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Review

Developmental experiences and the oxytocin receptor system

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ABSTRACT

The long-term effects of developmental experiences on social behavior, and the neuropeptide systems such as oxytocin which subserve the behavior, are still little understood. In this article, we review various types of early experience, including normal development, knockout models, pharmacological exposures, and early social experiences. We consider the processes by which experience can affect oxytocin receptor binding, and what is known about the directionality of experience effects on oxytocin receptors. Finally, we attempt to synthesize the literature into a predictive model as to the direction of early experience effects on oxytocin receptor binding potential, and whether these changes have functional significance. These predictions are relevant to current human health practice, given proposals to use chronic intranasal oxytocin to treat developmental disorders including autism and schizophrenia.

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Contents

Introduction

The oxytocin (OT) neuropeptide system, as well as the closely related vasopressin (AVP) system, play central roles in the regulation of social behaviors in mammals (Carter et al., 1995, 2008a,b; Young et al., 2011; Young, 2009), with involvement in behaviors including but not limited to maternal and paternal care, pair-bonding, social investigation, and sexual behavior. Recent studies have also confirmed the ability of early experiences, whether relevant to natural experience (ex. variation in social grouping), behavioral experiences outside of natural experience (ex. experimenter handling), or pharmacological manipulation, to lead to long-term changes in both social behavior and neuropeptide systems in adults (Ahern and Young, 2009; Bales and Carter, 2003a,b; Bales et al., 2007a,b,c; Carter et al., 2008a,b; Lukas et al., 2010).

What is often surprising is the direction of these changes, given the long-standing characterization of OT as a "pro-social" hormone associated with positive social behaviors (Carter et al., 1992; Zak et al., 2004). For instance, OT exposure in adulthood facilitates the formation of a pair-bond in female prairie voles (*Microtus ochrogaster*) (Cho et al., 1999; Williams et al., 1994). Pair-bonds are usually measured by a significant preference for the familiar partner over a stranger (Williams et al., 1992). However, some dosages of neonatally administered OT lead to an adult preference for the stranger over the partner (Bales et al., 2007a). Furthermore, AVP V1a-type receptors are changed by this early OT manipulation while OT receptors (OTR) remain unchanged (Bales et al., 2007b). In a second example, we have shown that a manipulation in which prairie vole parents are moved in a cup during cage changes (rather than handled by the scruff of the neck as is common in many vole colonies), causes a less social and more anxious phenotype in offspring (Bales et al., 2007c). This "reduced handling" manipulation also causes up-regulation of OTR in several areas, including the nucleus accumbens (Nacc), bed nucleus of the stria terminalis (BNST), and lateral septum

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(LS) in females (Bales et al., 2011). Thus, OTR are higher in the same animals that are less social (including not forming pair-bonds normally).

A long-standing hypothesis is that many of these developmental behavioral changes are facilitated through changes either in OTR or one of the three subtypes of AVP receptor, usually AVP V1a which are abundant throughout the brain (Burbach et al., 1995). It is clear that OTR can undergo large up- and down-regulations even in adulthood, for instance during pregnancy both in the uterus (Soloff et al., 1979) and centrally (Insel, 1990). In this review, we will discuss what is known about the long-term effects of developmental experiences and how we might understand how these changes occur via the OTR and AVP V1a receptor systems, with some reference to changes in production of the peptides as well.

Normal development of OTR

OTR are seven transmembrane G-protein coupled receptors (Gimpl and Fahrenholz, 2001). To date, only one OTR has been cloned, although the existence of subtypes has been postulated (Verbalis, 1999). This possibility is especially interesting given the recent finding of an alternate form of OT in some species of New World monkeys (Lee et al., 2011). OT, as well as the AVP receptor types 1a and 1b, couples to the PI/Ca++ signal transduction pathway (Burbach et al., 1995).

