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Vasopressin, oxytocin and social behaviour

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Understanding the neurobiology of social behaviour in mammals has been considerably advanced by the findings from two species of vole, one of which is monogamous and pair bonds whereas the other species is promiscuous and fails to form any long-lasting social relationships. The combination of neurobehavioural studies and molecular genetics has determined behavioural differences between the two species linked to the neural distribution of vasopressin 1A receptor in the male brain. More importantly, vasopressin 1A receptor gene transfer including the upstream regulatory sequence has enhanced male social affiliation in a non-monogamous species. Male affiliative bonding depends upon release of both vasopressin and dopamine in the ventral striatum enhancing the reward value of odour cues that signal identity.

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Abbreviations

AVP	vasopressin
AVT	vasotocin
DA	dopamine
ER-α	oestrogen receptor α
ER-β	oestrogen receptor β
IT	isotocin
MPOA	medial preoptic area
NAcc	nucleus accumbens
OT	oxytocin
V1aR	vasopressin 1A receptor

Introduction

The nine amino-acid peptide family (nonapeptides) have a long history of regulating social behaviour [1], with structurally similar peptides having evolutionary conserved functions in both invertebrates and vertebrates. Annetocin and conopressin, both of which are ancestral nonapeptides, are known to regulate reproductive behaviour in annelids and snails, respectively [2,3]. Whereas these invertebrates have a single oxytocin-vasopressin complex (OT–AVP), a gene duplication early in evolution appears to have given rise to two separate peptide lineages in vertebrates. In non-mammalian vertebrates, vasotocin (AVT) shares similar roles with mammalian AVP, whereas mesotocin and teleost isotocin (IT) are functionally similar to mammalian OT. Interestingly, the neuronal expression and gene regulation of these peptide hormones appear to be conserved across vertebrates. Indeed, pufferfish AVT and IT genes that are inserted into the mouse genome are selectively expressed in the hypothalamic vasopressinergic and oxytocinergic neurons, respectively [4•]. The behavioural functions of these neuropeptides are also conserved, with AVT and AVP particularly influencing male courtship, affiliation and aggression in a wide range of taxa [5–9]. The regulation of male social behaviour by AVT and AVP is conferred by its higher expression in males and the presence of steroid-sensitive brain sexual dimorphisms in AVT and AVP neurons [10]. Female social behaviour in non-mammalian vertebrates is also associated with nonapeptides from the AVT lineage [11], but in mammals with extended social care directed towards kin OT takes a more dominant role in social interactions [12]. Here, we review recent findings on the neuropeptidergic regulation of monogamous bonding in prairie voles and examine how conserved mechanisms also underpin mate recognition and mother–infant recognition in promiscuous species. Common to making these recognition cues 'special' is the brain's reward mechanisms centred around the ventral striatum.

What is special about mammalian social behaviour?

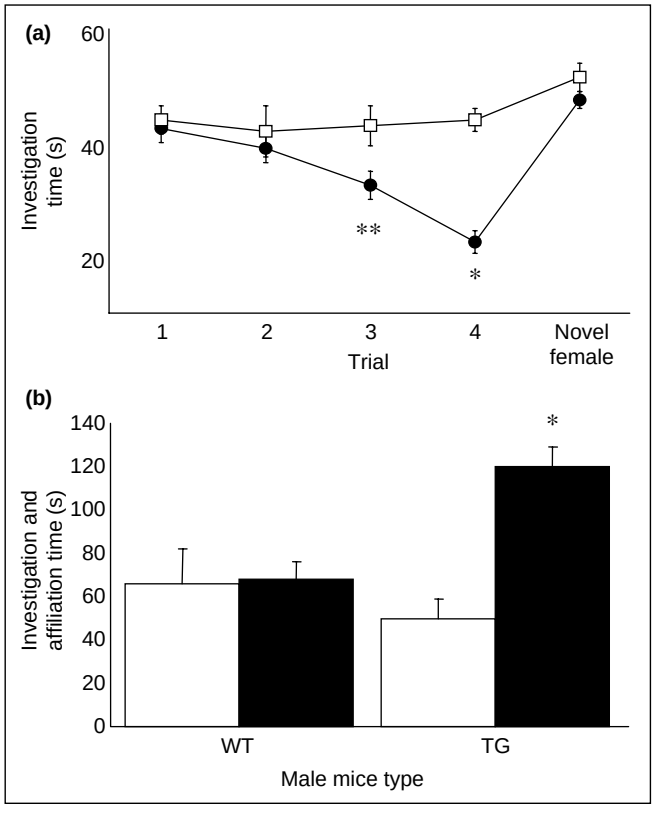
In mammals, the social behaviour of males and females reflects their different reproductive strategies. Reproductive success in males is determined through competition with other males to mate with as many females as possible. Hence, males rarely form strong social relationships and male coalitions are typically hierarchical with emphasis upon aggressive rather than affiliative behaviour. Females have a different strategy. They invest in the production of relatively few offspring with reproductive success being determined by the quality of care and the ability to enable infant survival beyond the weaning age. Females, therefore, form strong social bonds with their infants and their female–female relationships are affiliative, especially among matrilineal kin who often assist with infant care. In a minority of mammalian populations (less than 5%) a promiscuous male strategy is not an option owing to the low population density of females. In this situation males form a partner preference (bond)

