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Review

Toward understanding how early-life social experiences alter oxytocin- and vasopressin-regulated social behaviors

Alexa H. Veenema *

Neurobiology of Social Behavior Laboratory, Department of Psychology, Boston College, 140 Commonwealth Avenue, McGuinn 522, Chestnut Hill, MA 02467, USA

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ABSTRACT

The early-life social environment has profound effects on brain development and subsequent expression of social behavior. Oxytocin and vasopressin are expressed and released in the brain and are important regulators of social behavior. Accordingly, the early social environment may alter social behaviors via changes in the oxytocin and/or vasopressin systems. To test this hypothesis, and to gain mechanistic insights, rodent models mimicking either a deprived (e.g. maternal separation) or enriched (e.g. neonatal handling) early social environment have been utilized. Findings indeed show that differences in the quality of the early social environment are associated with brain region-specific alterations in oxytocin and vasopressin expression and oxytocin receptor and vasopressin 1a receptor binding. Early social environment-induced changes in oxytocin and vasopressin systems were associated with changes in several forms of social behavior, including maternal care, aggression, play-fighting, and social recognition. First studies provide evidence for a causal link between altered vasopressin responsiveness and impairments in social recognition in rats exposed to maternal separation and a role for epigenetic mechanisms to explain persistent increases in vasopressin expression in mice exposed to maternal separation. Overall, initial findings suggest that oxytocin and vasopressin systems may mediate early social environment-induced alterations in social behavior. Additional comprehensive studies will be necessary to advance our understanding to what extent changes in oxytocin and vasopressin underlie early social environment-induced alterations in social behavior.
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Contents

Introduction

The early social environment plays an important role in shaping individual differences in social behavior. In mammals, the early social environment mainly consists of parent–offspring (often mother–infant) interactions. These interactions are very intense and span a

* Fax: +1 617 552 0523.
E-mail address: alexa.veenema@bc.edu.

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considerable period of offspring development. The high amount of physical contact with the mother is, apart from warmth and nutrition, important for the infant's overall maturation, as it constraints physiological and behavioral responses to stressful stimuli (Kaffman and Meaney, 2007; Kraemer, 1997; Kuhn and Schanberg, 1998; Levine, 2005). Social interactions with the adult caregiver are also essential for the development of social skills of the offspring. Thus, physical contact and social interactions may provide important mechanisms through which the quality of the early social environment is transmitted to the offspring (Champagne, 2008). Accordingly, parent–offspring interactions may play a critical role in mediating adaptive responses of the offspring to specific early environmental conditions. For example, low levels of maternal care may reflect an adverse environment and the offspring should show a behavioral phenotype that will prepare them for particular environmental demands (Champagne, 2008). On the other hand, higher levels of maternal care may reflect an enriched environment. Individuals reared in either deprived or enriched social environments should be prepared for survival in such environments. Accordingly, early social experience-induced differences in social behavior can be seen as adaptive responses to prepare an individual for life in that particular early social environment. Yet, functional behavioral adaptations may have their trade-offs. For example, low socio-economic status has been associated with increased hypothalamic–pituitary–adrenal (HPA) axis reactivity which may serve to better prepare the individual for conditions of threat on a day-to-day basis (Miller et al., 2009). However, long-term increases in HPA axis activity have lasting negative effects on mental and physical health (De Kloet et al., 2005). In addition to trade-offs, social disorders may also develop when the rearing environment is not a good predictor of the adult environment. For example, it has been suggested that adult diseases like depression might not be promoted by early life adversity per se, but by a mismatch of the early and the later actual environment (Schmidt, 2011). Both trade-offs and mismatches play a role in the development of social disorders as a function of the early social environment. Thus, the early social environment can lead to divergent developmental pathways with implications for the adult brain and behavior. A better understanding of the impact of early-life social experiences on the development of social behavioral phenotypes and their underlying brain mechanisms is important to understand individual differences in and pathological forms of social behavior.

Oxytocin and vasopressin as modulators of social behavior

Social behaviors are complex because they require the integration of emotional, cognitive, and motivational processes with internal and external rewarding stimuli (O'Connell and Hofmann, 2011). The neuropeptides oxytocin (OT) and arginine vasopressin (VP) have been widely implicated in the regulation of social behavior in mammalian species ranging from rodents to humans. For example, OT promotes maternal care (Fahrbach et al., 1984), social recognition (Ferguson et al., 2001), and social trust (Kosfeld et al., 2005). VP regulates parental behavior (Bosch and Neumann, 2008; Wang et al., 1994), aggression (Ferris and Potegal, 1988; Gobrogge et al., 2009; Veenema et al., 2010), social scent marking (Ferris et al., 1984), and social recognition (Veenema et al., 2011; Dantzer et al., 1988; Engelmann and Landgraf, 1994). For more in depth reviews on the roles of OT and VP in social behavior, see e.g. Caldwell and Young (2006), Donaldson and Young (2008), Goodson and Thompson (2010), and Veenema and Neumann (2008).