Some general principles of receptors during central nervous system development are useful to review. The expression and distribution of metabotropic receptors in particular are often drastically different during development than in adulthood, with transient expression suggesting that function may vary during development (Shaw, 1996). This adult expression may be affected by agonism of the receptors (for instance, due to pharmacological interventions) or disruption of normal afferent input during development (for instance, lack of normal touch leading to lack of OT release). In particular, desensitization of the receptor, or reduction of second messenger activity, can occur; this can lead to down-regulation including enzymatic degradation of the receptor (Shaw, 1996). In G-protein coupled receptors including OTR and AVP V1a receptors, desensitization is often due to receptor phosphorylation (Ancellin et al., 1999; Evans et al., 1997; Sibley et al., 1987) and internalization (Gimpl and Fahrenholz, 2001). Desensitization is known to occur with OTR in adulthood; continuous infusion of OT leads to receptor down-regulation (Insel et al., 1992). It is also possible for receptor affinity to change during development (Shaw et al., 1985), although that does not seem to be the case for OTR (Tribollet et al., 1989). Infant OTR also share electrophysiological characteristics with adult receptors and are therefore probably functional (Tribollet et al., 1989).

OTR in the rat brain are present during development, as detected by gene expression (Chen et al., 2000; Yoshimura et al., 1996) and receptor binding autoradiography (Tribollet et al., 1989), during embryonic life beginning at E12–14. AVP V1a and V2 are also detectable in rat telencephalon from E12 (Chen et al., 2000). In rats, two populations of OTR gene expression can be differentiated, one group that is expressed transiently [including the caudate putamen (CP), cingulate cortex (CC), anterior thalamic nuclei, and ventral tegmental area] and a group that has constant, abundant expression [including the anterior olfactory nucleus, tenia tecta, BNST, ventromedial hypothalamic nucleus (VMH)] (Yoshimura et al., 1996). The gene expression results are mostly consistent with receptor binding assays which showed a distinct “infant” pattern (i.e. transient expression) vs. “adult” pattern which was established around PND 19–22, with some additional changes around day 40 (puberty), including an increase in binding in the ventral pallidum and ventromedial hypothalamic nucleus. As with OTR gene expression, OTR binding in the posterior cingulate (PCC) and some other areas is high at PND 10 and no longer present in adults (Shapiro and Insel, 1989), while binding in the bed nucleus of the stria terminalis appears later and is present in the adult. One major difference was that OTR gene expression was detectable in the ventromedial hypothalamus and bed nucleus much earlier than receptor binding (Shapiro and Insel, 1989; Tribollet et al., 1989; Yoshimura et al., 1996).

In one study, AVP receptor binding was detectable with autoradiography from E20 in the septum and the lateral reticular nucleus in Wistar rats. Specific binding was first detected at E16 in a second study (Tribollet et al., 1991). AVP V1a mRNA was detectable on E12 in the telencephalon (Chen et al., 2000). As with OTR, AVP receptor expression is transient in several areas (including the dorsal raphe, locus coeruleus, etc.) during development, with much lower expression in the adult. Also as with OTR, infant AVP receptors appear to be functional as determined by electrophysiology (Tribollet et al., 1991).

Data on development of OTR and AVP V1a in species other than rats are sparse. Just as OTR and AVP V1a vary by species in adult animals (Beery et al., 2008; Campbell et al., 2009; Insel and Shapiro, 1992; Shapiro and Insel, 1992;Young et al., 1996), they may also vary in infants of different species. In the LS, in which OTR binding differs between adult prairie and montane voles (*Microtus montanus*), species differences in OTR binding were not apparent until the third postnatal week (Wang and Young, 1997). Species differences in AVP V1a in the LS were apparent at postnatal week two (Wang et al., 1997a,b). Overall, findings in prairie voles suggested transient expression and reorganization of AVP V1a receptors, as was also the case for rats (Wang et al., 1997a,b). Given the large variety of expression of OTR and AVP V1a in adults of some species such as prairie voles (Phelps and Young, 2003), as well as differences in distribution between the few species already examined (including monogamous and polygynous voles, rats, mice, tuco-tucos, and singing mice) there is a strong argument for more basic data on development of these receptor systems in different species.

