes the OTR, correlate with changes in the processing of social information and functional magnetic resonance imaging assays of NAc activation patterns. These studies add to the growing body of evidence that OTRs in the NAc play an important role in mediating social cognition and that *OXTR* polymorphisms interact with life events to have an important influence on how individuals react to social cues.

In the lay press, OT is often referred to as the “love hormone.” However, as evidenced by the distinctions drawn between “storge,” “eros,” and “philia,” the Ancient Greeks recognized that “love” takes many forms depending on its social context (e.g., maternal, erotic, communal). To date, it is unknown how OT is able to mediate differentially these distinct types of love. Emerging evidence suggests the possibility that the mode of transmission (paracrine or synaptic) and the brain regions targeted by the regulation of receptor expression dictate this specificity (Figure 1). For example, OT released by the hypothalamus into the systemic circulation via axon terminals in the posterior pituitary binds to OTRs in the uterus and mammary glands to mediate parturition and lactation. The magnocellular hypothalamic neurons responsible for this systemic release are also capable of releasing OT, via a somatodendritic mechanism,

into circulating cerebrospinal fluid (5). By bathing the entire brain in OT, this mechanism has the spatial and temporal characteristics of a hormone. Such paracrine release of OT is coupled, around the time of parturition, to upregulation of OTRs in the bed nucleus of the stria terminalis, amygdala, olfactory bulb, and medial preoptic area. Together, these mechanisms are thought to mediate maternal attachment to the newborn (1,2).

Similarly, in both males and females, stimulation of the genitals and nipples during sexual intercourse causes the release of OT by magnocellular neurons of the hypothalamus. The systemic response includes vaginal lubrication or penile erection, orgasm, and ejaculation. In the central nervous system, the notion that activation of OTRs enables pair bonding is supported by the observation of relatively elevated levels of OTR expression in the NAc in monogamous rodent species (e.g., prairie voles) compared with polygamous species (e.g., montane voles, mice, rats) (1,2). The mode of central OT release for these monogamous attachments is thought to be paracrine for two reasons: 1) in the prairie vole, upregulation of OTRs in various brain regions is not paralleled by concomitant increases in synaptic inputs to these regions (5); and 2) in rats and mice, magnocellular inputs from the supraoptic nucleus to the NAc are absent (3,6).

In contrast to maternal and monogamous attachments, more recent evidence suggests that social attachments between group members (i.e., “consociate” attachments) likely require OT synaptically released by parvocellular neurons of the paraventricular nucleus. This hypothalamic nucleus sends axon terminals to the NAc, where OT activates OTRs and induces plasticity at excitatory synapses (3). Thus, while both monogamous and consociate attachments activate OTRs in the NAc, the mode of oxytocinergic transmission is likely to be distinct. This difference may be ethologically relevant because the selection of group members involves discrimination between behaviors that benefit the group versus behaviors that do not. In contrast, “falling in love” produces a generalized euphoria that may enable mate selection while obscuring subsequent shortcomings of the mating decision. Moreover, consociate attachments might be more readily encoded by temporally precise, synapse-specific release of OT at axon terminals, whereas the euphoria of love might be better encoded by broader activation of OTRs by OT released somatodendritically into the circulating cerebrospinal fluid.

Although most of the above-described mechanisms have been primarily elucidated in comparative studies of animals, identification of nearly 30 single nucleotide polymorphisms (SNPs) in the *OXTR* gene (7) has enabled further investigations in humans. The human *OXTR* gene is located on chromosome 3p25 and contains four exons and three introns. To date, two SNPs in the third intron (rs53576 and rs2254298) have received the most attention because numerous studies have noted overtransmission of these common variants in families of patients with autism and have correlated these with measures of social skills in individuals with autistic spectrum disorder (8). Nevertheless, a recent meta-analysis showed that these two *OXTR* polymorphisms failed to explain a significant part of human social behavior (9), perhaps because measured outcome domains across studies were so

From the Department of Neuroscience and Brain Science Institute (GD), Johns Hopkins University, School of Medicine, Baltimore, Maryland; and Nancy Pritzker Laboratory (RCM), Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California.

Address correspondence to Robert C. Malenka, M.D., Ph.D., Lokey Stem Cell Research Building, Stanford University School of Medicine, 265 Campus Drive, Room G1021, Palo Alto, CA 94305-5453; E-mail: malenka@stanford.edu.