OT and VP are synthesized in magnocellular neurons of the hypothalamic paraventricular nucleus (PVN) and supraoptic nucleus (SON) and are transported along their axons to the posterior pituitary and released from there into the blood stream to act on target organs in the periphery. VP from parvocellular neurons in the PVN is transported via the median eminence to the anterior pituitary where it stimulates the release of ACTH into the blood stream. OT and VP synthesized in the PVN and SON are also released in forebrain and hindbrain regions via axonal projections (Sofroniew, 1983), from dendrites (Landgraf and Neumann, 2004; Ludwig and Leng, 2006) and in an en passant or parasynaptic manner (Griffin et al., 2010; Ross and Young, 2009). OT may also be synthesized in additional hypothalamic and in extrahypothalamic areas and subsequently released in the brain (Ross and Young, 2009). VP is further synthesized in the bed nucleus of the stria terminalis (BNST), medial amygdala (MeA), locus coeruleus (Caffé and van Leeuwen, 1983), and it has been recently found to be synthesized in the olfactory bulb (Tobin et al., 2010). VP-expressing neurons in the BNST and MeA show projections to several forebrain regions, including the lateral septum (Caffé et al., 1987; De Vries and Buijs, 1983). VP and OT mediate their effects on social behavior via activation of the VP 1a receptor (V1aR), the VP 1b receptor (V1bR), and the OT receptor (OTR) that are expressed in many brain regions (including cortical, limbic, hypothalamic and brain stem areas) (Barberis and Tribollet, 1996). While OT and VP synthesizing brain regions and their fiber projections seem highly conserved (Goodson, 2008), V1aR and OTR distribution patterns in the brain show high variations across species (Donaldson and Young, 2008; Insel, 2010). Such differences in receptor distributions may mediate species-typical social systems (e.g. differences in grouping preferences, like territorial vs. gregarious, and differences in mating systems, like monogamous vs. polygamous) (Ophir, 2011). Within one species, differences in the activation of distinct OT and VP cell groups as well as differences in density of receptors may allow for individual differences in the expression of social behavior.

OT and VP differ by two out of nine amino acids and may exhibit some receptor cross-reactivity (Barberis and Tribollet, 1996), allowing potential interactions between the two neuropeptide systems. OT and VP can be detected in the rat brain early in development, with VP appearing in the SON and PVN during embryonic development and OT is detected in the SON and PVN within a few days after birth (Bloch et al., 1990; Buijs et al., 1980; Choy and Watkins, 1979; Van Tol et al., 1986). VP in the BNST and MeA is detected during early postnatal development (Szot and Dorsa, 1993). Together, this suggests that the early social environment has the potential to substantially shape OT and VP systems, which, in turn, will alter the expression and regulation of social behavior throughout life. The following paragraphs discuss this topic in more detail. Specifically, findings in rodent models of early-life social deprivation and early-life social enrichment with relevance to alterations in OT/VP systems and social behavior are discussed. When possible a link to human studies is provided. Initial studies exploring underlying mechanisms and causation to alterations in social behavior are also discussed. Finally, suggestions for future directions are provided.

Effects of deprived and enriched early social environments on OT and VP systems

Exposure to a deprived early-life social environment has been associated with increases in anxiety- and depression-like behaviors (Heim and Nemeroff, 2001) and increases in aggression (Veenema, 2009). The most commonly used rodent model of early social deprivation is maternal separation of rats or mice (daily 3-h separation of litters from the dam during the first two weeks of life). By contrast, exposure to an enriched early-life social environment seems to decrease anxiety and stress response systems and increase social competence (Branchi, 2009; Korosi and Baram, 2010; Levine, 1957). Rodent models of early social enrichment include neonatal handling of rats and communal rearing of mice. Naturally occurring differences in levels of maternal care in rats are also being used as models of deprived vs. enriched early-life social environments (Champagne, 2011). Table 1 provides an overview and brief description of relevant rodent models of deprived and enriched early-life social environment.