Knockout mice and OTR

What happens to OTR and AVP V1a in the absence of other types of developmental signaling, particularly absence of the peptide? Knockout mice can give us valuable information on the effects of early experience on OTR. The first and most interesting case would probably be the OT knockout mouse (OTKO) itself; this mouse displays no OT mRNA content in the supraoptic or paraventricular nuclei, although there is no change in AVP production from wild-type (Nishimori et al., 1996). Despite this complete absence of OT developmentally, OTR binding in adult knockouts was similar in all regions studied. AVP V1a receptors were not examined in this study.

It was of note in the previous study that OTKO had normal sexual behavior and fertility, making the VMH of particular interest. A subsequent study compared VMH neurons in OTKO with wild-type littermate controls. Using electrophysiological methods, Ragnauth et al. (2004) showed that VMH neurons in female knockout mice were less responsive than those in wild-type mice; the same was not true for males. In males (females were not tested), neuronal responses to OT were more sensitive in the OTKO. Most OT-responsive neurons, in both knockout and wild-types, were also responsive to AVP (Ragnauth et al., 2004). Thus, AVP may be compensating for a lack of OT in OTKO mice.

Other types of knockouts also affect OTR. Haploinsufficient (+/−) reeler mice, which show down-regulation of reelin (a protein involved in neuronal migration), also show down-regulation of OTR (Liu et al., 2005). Reelin may also be involved in behavioral phenotypes similar to those found in schizophrenia and bipolar disorder (Teixeira et al., 2011). Peg3 knockout mouse females show reduced exploration and maternal care of pups, as well as higher maternal aggression. These females also had reduced OTR binding in the LS and medial preoptic areas (MPOA), neural areas crucial for maternal

behavior (Champagne et al., 2009). The intervening mechanisms for reduced OTR binding in these knockouts remain to be delineated.

Brattleboro rats, which lack AVP due to a natural mutation, showed developmental differences (when compared to Wistar rats) in AVP receptor expression, with up-regulations in some regions and down-regulations in other [notably, the central amygdala (CeA), dorsal hippocampus, and PCC] (Snijdewint et al., 1989). A second study found no differences between Long–Evans and Brattleboro rats in AVP receptor binding in five areas, including the caudate (CP), hippocampus (Hipp), cingulate cortex, septum, and amygdala (Petracca et al., 1986). Studies from various knockouts and mutants therefore seem to suggest a large role for systems other than OT itself to affect the developmental regulation of OTR, including possible compensatory roles for the absence of OT itself. In particular, it will be important to characterize AVP V1a receptor binding in OT knockout mice.

Early social experience and pharmacology; long-term effects on OTR and AVP V1a

Experiences ranging from mild to moderate changes, such as early handling and altered family structure, to more extreme changes including neonatal stress and pharmacological manipulations, can potentially produce changes in neuropeptide receptor expression and regulation. In this section, we review these manipulations and their effects on OT receptors (summarized in Table 1). One classic psychobiological paradigm is that of early handling or maternal separation (Denenberg et al., 1962; Levine, 1957; Levine and Lewis, 1959). In prairie voles, alterations in how animals are handled by experimenters during the first postnatal week result in changes in OTR binding (Bales et al., 2011). In a series of experiments, during cage changes parent prairie voles were either lifted by the scruff of the neck on various postnatal days (PND 1, PND 7, or PND 1–7) or transferred in a cup without the experimenter touching them ("reduced handling"). Females receiving reduced amounts of handling during the first week postpartum displayed increases in OTR binding in the Nacc, LS, and BNST compared to animals handled on PND 1, PND 7, and PND 1–7. Similar results were seen in males, where reduced early handling resulted in an increase in OTR binding in the BNST when compared to PND 1 handled animals. Reduced early handling in males also resulted in lower OT immunoreactivity (*ir*) in the supraoptic nucleus of the hypothalamus.

