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Sex differences in the regulation of social and anxiety-related behaviors: insights from vasopressin and oxytocin brain systems

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To understand how the brain regulates behavior, many variables must be taken into account, with sex as a prominent variable. In this review, we will discuss recent human and rodent studies showing the sex-specific involvement of the neuropeptides vasopressin and oxytocin in social and anxiety-related behaviors. We discuss that sex differences can be evident at pre-pubertal ages as seen in the sex-specific regulation of social recognition, social play, and anxiety by the vasopressin system in juvenile rats. We further discuss that the oxytocin system in humans and rodents alters brain activation, anxiety, and sociosexual motivation in sex-specific ways. Finally, we propose that knowledge of vasopressin and oxytocin mediated sex-specific brain mechanisms can provide essential insights into how these neuropeptide systems contribute to sex-specific vulnerability as well as resilience to perturbations, with subsequent relevance to social and emotional disorders.

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Studying both sexes provides a more complete understanding of how the brain modulates behavior

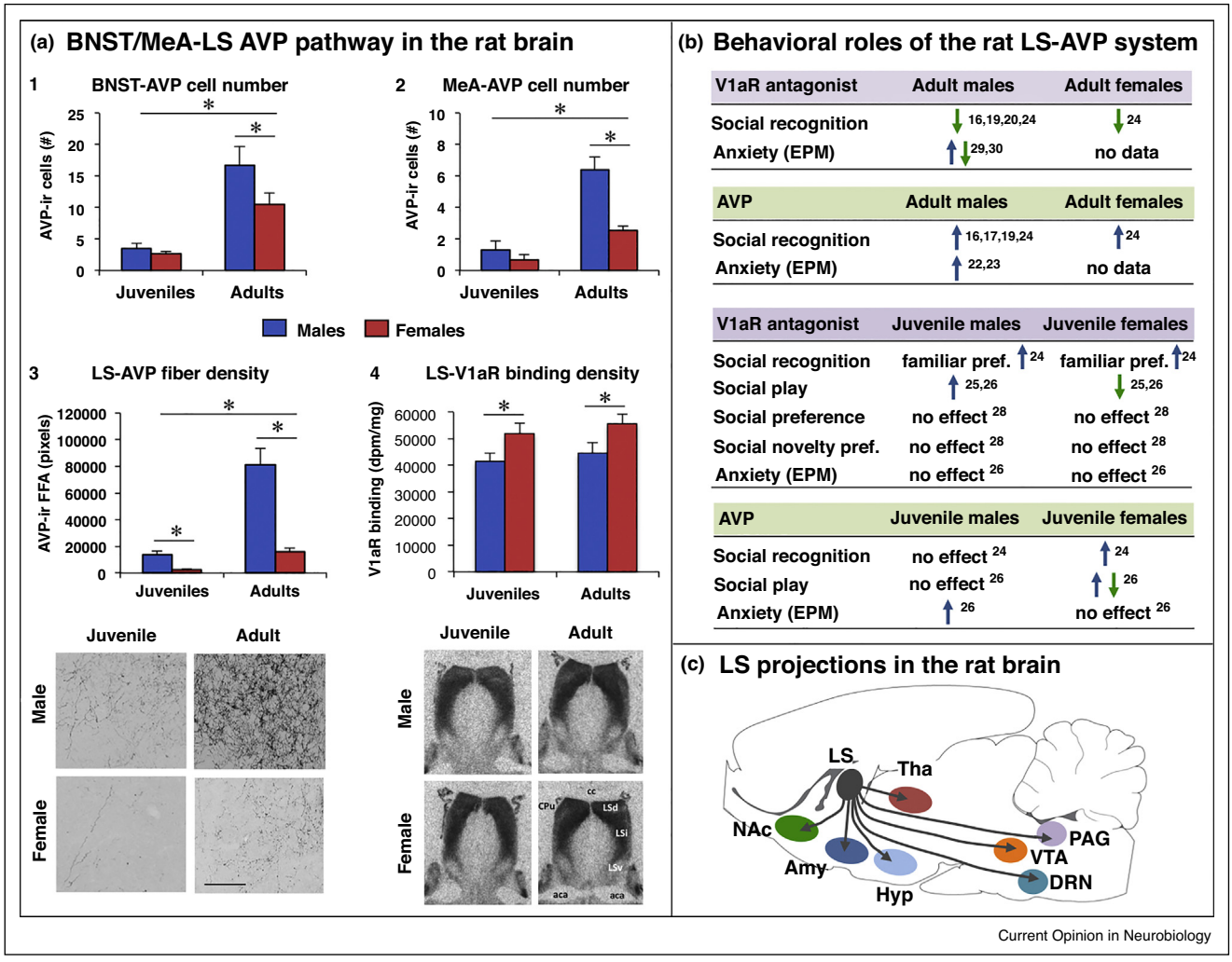
The 2014 National Institutes of Health policy of implementing sex as biological variable has stimulated a lot of discussion, with pros and cons of the policy voiced by a wide variety of scientists [1–5]. There is a strong tendency of simplifying and standardizing experimental designs and methods, including using a limited number of model organisms, contexts, and behavioral tests, and limiting studies to one sex [6–8,9••]. This approach has been essential to gain a basic understanding of how the brain modulates behavior. Yet, we have obtained a very narrow and incomplete view of brain function [6]. In a first step to gain a more complete and meaningful understanding of how the brain mediates behavior, both sexes must be studied. Although males and females may be similar at the behavioral level, they often use different mechanisms to respond to social and emotional challenges and opportunities [10,11•]. To illustrate the importance of studying both sexes, this mini-review will highlight a few recent studies that have provided insights into the behavioral roles of the neuropeptides vasopressin (AVP) and oxytocin (OXT) in males and females, often with intriguing sex-specific outcomes.

