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Oxytocin: The Neuropeptide of Love Reveals Some of Its Secrets

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The neuropeptide oxytocin is synthesized in the brain and released from neurohypophyseal terminals into the blood and within defined brain regions that regulate emotional, cognitive, and social behaviors. A recent study of *CD38*$^{-/-}$ mice (Jin et al., 2007) has demonstrated an essential role for the transmembrane receptor CD38 in secretion of oxytocin into the blood.

The neuropeptide oxytocin has attracted intense attention due to the discovery of its amazing variety of behavioral functions. Oxytocin and the related nonapeptide vasopressin are essential parts of the hypothalamo-neurohypophyseal system. First described in 1928 by the German biologist Ernst Scharrer in fish, this clearly delineated, compact arrangement of relatively large neurons at the base of the brain with long axonal projections to the neurohypophysis and contacts with blood capillaries has served as a valuable model system in neuroendocrinology and neuroscience. Oxytocin was the first neuropeptide to be characterized (by Du Vigneaud and, independently, by Acher in the 1950s). Studies of oxytocin have provided key insights into the bursting pacemaker activity of neurosecretory neurons, neuropeptidergic pathways and release patterns within the brain, neuronal-glial interactive plasticity, neuropeptide receptor antagonists, and, importantly, behavior (reviewed in Poulain et al., 2002). Work over the past two decades has illuminated the molecular and cellular mechanisms of neuronal oxytocin synthesis, transport, processing, and release, both into the blood and within the brain (Landgraf and Neumann, 2004). These findings have been causally linked to behavioral and other phenomena in both animal and human studies (Figure 1). Brain oxytocin modulates social behaviors, including maternal care and aggression, pair bonding, sexual behavior, social memory and support, and human trust, and downregulates stress responses, including anxiety. Thus, while neuropeptides such as vasopressin and CRH might represent the Homerian sea monsters Scylla and Charybdis in behavioral regulation, oxytocin, like Circe and Thetis (who guided Odysseus to avoid both dangers) would mediate anxiolytic and prosocial influences, beneficial to relief, reproduction, and love (Landgraf et al., 2007). This system is therefore one of the most promising neuromodulator/neurotransmitter systems of the brain for psychotherapeutic intervention and treatment of numerous psychiatric illnesses, for example social phobia, autism, and postpartum depression.

A recent article in *Nature* by Higashida and colleagues (Jin et al., 2007) sheds a bright light on the molecular and cellular mechanisms of neuronal oxytocin release. The authors apply an impressive variety of molecular, cellular, neuroendocrine, and behavioral techniques to convincingly characterize the transmembrane receptor CD38 as an essential component in the secretory machinery of oxytocin neurons. CD38 can catalyze the formation of the second messengers cyclic ADP-ribose (cADPR) and nicotinic acid adenine dinucleotide phosphate (NAADP), which are essential for the activation of intracellular Ca^{2+} stores (Empson and Galione, 1997). In the presence of calmodulin, increasing the concentration of cADPR increases the sensitivity of Ca^{2+}-induced Ca^{2+} release (Lee, 2005). Thus, application of cADPR through a patch-clamp pipette augments the action-potential-induced, and ryanodine-sensitive, rise in intracellular Ca^{2+}. These CD38-dependent cADPR and NAADP signaling