Other studies have documented differences in OT and AVP-*ir* after early handling, although they did not measure the receptor systems as well. Female rats handled on PND 1–10 displayed decreased OT-*ir* in the parvocellular paraventricular nucleus of the hypothalamus (pPVN) compared to animals not handled, while males receiving early handling showed a decrease in OT-*ir* in the pPVN and an increase in AVP-*ir* in the magnocellular PVN (mPVN) compared to non-handled animals (Todeschin et al., 2009; Winkelmann-Duarte et al., 2007).

Early social rearing conditions also play a role in OTR and AVP V1a binding. In a mouse model of social enrichment, Balb/c females reared communally have higher OTR binding in the dorsal and ventral LS, BNST, agranular insular cortex (InsCtx), and endopiriform cortex. AVP V1a binding was reduced in the dorsal LS (Curley et al., 2009a, b). Some of these changes persisted into the second generation of female offspring — there was a trend for increased OTR binding in the ventral LS and a decrease in AVP V1a binding in the dorsal LS. Using the monogamous prairie vole as a model of varying early family structure, offspring reared biparentally tend to show an increase in OTR binding in the BNST compared to offspring reared by single mothers (Ahern and Young, 2009). Rearing conditions have also been studied in non-human primates, although OTR have rarely been successfully studied in primate brains. In the rhesus monkey, nursery reared monkeys who have been removed from their mother within 48 h of parturition and reared individually in a nursery show decreases in cerebrospinal fluid oxytocin at 18, 24, and 36 months of age compared to monkeys reared in semi-natural environments by their mother (Winslow et al., 2003).

Varying the weaning age of offspring (and thus both housing conditions and social conditions) also resulted in an increase in neuropeptide binding in female C57BL/6J mice (Curley et al., 2009a,b). Those females allowed to remain in the natal nest until PND 28

Table 1
We attempt to summarize published data on early pharmacological and social experiences which might be expected to be manipulations of OT, and their long-term outcome as far as OTR and V1a receptor systems. Early OT conditions are defined as: Acute supraphysiological: single exposure exogenous treatments; Chronic supraphysiological: multiple exposure exogenous treatments; High physiological: treatment conditions which might be expected to induce high endogenous levels of OT, with either a positive or negative valence; Low physiological: treatment conditions which might be expected to induce low endogenous levels of OT. Only in the case of pharmacology is the actual level of early OT known for any of these studies.

Type of experience	Species	Presumed early OT condition	Adult OTR	Adult V1a	Reference
PND 1 OT administration (males)	Prairie vole	Acute supraphysiological	No change	Higher in PCC	Bales et al. (2007b)
PND 1 OTA administration (males)	Prairie vole	Acute supraphysiological	No change	Lower in MPOA, BNST, and LS	Bales et al. (2007b)
PND 1 OT administration (females)	Prairie vole	Acute supraphysiological	No change	Lower in MPOA, BNST, LS, PCC, and MdThal	Bales et al. (2007b)
PND 1 OTA administration (females)	Prairie vole	Acute supraphysiological	No change	Lower in BNST and PCC	Bales et al. (2007b)
Exposed prenatally to estrogenic compounds	Pine vole	Chronic supraphysiological ???	Decrease in CC	Not examined	Engell et al. (2006)
Raised biparentally vs. single mother	Prairie vole	High physiological (positive valence)	Marginally higher in BNST in biparental offspring	No change	Ahern and Young, (2009)
Raised communally vs. single mother	Mouse	High physiological (positive valence)	Higher in dorsal and ventral LS, BNST, agranular InsCtx, and endopiriform Ctx (after communal rearing)	Decreased in dorsal LS after communal rearing	Curley et al. (2009a)
High licking mother (female offspring)	Rat	High physiological (positive valence)	Higher in CeA and BNST Following adult estrogen treatment, higher in MPOA and LS	No change	Champagne et al. (2001) and Francis et al. (2000, 2002)
High licking mother (male offspring)	Rat	High physiological (positive valence)	No change	Higher in CeA	Francis et al. (2002)
Maternal separation (males)	Rat	High physiological (negative valence)	Decreased in agranular InsCtx, LS, and CP; increased in MPOA and VMH	Decreased in Arc; increased in LS, dentate, and piriform cortex	Lukas et al. (2010)
Reduced handling (females)	Prairie vole	Low physiological	High in Nacc, LS, and BNST	No change	Bales et al. (2011)
Reduced handling (males)	Prairie vole	Low physiological	High in BNST; no change in LS and Nacc	No change	Bales et al. (2011)
Knockout	Mouse	None	No change	Not examined	Nishimori et al. (1996)