Involvement of the AVP system in the sex-specific regulation of social and anxiety-related behaviors (Figure 1)

AVP is synthesized in several hypothalamic and extrahypothalamic regions and can modulate the activation of numerous brain regions through the AVP V1a receptor (V1aR). In this section, we will discuss recent studies that focused on the behavioral roles of the AVP system in the lateral septum (LS), a key brain region involved in the regulation of emotion, reward, and social behavior [12•]. The LS receives vasopressinergic innervations from the bed nucleus of the stria terminalis (BNST) and medial amygdala (MeA) [13,14]. The LS-AVP system in the rat shows complex sex differences: compared to females, adult males have denser AVP axonal fibers, but less V1aR binding [15•,16–18] (Figure 1a). Many studies have shown an important role of the LS-AVP system in the regulation of various social behaviors in adult male rodents [19–26]. Recent comparative studies have demonstrated the involvement of the LS-AVP system in social behavior regulation in females as well. In detail, application of a V1aR antagonist into the LS impaired social recognition in both adult male and female rats [17] (Figure 1d). Likewise, administration of AVP into the LS prolonged social recognition in both adult male and female rats [17] (Figure 1d). Together, these findings indicate that, despite sex differences in AVP fiber and V1aR densities, the LS-AVP system in adult rats seems to play a similar role in the regulation of social recognition in males and females.

Interestingly, a similar analysis of juvenile (5-week-old) rats revealed sex differences in the function of the LS-AVP system. LS-AVP fiber density is significantly lower

Figure 1



Sex differences in the vasopressin (AVP) system in the rat brain and sex-specific regulation of behavior by the lateral septum (LS) AVP system in rats. **(a)** Sex differences are found in the AVP pathway from bed nucleus of the stria terminalis (BNST) and medial amygdala (MeA) to the lateral septum (LS): (1) Adult male rats have more AVP-immunoreactive (AVP-ir) cells in the posterior BNST than adult female rats, while there are fewer cells and no sex difference in juvenile rats [adapted from Ref. [16]]. (2) Adult male rats have more AVP-immunoreactive (AVP-ir) cells in the posterodorsal MeA than adult female rats, while there are fewer cells and no sex difference in juvenile rats [adapted from Ref. [16]]. (3) In the ventral caudal part of the LS, adult and juvenile male rats show denser AVP-ir fibers than females, and adults show denser AVP-ir fibers than juveniles [adapted from Ref. [16]]. Photomicrographs (scale bar = 100 μm) depict AVP-ir fibers in the ventral caudal part of the LS of a juvenile and adult male and female rat [adapted from Ref. [16]]. (4) In the dorsolateral LS, juvenile female rats have denser AVP V1a receptor (V1aR) binding than juvenile male rats, and adults show denser V1aR binding than juveniles [adapted from Ref. [17]]. Autoradiographs show dense V1aR binding in the dorsolateral LS, which includes the dorsal part of the LS (LSd) and the lateral portion of the intermediate part of the LS (LSi) [adapted from Ref. [17]]. **(b)** Pharmacological studies in adult rats demonstrate that, despite sex differences in the LS-AVP system, V1aR antagonist impairs and exogenous AVP improves social recognition in both male [17,19,20,22,23] and female [17] rats. The role of the LS-AVP system is more complicated in juvenile rats: the LS-AVP system regulates social play (V1aR antagonist, exogenous AVP) [27•,28] and social recognition (exogenous AVP) [17] in sex-specific ways. It should be noted that the same dose of the V1aR antagonist $d(CH_2)_5[Tyr(Me)^2]AVP$ (10 ng/0.5 μl) and the same dose of AVP (200 pg/0.5 μl) were used in [27•,28], suggesting age differences in the role of the LS-AVP system regulating social recognition. Social recognition is reflected by the ability to discriminate between a novel and a familiar same-sex 3-week-old stimulus rat; Social preference is reflected by the preference to investigate a novel conspecific over a novel object; Social novelty preference is reflected by the preference to investigate a novel conspecific over a cage mate. The role of the LS-AVP system in anxiety-related behavior as determined on the elevated plus-maze (EPM) reveals for the most part anxiogenic effects of LS-AVP in adult and juvenile male rats. It should be noted that an increase in anxiety was seen after chronic V1aR antagonist application in the LS [32], while a decrease in anxiety was seen after a single V1aR antagonist application in the LS [31]. **(c)** The LS has many projections to telencephalon, diencephalon and mesencephalon, with the most notable output to the ventral tegmental area (VTA), nucleus accumbens (NAc), periaqueductal grey (PAG), dorsal raphe nucleus (DRN), hypothalamus (HYP), amygdala (AMY), and thalamus (THA) [12•,35]. It is possible that sex differences in the behavioral effects of LS-AVP manipulations can be, in part, attributed to sex differences in the recruitment of specific LS outputs to mediate behavior. These can include LS-induced changes in mesolimbic reward systems (through e.g., VTA and Nac), neuroendocrine and autonomic projections (through e.g., HYP, PAG, and indirectly via