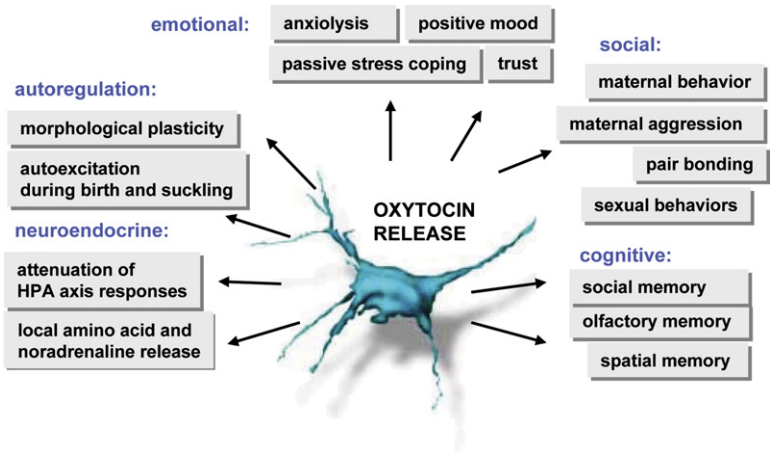

Figure 1. Multiple Actions of Brain Oxytocin
Oxytocin is released within defined brain regions upon appropriate stimulation, where it regulates not only neuroendocrine and autonomic functions related to reproduction but also prosocial behaviors (supported by its cognitive effects) and emotional responses contributing to the general phenomena of relaxation, trust, and psychological stability.

pathways play an essential role in exocytosis of neurotransmitters in both invertebrates and vertebrates (Lee, 2005).

Jin et al. (2007) use mice lacking the *CD38* gene (*CD38*$^{-/-}$) to demonstrate that this transmembrane protein is essential for adequate oxytocin release from hypothalamic neurons. *CD38*$^{-/-}$ mice have reduced plasma oxytocin concentrations, and their hypophyseal terminals contain more oxytocin as well as dense core vesicles, indicating excessive peptide storage and impaired peptide release. Moreover, the authors' findings strongly suggest the critical involvement of cADPR-mediated and NAADP-sensitive Ca^{2+} mobilization from intracellular stores in oxytocin release from neurohypophyseal terminals, as oxytocin secretion can be evoked by 100 nM NAADP in *CD38*$^{-/-}$ mice. Interestingly, release of vasopressin was apparently normal in *CD38*$^{-/-}$ mice. This is evidence for a highly neuropeptide-selective neurosecretory mechanism and might explain stimulus-dependent activation of either oxytocin or vasopressin secretion.

The impairment of neuronal oxytocin release in *CD38*$^{-/-}$ mice is accompanied by significant behavioral abnormalities. For example, the latency to retrieve pups in the home cage is prolonged, indicating impaired maternal care under stressful conditions, which is likely related to a deficit in intracerebral oxytocin release. However, growth and development of pups in offspring of *CD38*$^{-/-}$ dams was not altered, indicating normal maternal behavior under unstressed conditions in the home cage. Taking into account that oxytocin is the only factor that triggers milk ejection in response to the suckling stimulus (Nishimori et al., 1996), it seems that CD38 is only a cofactor for suckling-induced oxytocin secretion. It would be interesting to see whether lack of CD38 has consequences not only on basal but also on stimulated oxytocin secretion into blood, for example in response to suckling or during exposure to stressors.

Importantly, *CD38*$^{-/-}$ mice show substantial impairment of social memory and in the recognition of a conspecific female. This is in agreement with the demonstration that intracerebral oxytocin is important for social memory (Dluzen et al., 2000; Ferguson et al., 2000). Jin et al. (2007) go on to rescue deficits in oxytocin release and related behaviors by infusion of a lentiviral vector carrying the human *CD38* gene into the ventricular system of the brain, with consequent increases in CD38 protein expression in the hypothalamus and neurohypophysis. These data show that the rise in intracellular Ca^{2+} and subsequent oxytocin release require this transmembrane protein.

Jin et al. (2007) also demonstrate rescue of the behavioral abnormalities of *CD38*$^{-/-}$ mice by peripheral oxytocin injection. One interpretation of the data is that the cognitive deficits seen in the knockouts stem from impaired oxytocin release. However, taking into account the relatively high plasma and CSF oxytocin concentrations in mice of about 200 ng/ml in *CD38*$^{-/-}$ and 400 ng/ml in *CD38*$^{+/+}$ (roughly 10,000-fold higher than in rats or humans), it is puzzling how subcutaneous injection of a total of 1–10 ng/kg (i.e., of about 30 to 300 pg per adult mouse; see Supplementary Figure S7 in Jin et al., 2007) could substantially increase CSF oxytocin concentrations in *CD38*$^{-/-}$ mice (from ~200 to 350 ng/ml). This would imply a selective neuropeptide uptake into the brain, complicated or limited by the presence of the blood-brain barrier. Moreover, the general well-being of the *CD38*$^{-/-}$ mice (as measured by behavioral indicators including locomotion and anxiety) would seem to rule out a pathologically increased permeability of the blood-brain barrier in these animals. Another possibility, which warrants further study, is that small additional quantities of oxytocin might trigger substantial oxytocin release from the described overfull neuronal stores via autoexcitatory mechanisms.