showed an increase in AVP V1a binding in the BNST and MPOA and a trend for an increase in OTR binding in the Nacc shell compared to females weaned on PND 21. This experiment demonstrates that the effects of social and housing conditions on neuropeptide receptors are not limited to early life; which was further demonstrated by experiments with environmental enrichment in rats. In adult female rat offspring, those raised by high licking and grooming (LG) dams in an impoverished environment showed decreased OTR binding in the MPOA and CeA while offspring of low LG dams raised in an enriched environment display increased OTR binding in the MPOA, CeA, and PVN when compared to offspring of low LG dams reared under standard housing conditions (Champagne and Meaney, 2007). When taken together, these results would indicate that a more socially enriched early rearing environment results in long-term up-regulation of OTR and AVP V1a across species, sometimes transgenerationally.

Along with early social rearing conditions, the quality of early care that offspring receive can affect receptor binding. For instance, maternal licking/grooming (LG) behavior in rat dams can affect later receptor binding. In this model of high versus low LG behavior directed toward offspring, there is an up-regulation of OTR binding in many of the same areas that are seen increased in offspring reared in enriched early social environments. For females raised by high LG dams, OTR binding is increased in the MPOA, BNST, LS, PVN, and CeA (Champagne and Meaney, 2007; Francis et al., 2000, 2002) whereas AVP V1a binding in male offspring of high LG dams is increased in the CeA (Francis et al., 2002). Dams that exhibit high LG behaviors show increased OTR binding in the same brain areas as their offspring (Champagne et al., 2001). There is also evidence that these OTR are influenced by estrogen. In lactating compared to virgin females there is an increase in OTR binding in the MPOA, BNST, and LS and these increases are more pronounced in offspring of high LG dams (Francis et al., 2000). For virgin female offspring ovariectomized as adults and treated with an estrogen replacement, OTR binding was increased in the MPOA and LS in high LG but not low LG offspring (Champagne et al., 2001).

These differences observed in receptor binding are likely transmitted through differences in early maternal behavior. In this model of varying early maternal care, female offspring born to high LG dams exhibit high amounts of maternal care as adults, while females born to low LG dams exhibit low amounts of maternal care as adults. Evidence for behavioral transmission of maternal care comes from experiments in which offspring of high LG dams, cross-fostered just after birth to low LG dams, appear indistinguishable from pups born to and reared by low LG dams; exhibiting low amounts of licking and grooming as adults. Offspring of low LG dams cross-fostered to high LG dams display high amounts of maternal behavior as adults (Francis et al., 1999). These effects of rearing condition are also found when looking at behavioral and physiological stress responsiveness. As adults, offspring of high LG dams show a decreased HPA response to a restraint stress as well as increased glucocorticoid feedback sensitivity compared to offspring of low LG dams (Liu et al., 1997) and react less fearfully in novel situations than do low LG offspring (Caldji et al., 1998). When cross-fostered, biological offspring of low LG dams reared by high LG dams displayed decreased fearfulness in response to novelty, resembling biological offspring of high LG dams. The same was true for high LG offspring reared by low LG dams — these offspring showed increased fearfulness to novel situations (Francis et al., 1999). Given that maternal behavior and stress responsiveness have been shown to be transmissible behaviorally, it is likely that the same is true for the OT and AVP systems subserving the behaviors.

