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Oxytocin and sex differences in behavior

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Oxytocin is an evolutionarily ancient neuropeptide that is implicated in the neural modulation of behavior in vertebrates. While this system is well known for its species-specific effects, there is a lack of consensus regarding oxytocin's sex-specific effects — due in part to shortcomings in the way that studies have traditionally been designed. Sex differences in the neuroanatomy of the oxytocin system are not abundant and are generally not predictive of sex differences in behavior. Rather, it is possible that the differential evolution of these systems in males and females has resulted in sex differences in the sensitivity to oxytocin as well as sex differences in the function of the neural circuitry important for behavioral displays. This hypothesis is supported by work which suggests that sex differences in behavior are likely due to sex-specific patterns of activity between brain regions that have been implicated in the regulation of social behavior. It is also important to consider how oxytocin's sex-specific behavioral effects are shaped by social context, species evolution, and an animal's behavioral ecology.

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Introduction

One of the most fascinating aspects of the neurohomone oxytocin and its homologues are their fairly conserved role in the neural regulation of social behaviors. From *Caenorhabditis elegans* to *Homo sapiens*, oxytocin-related peptides act to modulate behavior, primarily promoting plasticity in innate behaviors [1–3,4•,5•,6,7]. However, the nuances of how oxytocin acts to affect behavior are highly varied. This is particularly true in the context of oxytocin's sex-specific effects, which, due in part to oxytocin's species-specific actions, makes it difficult to determine the 'when' and 'where' of oxytocin's action. In fact, definitive statements about oxytocin's effects with regard to the modulation of female versus male behavior are very difficult to make. Therefore, rather than attempt to provide a comprehensive review of oxytocin's effects on social behavior, which can be found elsewhere [1–3,4•], this review will focus on where scientific consensus exists in terms of oxytocin's effects on sex differences in mammalian behavior, with particular attention to social behaviors. To start this discussion though, where in the brain oxytocin may function in sex-specific ways must first be considered, with the following major caveat: sex differences in neuroanatomy are often not clearly related to sex differences in behavior [8,9••]. It is also important to note that there has not been a lot of direct testing of sex differences in oxytocin's behavioral effects, largely due to the fact that each sex is often studied in isolation, rather than at the same time with the same tests.

There are not many sex differences in oxytocin and oxytocin receptor distribution

There are very few sex differences in the sites of oxytocin synthesis. In all mammalian species in which oxytocin has been localized it is primarily produced in the paraventricular nucleus (PVN) and the supraoptic nucleus (SON) of the hypothalamus. In some species, there are also additional sites of synthesis, including the bed nucleus of the stria terminalis (BNST), the medial preoptic area (MPOA), the lateral hypothalamus (LH), and the medial amygdala (MeA) (please see [4•] for a comprehensive review). In rodents, there are no reported sex differences in oxytocin mRNA expression in the PVN and SON of any species (for review see [4•]) and a recent report in Wistar rats found no sex differences in oxytocin immunoreactivity in either the number of cell bodies or the density of fibers in brain areas outside of the PVN and SON [10•]. In primates there are no reports of sex differences in oxytocin immunoreactive fibers in macaques [11], marmosets [12], or humans [13–15]. Essentially, the only reported sex differences in oxytocin are in the number of immunoreactive fibers in rodents and these findings are species- and brain-region specific. When sex differences are detected, females are reported as having more oxytocin immunoreactive fibers than males [16–19]. These studies may indicate that sex differences in oxytocin function are due to its rate of axonal transport or secretion in response to physiological challenges, rather than to absolute amounts.

Oxytocin receptor expression, on the other hand, varies widely in its distribution and density between species. Two brain regions in which sex differences in the

oxytocin receptor are regularly reported are the BNST and the MeA, with males typically having more oxytocin receptors in these brain regions than females [16–19,20•]. Though, there are studies which have found sex differences in the other direction (female > male) within other brain regions [21–25]. Generally speaking, what is lacking, is scientific agreement on where there are consistently observed sex differences in oxytocin receptors. In almost all of the aforementioned studies, oxytocin receptor binding only differs in a few brain areas and there is considerable species variation.