with females, defend them against intruders and participate in parental care [13].

These gender specific aspects of mammalian social behaviour are underpinned by the neuropeptides OT and AVP. In females, the hormones of pregnancy (progesterone followed by oestrogen) prime the brain for synthesis of OT and its receptors. OT release at parturition coordinates maternal behaviour and physiology (i.e. uterine contractions, pain suppression at the spinal level and milk letdown) to ensure successful maternal care [14,15]. An important component of maternal care is the need to recognize offspring, which in most mammals involves olfaction. The hormones of pregnancy induce the synthesis of OT receptors in the central olfactory projections (olfactory bulb, medial amygdala and medial preoptic area [MPOA]) [16], as well as OT and dopamine (DA) receptors in the nucleus accumbens (NAcc) [17••], which is an area of the brain concerned with social reward. Together these systems synchronise the process of olfactory recognition of pups with maternal motivation, ensuring the transition from pup avoidance to pro-active retrieval in the context of maternal behaviour.

OT and AVP are also crucial for the regulation of other aspects of mammalian social behaviour. Intra-cerebral administration of AVP has demonstrated its importance for male territorial marking, aggressive behaviour, social recognition and anxiety [18–21]. Although there are three receptors for AVP (V1a, V1b and V2) the vasopressin 1A receptor (V1aR), which is widely distributed in the brain, has been considered to take the predominant role in male social behaviour. Recently, mutant mice null for the V1aR have been generated and olfactory investigation tests have revealed that males exhibit markedly reduced anxiety-like behaviour and impaired social recognition (Figure 1a) [22••]. Studies employing pharmacological antagonists suggested the V1b receptor may take a role in regulating anxiety but this finding is not supported with null mutants, although they do show a reduction in aggressive behaviour [23]. In small rodents, cerebral ventricular infusions of OT lead to a general non-

Figure 1



V1aR and male social behaviour. **(a)** Social recognition in control (filled circles) and V1aR knockout (open squares) mice. Control male mice are able to habituate to the same female presented on four consecutive one minute trials and then dishabituate to a novel female. Mice lacking V1aR expression investigate the first female as if she was unfamiliar on all four trials. **(b)** The social behaviour of wild type male mice (WT) and mice with an insertion of the prairie vole V1aR transgene (TG). When administered with AVP (filled bars) compared to administration of saline (open bars), TG mice with a prairie vole pattern of V1aR expression increased their affiliative behaviours (olfactory investigation and grooming) towards a stimulus female. WT mice did not increase their affiliative behaviour. All data are mean ± sem. In the schematic *$P < 0.05$, **$P < 0.005$. Figure adapted from [22••,35].