If early environmental enrichment and increased maternal behavior can be seen as positive experiences during development, neonatal stress and maternal separation could be viewed as the opposite. Areas that showed an increase in OTR binding as a result of high LG care during neonatal development often showed reduced binding in response to neonatal stress. Adult female rat offspring of high LG dams that experienced a repeated restraint stressor during gestation had decreased OTR binding in the MPOA, BNST, and CeA compared to offspring of high LG dams that did not experience stress (Champagne and Meaney, 2006). This effect was found to be transmissible to the next generation — female offspring of these dams displayed the same decreases in OTR receptor binding even though they were reared under standard housing conditions. Long-term maternal separation has similar effects on neuropeptide binding. Daily 3-hour maternal separations in male rats resulted in a decrease in OTR binding in the agranular InsCtx, LS, and CP, and an increase in OTR binding in the MPOA and VMH (Lukas et al., 2010). AVP V1a binding was increased in the LS, dentate gyrus, and piriform cortex and decreased in the arcuate nucleus (Arc). This long-term separation also results in a decrease in OT-*ir* in the PVN in females and a decrease in AVP-*ir* in the PVN in males (Veenema et al., 2007) as well as an increase in OT-positive cells and a decrease in AVP-positive cells in the PVN of male mice (Tsuda et al., 2011).

While environmental changes and social experiences have an impact on the central OT and AVP system, pharmacological manipulations have the potential to alter these systems as well. In the prairie vole, a single intraperitoneal administration of OT on PND 1 in females decreases AVP V1a binding in the MPOA, BNST, LS, PCC, and mediodorsal thalamus (MdThal) in adults (Bales et al., 2007a,b,c), decreases AVP-*ir* in the supraoptic nucleus (SON) in adults (Kramer et al., 2006), and increases OT-*ir* in the PVN at weaning (Yamamoto et al., 2004). The same administration in males results in an increase in adult AVP V1a binding in the PCC (Bales et al., 2007a,b,c). A single PND 1 administration of an OT antagonist (OTA) in females leads to a decrease in AVP V1a binding in the BNST and PCC as adults (Bales et al., 2007a,b,c) and an increase in OT-*ir* in the PVN at weaning (Yamamoto et al., 2004). Males receiving an OTA administration on PND 1 display decreased AVP V1a binding in the MPOA, BNST and LS as adults (Bales et al., 2007a,b,c) and a decrease in AVP-*ir* in the PVN at weaning (Yamamoto et al., 2004). However, neonatal OT or OTA did not affect OTR or dopamine D2 receptor binding measured in adults.

There is also evidence that the OT system may potentially be a target for endocrine disrupting compounds (EDC), substances that behave in a similar fashion to endogenous hormones. In the female pine vole (*Microtus pinetorum*), exposure to methoxychlor (MXC), an EDC with estrogenic and anti-androgenic properties, throughout gestation and lactation results in a decrease in OTR binding in the CC in offspring (Engell et al., 2006). Female rats exposed on PND 0–3 to bisphenol-A (BPA), an EDC that mimics the actions of estrogen, led to an increase in OT-*ir* in the PVN (Adewale et al., 2011).

It is worth noting that exogenous exposure to OT, both neonatally and in adulthood, has consequences for receptor systems beyond OTR and AVP V1a receptors. Female prairie voles treated with i.p. OT on PND 1 showed an increase in estrogen receptor α (ERα) mRNA in the hypothalamus and hippocampus 2 h after treatment while administration of an OTA resulted in a decrease in ERα mRNA in the hippocampus compared to those treatment with saline (Pournajafi-Nazarloo et al., 2007). These effects were specific to the ER subtype in that ERβ subtypes showed no changes to treatments. At weaning (PND 21), female prairie voles treated on PND 1 with a single i.p. injection of OT had increased ERα-*ir* in the VMH and decreased ERα-*ir* in the MPOA compared to controls. Males receiving OTA on PND 1 showed a trend for decreased ERα-*ir* in the medial amygdala compared to controls (Yamamoto et al., 2006). As adults, a single i.p. treatment with OT on PND 1 resulted in an increase in ERα-*ir* in the ventral LS, VMH and central amygdala in females compared to control animals while males showed an increase in ERα-*ir* in the BNST compared to controls following PND 1 treatment with OTA (Kramer et al., 2007). Chronic early OT manipulations produced similar results. Female rats treated once daily from PND 1 to 7 with OT showed an

increase in ERα-*ir* in the VMH while OTA treatment resulted in a decrease in ERα-*ir* in the MPOA (Perry et al., 2009).