On the basis of these data, most species do not appear to have any obvious sex-differences in the oxytocin system that can easily be correlated with sex differences in behavior. However, it must be stated that structure and function do not always associate with one another [8]. Therefore, it is likely that sex-specific development of the neural circuitry and differences in the patterns of activation across brain regions underlie oxytocin's sex-specific effects on behavior. This hypothesis is supported by a recent fMRI study in rats, which found that oxytocin administered centrally or peripherally results in sex differences in brain activation, both in terms of pattern and magnitude [26].

While the studies mentioned above were conducted in adults, and in some instances in juveniles, earlier in development there are some marked sex differences in the oxytocin system. In C56BL/6J female mice oxytocin mRNA, as measured by quantitative PCR performed on whole heads, is detectable as early as embryonic day (ED) 16.5. In males, oxytocin mRNA is not detectable until postnatal day (PND) 2. Females also have more oxytocin on PND2 than males and across embryonic development females have more Oxtr mRNA than males, specifically on E14.5, E16.5, E18.5, and PND2 [27•] (Figure 1). In the postnatal period, these sex differences disappear with no observable sex differences Oxtr density [28]. What these sex differences in the developing oxytocin system may or may not mean to behavior is unknown, as well as largely unexplored in other species. Though, it is known that manipulation of the oxytocin system in early postnatal life, at least in some rodents, can have sex-specific effects on behavior. This suggests that the oxytocin system may play a role in the sexual differentiation of the brain [29].

Sex differences in oxytocin's behavioral effects can be found across the lifespan

Uncovering oxytocin's contributions to sex differences in behavior is a challenge, possibly due to differential evolution of this system in the two sexes [30]. Although, new scientific tools continue to emerge and further refine our understanding of oxytocin's contributions to behavior. That said, the vast majority of studies that have examined oxytocin's contributions to sex differences in behavior have taken a pharmacological approach. As would be expected, with these data sets there is often a disconnect between what is observed following treatment with an oxytocin receptor antagonist, which blocks endogenous oxytocin signaling through its native receptor, versus treatment with oxytocin or an oxytocin receptor agonist, which competes with endogenous oxytocin; researchers are quite limited in their ability to manipulate the amount of endogenous oxytocin released. Genetic studies have gotten around some of the issues associated with pharmacological treatments, but they too have their limitations. More recently there have been studies that have quantified endogenous oxytocin release using microdialysis followed by radioimmunoassay, but these studies are still relatively few in number [31–36,37••]. Nonetheless, combining these data sets has increased our understanding of the role of oxytocin in sex-specific behaviors.

Early life

Some sex-specific behavioral effects are observed following postnatal manipulation of the oxytocin system in socially monogamous prairie voles (*Microtus ochrogaster*) and mandarin voles (*Lasiopodomys mandarinus*). These manipulations are in the form of single injections of oxytocin or oxytocin receptor antagonists during early postnatal life followed by behavioral testing in adulthood. In female prairie and mandarin voles, an intraperitoneal injection of oxytocin on PND1 increases female-directed aggression, but does not affect male-directed aggression in males [38,39]. However, in male prairie voles, oxytocin on PND1 facilitates pair bond formation [40], but the same effect is not observed in females unless a higher dose is used [41]. In mandarin voles, the effects of PND1 oxytocin treatment on pair bonding are opposite that observed in prairie voles, with PND1 oxytocin treatment in females facilitating partner preference within 24 hours of cohabitation, but suppressing the maintenance of partner preference, with no effect on male partner preference formation or maintenance. Rather, male mandarin voles increase their mounting behavior, though it should be noted that females did not display sexual behavior because they were tested on diestrous, so there may have been undetected effects on female sexual behavior [42]. In terms of alloparental care, in male prairie voles, PND1 injections of an oxytocin receptor antagonist increase pup-directed aggression and decrease paternal care; similar effects are not observed in females [43]. Thus, the sex-specific effects of oxytocin in these two species of voles seems to be that female mate-guarding may be sensitive to oxytocin injections in early life.

Sociability and alloparenting have also been tested in a non-monogamous species, ICR mice (*Mus musculus*), using a similar protocol as that described above, with male and female mice treated with either oxytocin or an oxytocin receptor antagonist on PND0. In these experiments, the results differed significantly from what was