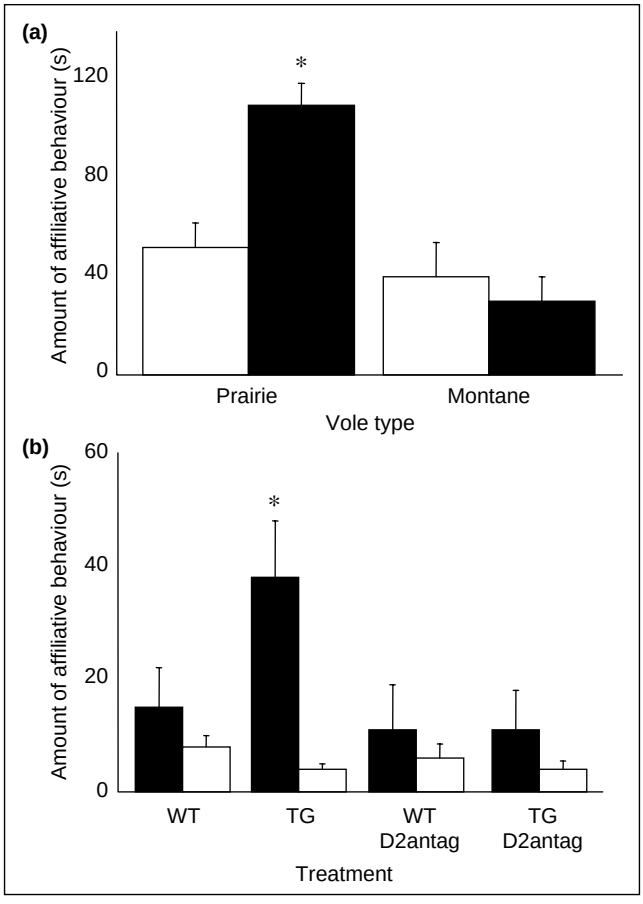
selective increase in social affiliation and reduction in anxiety and aggression [24–28]. In both sexes, overcoming anxieties such as neophobia, and inhibiting aggression are prerequisites to increasing social contact thereby enabling the formation of social bonds.

Mammalian social bonding

The mammalian genus *Microtus*, has provided an excellent model for the study of social relationships. Prairie voles (*Microtus ochrogaster*) are socially monogamous with biparental care, whereas the closely related meadow vole (*Microtus pennsylvanicus*) is solitary and promiscuous [29]. Female prairie voles are brought into oestrus by both chemosignals from males and sustained mating. This induces central OT release and enables females to form a long-lasting selective partner bond. In the absence of both mating and the concomitant OT release, central infusions of OT, or pulsatile peripheral administration, can also induce partner preferences in sexually naïve female prairie voles [30,31]. Furthermore, if pre-treated with selective OT antagonists, mated female prairie voles fail to show these selective partner preferences, which indicates that this peptide is required to both increase social contact and form selective bonds [26]. In effect, the vaginal stimulation created by sustained mating induces effects similar to parturition, namely olfactory recognition and social reward, but the selective bond in this context is with the male partner and not the offspring.

In the male prairie vole, AVP is released centrally following either cohabitation or mating with a female leading to the development of a pair-bond, increased aggression towards strange males and paternal care (Figure 2a) [18]. Treatment of males with an AVP antagonist prevents the development of partner preference and parental care after mating. Significantly, the differences in social behaviour of prairie and meadow voles are associated with variation in the neural expression of AVP receptors. When compared with non-monogamous voles, monogamous species have lower densities of V1aRs in the lateral septum, lateral habenula and central gray and higher expression in the ventral forebrain and mesolimbic DA reward pathway [32–34]. Although the sequence of the V1aR gene is >99% convergent between these two species, they differ in the 5′ regulatory region of the gene. The monogamous species have a repetitive microsatellite sequence that is absent in the promiscuous species, which might account for the different distribution of receptors and hence social behaviour [35,36]. Interestingly, the ventral forebrain expression of V1aR is also higher in the monogamous California deer mouse and marmoset monkey when compared with that of closely related promiscuous species, which suggests convergent evolution of AVP-mediated circuits as a proximate mechanism for social attachment in monogamous species [37–39].