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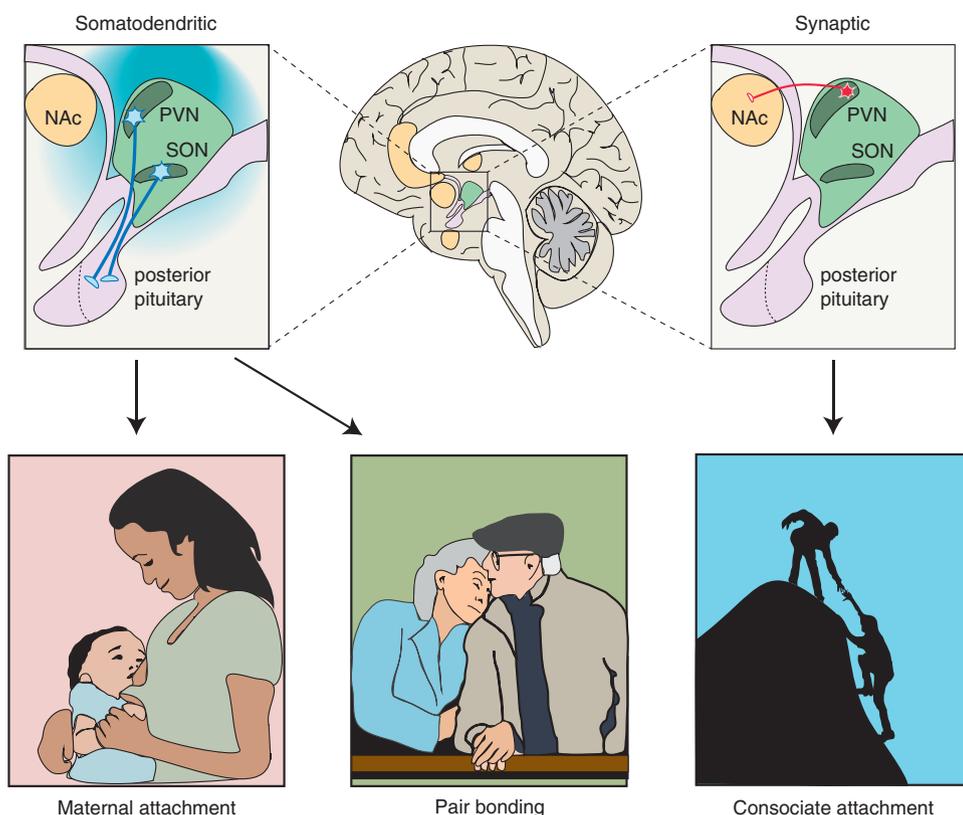


Figure 1. Oxytocin is produced by two cell types within the hypothalamus: magnocellular and parvocellular. Magnocellular neurons (blue) in the PVN and SON of the hypothalamus send axons to the posterior pituitary, which provides access to the periphery via the portal circulation. Additionally, these magnocellular neurons can release oxytocin into the central nervous system by somatodendritic release into the circulating cerebrospinal fluid. This mechanism of release is thought to mediate the paracrine functions of oxytocin, such as maternal attachment and pair bonding. Parvocellular neurons (red), found exclusively in the PVN, send axonal projections directly to target regions in the central nervous system, including the NAc. Synaptically released oxytocin is thought to mediate neurotransmitter functions of oxytocin, such as consociate attachments. NAc, nucleus accumbens; PVN, paraventricular nucleus; SON, supraoptic nucleus.

heterogeneous (including self-report questionnaires on empathy, attachment style, or prosocial temperament; observed attachment behavior and aggression to a fictive opponent; and psychopathologies such as depression, disruptive behavior disorder, and autism).

More recently, this type of polymorphism analysis has been extended to correlate behaviors modified by *OXTR* SNPs with anatomic mapping using functional magnetic resonance imaging. Loth *et al.* (4) show that the minor genotype of the rs237915 *OXTR* SNP is associated with decreased activation of the NAc in response to passive viewing of angry faces. Although carriers of this variant were more resilient against the effect of stressful life experiences, they were also more likely to have emotional and peer problems in low-stress environments. It is unknown whether this variant is also associated with autism. Future inclusion of this SNP for genome-wide association studies of autism would be informative. In the meantime, it is relevant that more recent studies have reported that individuals with autistic spectrum disorder display diminished neural activity in NAc during socially motivated play (10).

Interpretation of future studies will depend on understanding how identified *OXTR* gene polymorphisms alter receptor function. These SNPs may alter OTR expression, splicing, folding, posttranslational modifications, functions such as G-protein activation, or targeting. Future studies in animal models will enable a better understanding of the cellular and circuit consequences of these genetic alterations. For now, this latest work from Loth *et al.* (4), along with the enormous interest in the therapeutic possibilities of OT administration for neuropsychiatric disorders, provides further evidence of the importance of elucidating the actions of OT in the NAc and other key nodes of reward circuitry. It will also be important to remember that OT plays various distinct roles in social cognition in many different contexts. A broad array of sophisticated animal and human studies will be

necessary to elucidate fully the complexity of the circuits on which OT acts and how OTR polymorphisms influence gene-environment interactions to affect these circuits in adaptive or pathologic ways.

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