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Review

Vasopressin and oxytocin receptor systems in the brain: Sex differences and sex-specific regulation of social behavior

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ABSTRACT

The neuropeptides vasopressin (VP) and oxytocin (OT) and their receptors in the brain are involved in the regulation of various social behaviors and have emerged as drug targets for the treatment of social dysfunction in several sex-biased neuropsychiatric disorders. Sex differences in the VP and OT systems may therefore be implicated in sex-specific regulation of healthy as well as impaired social behaviors. We begin this review by highlighting the sex differences, or lack of sex differences, in VP and OT synthesis in the brain. We then discuss the evidence showing the presence or absence of sex differences in VP and OT receptors in rodents and humans, as well as showing new data of sexually dimorphic V1a receptor binding in the rat brain. Importantly, we find that there is lack of comprehensive analysis of sex differences in these systems in common laboratory species, and we find that, when sex differences are present, they are highly brain region- and species-specific. Interestingly, VP system parameters (VP and V1aR) are typically higher in males, while sex differences in the OT system are not always in the same direction, often showing higher OT expression in females, but higher OT receptor expression in males. Furthermore, VP and OT receptor systems show distinct and largely non-overlapping expression in the rodent brain, which may cause these receptors to have either complementary or opposing functional roles in the sex-specific regulation of social behavior. Though still in need of further research, we close by discussing how manipulations of the VP and OT systems have given important insights into the involvement of these neuropeptide systems in the sex-specific regulation of social behavior in rodents and humans.

1. Introduction

The neuropeptides vasopressin (VP) and oxytocin (OT) are involved in the regulation of diverse social behaviors such as social recognition, pair-bonding, and social cognition in mammals, including humans (Veenema and Neumann, 2008; Ross and Young, 2009; Meyer-Lindenberg et al., 2011; Albers, 2014). VP and OT are evolutionarily conserved, differing from each other by only two amino acids. Importantly, VP and OT often regulate social behavior in sex-specific ways. This may be due to sex differences in the brain VP and OT systems, which will be the overarching topic of this review. Importantly, VP and OT have been implicated in the etiology of psychiatric disorders, such as schizophrenia (Jobst et al., 2014), autism (Yang et al., 2010; Xu et al., 2013; LoParo and Waldman, 2014), depression (Yueng et al., 2014), and borderline personality disorder (Bertsch et al., 2013), disorders which show sex biases in prevalence, symptom severity, and treatment responses. Knowledge of sex differences in these systems, as well as how OT and VP may mediate sex-specific social behavior, may therefore provide useful insight into sex-specific treatment strategies for men and women diagnosed with psychiatric disorders characterized by social dysfunction.

We will start with a discussion on sex differences in VP and OT in the brains of rodents and humans (Section 2). We briefly summarize the well-known sex differences in VP synthesis and fiber distribution in the brain of rodents and other species (for a more extensive review, see De Vries and Panzica, 2006). Interestingly, compared to VP, there is much less research regarding sex differences in OT synthesis in the brain. We generally find that, while there are robust sex differences in VP synthesis in conserved brain regions across species, there are fewer sex differences in OT synthesis in the brain and such sex differences are specific to particular brain regions and species.

Compared to sex differences in VP and OT peptide synthesis, even less is known about sex differences in OT and VP receptors

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in the brain. We therefore discuss the current knowledge of sex differences in these receptor systems in rodent and human brains (Section 3), as well as show new data of sex differences in the VP V1a receptor (V1aR) in the rat brain (Section 3, Figs 1 and 2). Interestingly, of the relatively few studies across various species, males seem to have higher V1aR and OT receptor (OTR) expression compared to females.

Despite the reported sex differences in VP and OT systems, surprisingly few comparative studies have investigated the behavioral functions of OT and VP systems in males and females using the same design. Importantly, those studies that do investigate the role of VP and OT in social behavior in both sexes often demonstrate a robust sex-specific modulation of social behavior by VP and OT systems in a variety of rodent species and humans (Section 4). Finally, we provide a short general discussion on the main findings and propose future directions (Section 5). Interestingly, the expression of VP and OT receptors in the rodent brain are non-overlapping (Section 5, Fig 3), suggesting possible implications for either complementary or distinct behavioral functions of VP and OT, a rather unexplored but important area for future research.

2. Sex differences in vasopressin and oxytocin synthesis and projections in the brain

2.1. Vasopressin

VP acts as a hormone in the periphery and as a neuromodulator in the brain. VP-producing magnocellular neurons of the paraventricular nucleus (PVN) and supraoptic nucleus (SON) of the hypothalamus project to the posterior pituitary, where VP is released into the general circulation as a hormone (Brownstein et al., 1980; Young and Gainer, 2003). As a hormone, it is involved in the regulation of blood pressure and water retention in the body (Silva et al., 1969; Ishikawa, 1993). VP is also produced in parvocellular neurons of the PVN that project to the anterior pituitary (Armstrong, 2004). From here, VP stimulates the release of adrenocorticotropic hormone, which, in turn, stimulates glucocorticoid release from the adrenal cortex (Gillies et al., 1982). As such, VP is part of the hypothalamic–pituitary–adrenal (HPA) axis, a system involved in the neuroendocrine stress response (Herman, 1995; Volpi et al., 2004). In addition, VP-synthesizing cells in the PVN, SON, suprachiasmatic nucleus of the hypothalamus (SCN), bed nucleus of the stria terminalis (BNST) and medial amygdala (MeA) project centrally to multiple areas in the brain (Swaab et al., 1975; Buijs, 1978; Sofroniew and Weindl, 1978; Buijs and Swaab, 1979; Buijs, 1980; Sofroniew, 1980; Sofroniew, 1983; Rood and De Vries, 2011). It should be noted that a recent study in mice showed that the VP-synthesizing cells within the amygdala are located in the intra-amygdaloid BNST rather than the MeA (Otero-Garcia et al., 2014). However, it is not clear whether this is specific to mice or a more general feature. Therefore, we will refer to these VP-synthesizing cells as being located in the MeA across species. Upon its central release, VP can modulate the activation of many brain regions via binding to vasopressin receptors (discussed further in Section 3.1), thereby regulating social, emotional, and cognitive behaviors (Veenema and Neumann, 2008; Koshimizu et al., 2012; Albers, 2014).