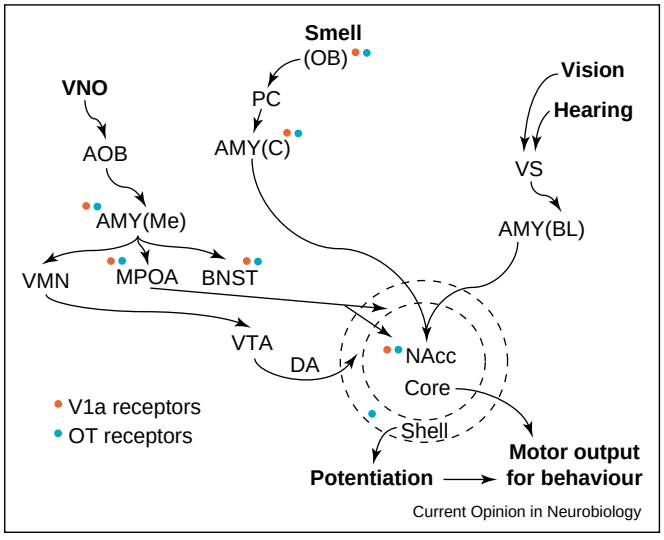
Figure 2



Interaction of AVP and DA in prairie vole pair bonding. **(a)** Male mongoamous prairie voles, but not promiscuous montane voles, spend significantly longer in affiliative behaviour (olfactory investigation and grooming) with a stimulus female after central administration of AVP (filled bars) compared to those subject to administration of saline (open bars). **(b)** Partner preference in control meadow voles (WT) and meadow voles with prairie vole V1aR transgene (TG). Male TG meadow voles spend significantly longer huddling with and olfactory investigating a previously mated female partner (filled bars) compared to a strange female (open bars), whereas WT meadow voles do not. This partner preference is eliminated if males are pre-treated with a DA D2 antagonist. All data are mean ± sem. In the schematic *P < 0.05. Figure adapted from refs [35,41••].

Recent transgenic studies have further explored the role of V1aRs in the regulation of mammalian social behaviour. Male mice expressing the prairie vole V1aR gene linked to its upstream sequence had similar V1aR brain expression to the monogamous prairie vole. Interestingly, when male mice were administered with exogenous AVP, only those carrying the V1aR transgene exhibited significantly increased affiliative behaviour towards females (Figure 1b) [35]. The same gene transferred into the rat septum leads to an increased ability of males to form social olfactory memories [40]. Moreover, overexpression of V1aR through a viral vector into the ventral forebrain of

Figure 3



The processing of information from recognition to action. The accessory (VNO) and main olfactory systems converge, through the amygdala, to the NAcc for the primary 'imprint' reinforced by mating. Activation of DA D2 and OT receptors in females and DA D2 and V1a receptors in males in the ventral striatum might underpin this associative learning and could be extended by further associations to incorporate vision and hearing, and update odour changes induced by diet and endocrine state. Abbreviations: AMY(BL), basolateral amygdala; AMY(C), central amygdala; AMY(Me), medial amygdala; AOB, accessory olfactory bulb; BNST, bed nucleus of the stria terminalis; OB, olfactory bulbs; PC, pyriform cortex; VMN, ventromedial nucleus of the hypothalamus; VNO, vomeronasal organ; VS, ventral subiculum; VTA, ventral tegmental area.

the non-monogamous male meadow voles heightens pair-bond formation even with a shortened cohabitation period and without the need for mating with the female partner (Figure 2b) [41••]. It does not, however, increase paternal care, which suggests that distinct neural circuits mediate paternal care and social-bond formation. Indeed, infusions of V1aR antagonists into the ventral forebrain selectively block female partner preference but not paternal care in male prairie voles, whereas infusions into the medial amygdala block paternal care but not partner preference [41••].