Chronic manipulation of the OT system in adult rodents has been shown to produce changes in the α2-adrenoceptor system, which is involved in regulation of epinephrine and norepinephrine release. Adult male rats given s.c. administration of OT for five consecutive days showed an increase in α2-adrenoceptor binding in the hypothalamus, amygdala, and paraventricular thalamic nucleus compared to saline-injected animals (Diaz-Cabiale et al., 2000). Female adult rats showed similar changes in the α2-adrenoceptor receptor system. Following ten days of OT treatment, ovariectomized (OVX) females showed an increase in α2-adrenoceptor binding the hypothalamus, amygdala, and nucleus of the solitary tract (NST) compared to OVX females treated for ten days with saline (Petersson et al., 2005). Changes are also seen in the glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) systems. Following five days of OT treatment, adult male rats had decreased GR mRNA in the CA1 + 2 and dentate gyrus regions of the hippocampus compared to controls and tended to have decreased GR mRNA in the CA3 region. These OT treated animals also had increased MR mRNA in the dentate gyrus (Petersson and Uvnas-Moberg, 2003). These results from adult manipulations, as well as those from neonatal OT manipulations indicate that effects of OT go beyond the OTR and AVP V1a receptor systems.

In summary, a large number of developmental experiences, including experimenter handling, enriched early social environments, varying quality of parenting received, and pharmacological exposures to OT itself, OTA, or endocrine disruptors, all have long-term effects on neuropeptide systems. Effects can include up- or down-regulation of OTR themselves, changes in OT peptide production, or changes in other systems such as AVP V1a receptors. How do we predict which systems early experiences might affect, and in what direction?

How do we understand the effects of early experience on OTR and AVP V1a?

If early exposures to experiences which affect OT are affecting OTR and AVP V1a over the lifespan, how might they be doing so? Will pharmacological experiences have different effects than more natural ones? Can we explain some of the contradictory results in the literature (such as high OTR in less social animals) based on their developmental experiences? In Table 1, we have organized the studies presented in the previous section and summarized the type of experience, the (usually hypothetical) way in which it may be affecting OT during the experience, and the long-term effects on OTR and AVP V1a. We have classified the early OT conditions as: 1) Acute supraphysiological: single exposure exogenous treatments; 2) Chronic supraphysiological: multiple exposure exogenous treatments; 3) High physiological: treatment conditions which might be expected to induce high endogenous levels of OT, with either a positive or negative valence; and 4) Low physiological: treatment conditions which might be expected to induce low endogenous levels of OT.

We are also assuming that high levels of OT may be induced by either positive social stimuli, such as warmth, touch, and high levels of parenting (Uvnas-Moberg, 1998), as well as negative social stimuli such as separation from the attachment figure or other distressed relationships (Grippo et al., 2007; Taylor et al., 2010). It should be immediately clear that only in the case of pharmacology is the actual level of early OT known for any of these treatment conditions, and then only the exogenous level is known, not the baseline endogenous level in the young animal. There are several notable exceptions in which effects on the developing OT system were actually measured during development. One is the 1994 study by Noonan et al. (1994), in which a 20-minute maternal separation from PND 2 to 8 reduced OTR binding in the hippocampus on day 8. However, this change in binding was transient and did not persist into adulthood. A second is the study by Yamamoto et al. (2004) which examined OT-*ir* changes, in response to neonatal OT administration, on days 8 and 21. Understanding the dynamics of these systems will require studying the dynamics of the peptides and the receptors at the time of the manipulation, as well as other developmental timepoints and including adulthood.

