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Sex-specific modulation of juvenile social play by vasopressin

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Summary Social play activities among juveniles are thought to contribute to the development of social and emotional skills in humans and animals. Conversely, social play deficits are observed in developmental neuropsychiatric disorders. Importantly, many of these disorders show sex differences in incidence, course of the disease, and severity of symptoms. We hypothesized that sex differences in the neural systems controlling social behavior can contribute to these differences. We therefore studied the involvement of the sexually dimorphic vasopressin and oxytocin systems, which have been implicated in these disorders, in juvenile social play behavior. Single-housed 5-week-old juvenile male and female rats were exposed in their home cage to an age-and sex-matched novel conspecific for 10 min, and social play behaviors were recorded. We found no consistent sex differences in duration or elements of social play in vehicle-treated rats. However, intracerebroventricular injection of the specific vasopressin 1a receptor (V1aR) antagonist $(CH_2)_5$Tyr(Me^2)AVP significantly reduced social play behaviors in males while increasing them in females. Intracerebroventricular injection of the specific oxytocin receptor antagonist des-Gly-NH_2,d$(CH_2)_5$[Tyr$(Me)^2$,Thr^4]OVT did not alter social play in either sex. To locate the effects of V1aR blockade on social play, we targeted the lateral septum, a sexually dimorphic brain region showing denser vasopressin fibers in males than in females and an abundant expression of V1aR in both sexes. Surprisingly, blockade of V1aR in the lateral septum increased social play behaviors in males, but decreased them in females. These findings suggest sex- and brain region-specific roles for vasopressin in the regulation of social play behavior in juvenile rats.

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1. Introduction

Social play (also referred to as play-fighting or rough-and-tumble play) is predominantly displayed by juvenile animals, including human children (Panksepp, 1981; Bekoff & Byers, 1998; Pellis & Iwaniuk, 2000; Burghardt, 2005). Social play is thought to contribute to the development of social and emotional skills in humans and animals (Baldwin, 1986; Pellegrini, 1988; Vanderschuren et al., 1997; Bekoff & Byers, 1998; Van den Berg et al., 1999; Guralnick et al., 2006; Cordoni & Palagi, 2011). Conversely, social play deficits are observed in neurodevelopmental disorders such as autism spectrum disorders (ASD), early-onset schizophrenia, and attention-deficit/hyperactivity disorder (Alessandri, 1992; Moller & Husby, 2000; Jordan, 2003). Importantly, many of these disorders show sex differences in incidence, course of the disease, and severity of symptoms. For example, ASD typically appear early in development and are four to eight times more common in males than in females (Fombonne, 2003; Beaudet, 2012). However, little is known about the neural basis of sex-biases in neurodevelopmental disorders.

The neuropeptides vasopressin (AVP) and oxytocin (OXT) have been found to modulate various social behaviors such as pair bonding, aggression, and social recognition in adult rodents (Donaldson & Young, 2008; Veenema & Neumann, 2008; Goodson & Thompson, 2010). In adult humans they have been found to modulate social trust, social cooperation, and social cognition in adult humans (Kosfeld et al., 2005; Guastella et al., 2010; Rilling et al., 2012). However, less is known about the involvement of AVP and OXT in juvenile social play behaviors. Importantly, the AVP and OXT systems are sexually dimorphic (De Vries, 2008). For example, males compared to females have more AVP-expressing cells in the bed nucleus of the stria terminalis (BNST) and medial amygdala (MeA) and denser AVP-axonal projections to limbic brain regions, especially to the lateral septum (LS) (De Vries et al., 1981; Van Leeuwen et al., 1985; Szot & Dorsa, 1993). This sex difference, already present in juveniles (De Vries et al., 1981), is found in many mammalian species (De Vries & Panzica, 2006). In addition, the synthesis of OXT in the hypothalamus is significantly higher in female than in male mice (Haussler et al., 1990) while OXT receptor (OTR) binding densities in several brain regions are higher in male than in female rats (Uhl-Bronner et al., 2005; K.M. Dumais and A.H. Veenema, unpublished observations). These findings suggest that AVP and OXT modulate social behaviors in sexually dimorphic ways, but do not necessarily suggest that these neuropeptides cause sex differences in behavior (De Vries, 2004). For example, AVP facilitates partner preference in male, but not female, prairie voles (Cushing et al., 2001). Moreover, reduced anxiety is found in AVP V1a receptor (V1aR) knockout male, but not female, mice (Bielsky et al., 2004, 2005). In humans, AVP has sex-specific effects on social communication (Thompson et al., 2006) and V1aR polymorphisms correlate with pair-bonding behavior in men, but not in women (Walum et al., 2008). Sex differences in behavioral or brain responses were also found after manipulations of the OXT brain system in voles (Insel & Hulihan, 1995) and after intranasal OXT application in humans (Kubzansky et al., 2012; Lischke et al., 2012).

To test the hypothesis that AVP and OXT also affect social behavior in sexually dimorphic ways during development, we studied the effects of acute pharmacological manipulations of the AVP and OXT systems on social play in 5-week-old male and female rats. We first studied the effects of intracerebroventricular (ICV) blockade of V1aR or ICV blockade of the OTR on social play behaviors. To test the hypothesis that the sexually dimorphic effects of ICV V1aR blockade were mediated by the sexually dimorphic projections of the BNST

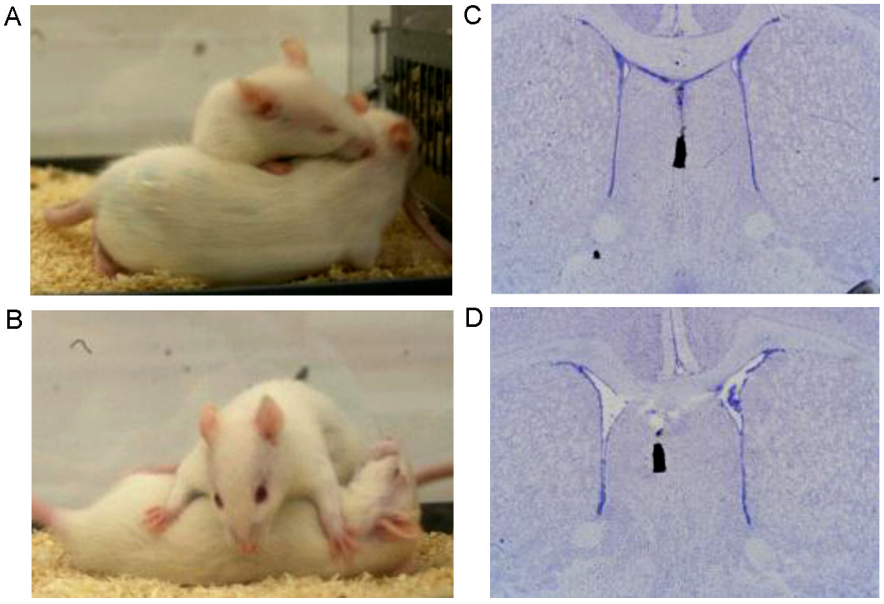

Figure 1 (A and B) Pictures illustrate behavioral elements/postures of social play in juvenile rats: (A) shows an attack toward the nape of the neck of the intruder rat; (B) shows pinning and supine positions. (C and D) Pictures of Nissl-stained coronal brain sections illustrate the injection location in the septum using charcoal as marker. For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.

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