Whatever the underlying mechanisms, the rescue of social memory by oxytocin in *CD38*$^{-/-}$ mice implies that lack of CD38 also affects intracerebral oxytocin release. Clearly, oxytocin release within distinct brain regions (which can be monitored in conscious mice by intracerebral microdialysis [Theodosis et al., 2004]) and into the blood may occur independently (Neumann et al., 1993). In particular, dendritic release follows different neuronal mechanisms (Ludwig et al., 2004). Thus, a distinction between neurohypophyseal oxytocin secretion and release within defined brain regions would help to interpret the behavioral alterations in *CD38*$^{-/-}$ mice.

Taken together, the comprehensive data of Higashida and coworkers (Jin et al., 2007) provide important insights into the complex mechanisms of oxytocin secretion, with CD38 being an essential part for appropriate neuropeptide responses and actions. Given

the behavioral consequences of lack of CD38, it seems likely that CD38-mediated mechanisms are also involved in the release of oxytocin (and possibly other neuropeptides) within the brain. The results make a search for human *CD38* mutations tempting, for example in patients with severe disturbances in social behaviors, including social phobia and autism.

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TOR and Aging: Less Is More

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Metabolism and mitochondrial activity are thought to be important determinants of life span. A new study in this issue of *Cell Metabolism* (Bonawitz et al., 2007) suggests that the TOR pathway controls mitochondrial respiration in yeast and that the harder mitochondria work, the longer yeast live.

In 1928, the noted but controversial biologist Raymond Pearl published a treatise entitled *The Rate of Living, Being an Account of Some Experimental Studies on the Biology of Life Duration*, in which he argued that metabolic rate was the key determinant of an organism's life span. The immediate impact and acceptance of Pearl's idea was muted, perhaps due to the author's own flamboyant past, which included advocating the consumption of significant quantities of alcohol as a way to prolong life. Nonetheless, in contrast to his other ignoble theories, Pearl's work on metabolism was not completely dismissed. Indeed, 30 years later, it would coalesce with the work of Denham Harman and his "free-radical theory of aging" to form a single notion, that aging represents the end result of metabolically induced oxidant-mediated damage.

The Pearl-Harman notion was that faster metabolism (increased oxygen consumption) leads to increased reactive oxygen species (ROS) formation and hence shorter life span. Surprisingly, three-quarters of a century after Pearl's initial treatise, the molecular basis for differences in metabolic rate within and between organisms, as well as the relationship between oxygen consumption and ROS formation, remains largely unknown. Now, a paper in this month's issue of *Cell Metabolism* begins to peel away the mystery surrounding some of these decades-old questions (Bonawitz et al., 2007).

The current work centers on the TOR pathway in yeast and its role in aging. Yeast aging is usually analyzed in one of two different assays. Replicative life span is defined as the number of times a mother yeast cell can give rise to a daughter bud, while chronological life span is the length of time that a nondividing yeast cell can remain viable in culture. In mammals, this distinction may be analogous to assessing aging in dividing versus postmitotic cells. *S. cerevisiae* has two TOR genes that are partially but not completely redundant. Yeast deleted in the *TOR2* gene are not viable, while deletion of *TOR1* increases replicative life span (Kaeberlein et al., 2005). In general, TOR represents a central signaling node that coordinates cell growth with the underlying cellular energy state. In the presence of nutrients, when the energy stores of a yeast cell are high, TOR coordinates increases in translation, transcription, and ribosomal biogenesis while inhibiting the self-consuming process of autophagy. Interestingly, diminished TOR signaling can also extend the life span of other organisms