Based on this table, we have summarized our thoughts as to how experiences that involve changes in OT should result in long-term changes in OTR and AVP V1a (Fig. 1). These predictions can then be used prospectively in future studies. Obviously, they will also need to be better delineated as to sex, neural area, timing of manipulation, etc. Should these predictions hold up, we will still need to determine the molecular mechanisms responsible for the developmental changes.

These predictions become especially important due to the proposals to use chronic intranasal OT as a treatment for developmental disorders including autism spectrum disorders (Guastella et al., 2010), social anxiety disorder (Guastella et al., 2009), fragile X syndrome (Hall et al., 2011), and schizophrenia (Feifel et al., 2010). We were able to identify no animal studies in the literature which examined the effects of *chronic* developmental exposure to OT on OT receptor systems with any mode of administration. If we assume that the closest analog would be being raised by a high LG mother, then we might expect up-regulation of OTR and V1a in relevant areas. However, there is no work suggesting that the OT levels being used intranasally are equivalent to physiological levels, or that the experience of receiving the OT would have a positive valence. It is also quite possible that chronic developmental OT will have significant dose effects that may be opposing at different dosages.

Also remaining to be delineated are the behavioral consequences of increased or decreased OT and AVP V1a receptor binding. In what cases is an increase in binding a compensatory mechanism that allows for normal behavior? In what cases is it associated with dysfunction, or perhaps only partly compensatory? For example, in what would seem to be opposing early experiences, offspring receiving increased amounts of touch and stimulation via increased maternal licking and grooming behavior show the same up-regulation in OTR binding (Champagne and Meaney, 2007; Francis et al., 2000, 2002)

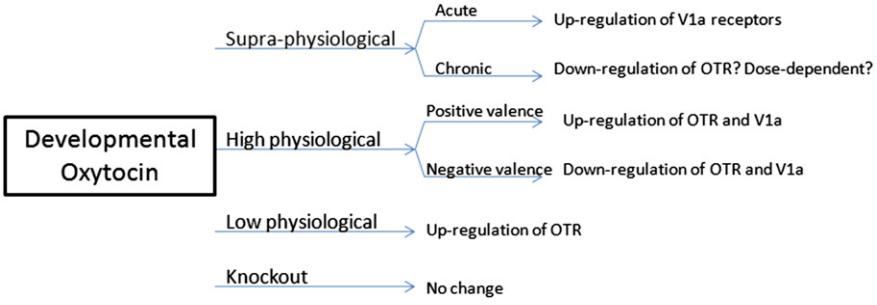

Fig. 1. Hypothesized relationships between developmental exposure to OT and outcomes for OTR and AVP V1a.

as do prairie vole offspring receiving reduced amounts of early stimulation through reduced amounts of early handling (Bales et al., 2011). However, the rats receiving increased stimulation show normal adult behavior, while voles in the reduced handling environments display reduced social behavior later in life. It is possible that the up-regulation in OTR binding in high LG offspring is a direct result of increased touch and stimulation, while the increase in binding following decreased early handling is an attempt by the system to compensate for the lack of early input. In addition, while voles receiving reduced stimulation showed increased OT receptor binding, OT production in the PVN was not significantly higher, and there were actually lower levels of OT production in the SON (Bales et al., 2011). Failure to display normal behavior might thus be due to other components of the OT system, such as peptide production. Measuring as many aspects of the systems as possible (OTR and AVP V1a, as well as OT and AVP production) in each developmental model will be key to understanding developmental dysregulation of the systems and consequences for behavior.

Conclusions

It is clear that we still have much to learn not only about the role of early experience in development of the OT and AVP systems, but also how this may differ by species and by type of experience. Key to understanding these developmental changes will be understanding what is occurring in the infant or juvenile at the time of the manipulation; also key will be examining concurrent changes in both the peptide and receptors. Understanding these changes may be crucial to predicting treatment outcomes for children and adolescents receiving chronic intranasal OT or other developmental manipulations of the OT system.

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