Importantly, VP synthesis and VP fiber projections are sexually dimorphic in specific areas of the brain (Tables 1 and 3). De Vries et al. (1981) were the first to discover the sexually dimorphic nature of VP in the rat brain, and reported that there were more VP-immunoreactive fibers in the lateral septum (LS) and lateral habenular nucleus in males compared to females (De Vries et al., 1981). De Vries and colleagues further discovered that this sex difference was androgen-dependent. Testosterone injections in females or in neonatally castrated males resulted in VP fiber density levels similar to that in control males when given in the first, second, or third week of life (De Vries et al., 1983). The sex difference in LS–VP fiber density originates primarily from VP neurons in the BNST, as lesions to the BNST, but not the PVN, decreased VP-immunoreactive fiber density in the LS (De Vries and Buijs, 1983). Additional studies found that LS–VP fibers also originate in the MeA (Caffé et al., 1987). Not surprisingly, VP synthesis in these areas is also sexually dimorphic, with males having a higher number of VP-immunoreactive neurons and higher VP mRNA expression in the BNST and MeA compared to females (Van Leeuwen et al., 1985; Miller et al., 1989; Wang and De Vries, 1995). VP synthesis in the BNST and MeA is also dependent on gonadal hormones, as castration in males decreased the number of VP-immunoreactive neurons and VP mRNA expression in the BNST and MeA (Van Leeuwen et al., 1985; Miller et al., 1992).

Although the aforementioned studies on sex differences were all performed in rats, similar sex differences in BNST and MeA VP have been found across a wide variety of rodent species (summarized in De Vries and Panzica, 2006), including mice (De Vries et al., 2002; Bakker et al., 2006; Gatewood et al., 2006; Rood et al., 2013), voles (Wang, 1995; Wang et al., 1996; Lonstein and De Vries, 1999), gerbils (Crenshaw et al., 1992), European hamsters (but season-dependent; Buijs et al., 1986), and garden dormice (but season-dependent; Hermes et al., 1990). Male prairie voles additionally show more VP-immunoreactive fibers in the ventral pallidum compared to females (Lim et al., 2004a). Non-mammalian vertebrates also show similar sex differences in vasotocin (homologous of VP) which is expressed in areas homologous to the BNST and MeA and in vasotocin projections from these areas (summarized in De Vries and Panzica, 2006). However, there are some exceptions, such as the Syrian hamster, which seems to lack VP cells in the BNST and MeA (Albers et al., 1991; Ferris et al., 1995; Miller et al., 1999). The presence of sex differences in BNST/MeA VP is less clear in primates, which could be due to limited number of studies. Of those studies that included both males and females, no sex differences in BNST-VP were found in macaques (Caffé et al., 1989) and humans (Fliers et al., 1986), whereas male marmosets have more VP-immunoreactive cells in the BNST than female marmosets (Wang et al., 1997a). None of these studies found VP-immunoreactive fibers in the LS, while VP-immunoreactive fibers were found in other brain areas (Caffé et al., 1989; Fliers et al., 1986; Wang et al., 1997b).

In contrast to the BNST and MeA, no sex differences in VP mRNA expression in the PVN have been found in adult rats (Table 4), nor in weanling (Paul et al., 2014) or juvenile (Taylor et al., 2012) rats. Less consistent are findings for VP synthesized in the SON. Although we did not find a sex difference in VP mRNA expression in the PVN of adult Wistar rats (Table 4), higher VP mRNA expression in the SON was found in juvenile male compared to juvenile female Wistar rats (Taylor et al., 2012) and larger VP neurons in the SON were found in adult male compared to adult female Sprague–Dawley rats (Madeira et al., 1993). The latter finding seems in line with higher plasma VP and urinary VP concentrations in male versus female Sprague–Dawley rats, a sex difference that was abolished by gonadectomy and restored by testosterone and ovarian hormone replacement in males and females, respectively (Share et al., 1988).

VP synthesis in hypothalamic regions of most other rodent species studied is not different between males and females, except for two species that do show sex differences (Tables 1–3). In detail, VP synthesis in hypothalamic regions is similar between male and female mice (PVN and SON: Joca et al., 2013; Steinman et al., 2015), voles (PVN, SON, SCN in prairie, pine, meadow, and montane voles: Wang, 1995; Wang et al., 1996), Mongolian gerbils (PVN, medial preoptic area [MPOA], lateral hypothalamus [LH] and