Importantly, the increased social bonding arising from greater V1aR levels in the ventral forebrain of meadow voles is not established if their dopamine D2 receptors have been blocked previously. Manipulation of either the neurotransmitter DA in the NAcc or AVP signalling in the ventral forebrain can prevent or stimulate the formation of partner preference in prairie voles [42•]. It is argued that partner bond formation by males is dependent upon an interaction between AVP and the DA reward system, with the release of DA during mating leading to an association between the familiar cues of the mate (e.g. odour) and reward [41••]. It is unclear whether AVP signalling acts directly upon the DA reward system or if its role is simply to increase social contact facilitating the association between odour and reward. A similar association between OT and DA pathways exists in female prairie voles, in which blockade of DA D2 receptors in the NAcc prevents OT-induced partner preference formation (Figure 3) [17••].

Olfaction and social reward

The brain's oxytocinergic system together with olfactory recognition underpins the formation of female social relationships, be they with mates, offspring or kin. The formation of these relationships requires familiarity, which for kin is brought about by prolonged contact and grooming. For completely novel stimuli such as strange males, or newly born offspring, however, overcoming neophobia is of some significance and it is noteworthy that OT knockout mice exhibit altered anxiety levels [43,44]. In the context of mate recognition by the female, the formation of this familiar relationship involves sexual activity, which can only occur when the female is in oestrus. Offspring recognition immediately follows parturition, the female having undergone pregnancy. Both pregnancy and oestrus provide an endocrine context for the synthesis of OT and OT receptors. Oestrogen acts through the oestrogen receptors ERα and ERβ; ERβ is expressed in the hypothalamic neurons that synthesize OT [45], whereas ERα is required for the synthesis of OT receptors in the amygdala [46]. Interestingly, both the ERα and the ERβ knockout mice are similarly impaired in social recognition tests as observed in the OT knockout mice [47,48,49••]. Hence, in the context of oestrus and parturition, the female's brain undergoes radical reorganisation with respect to the synthesis of OT and its

receptor. The key areas of the brain associated with social recognition and preference are the olfactory bulb, the amygdala and the NAcc.

Although the olfactory bulb has no oxytocinergic terminals there is an abundance of OT receptors. This mismatch of terminals with receptors is functionally addressed by the neurohumoral release of OT into cerebrospinal fluid at parturition and mating. These significant biological events produce the changes in sensitivity, synaptic efficacy and neural firing in the olfactory bulb that are part of the olfactory learning process for social familiarity [50,51]. Hence, OT infusions into the cerebral ventricles influence social olfactory memory in rats [52], whereas OT infusion in the olfactory bulb reversibly increases both the frequency and the amplitude of spontaneous excitatory postsynaptic currents of granule cells by both pre- and post-synaptic mechanisms [53]. Moreover, OT infusions into the amygdala, a primary relay for olfactory processing, restore social recognition in OT knockout mice [47]. The amygdala has reciprocal connections with the NAcc, and both structures show enhanced levels of immunoreactivity and increased DA transmission in rats following exposure to biologically significant odours [54]. OT receptors are particularly notable in both the shell and the core of the NAcc and have been implicated, together with DA release, in pair bond formation in the monogamous female vole [17••,32]. Moreover, if the socially relevant behaviour is experienced in the same context as neutral odours, and presumably other social sensory cues, a conditioned association of these second order cues as attractive behaviourally rewarding properties can develop (Figure 3) [55].

Conclusions

A wealth of data have appeared in recent years that have focused attention upon the role of OT and AVP in the regulation of social behaviour. These neuropeptides belong to a family of nonapeptides with a long evolutionary history of regulating invertebrate and vertebrate behaviour. In mammals, it is generally females that form social relationships mainly with other females and offspring, whereas social affiliation among males is much less common. However, most of our understanding of the neurobiology of social behaviour in mammals arises from the findings from two species of vole, one monogamous and the other promiscuous.

The biological complexity of monogamy can be reduced to differences in V1aR distribution in the male brain, which underlies the formation of female partner preference through olfactory reward. There are remarkable similarities in this monogamous male-based olfactory reward system to that which is well established across many female mammals; namely offspring bonding induced by parturition and male partner-preference induced by mating. Olfaction is the primary sensory mode in the majority of mammals and recent work has highlighted the associations among odour cues, OT, AVP and DA-reward systems in the brain during the formation of mammalian social relationships.

This association of odour cues with social reward is facilitated in the non-monogamous species by infusions of receptor agonists for these neuropeptides and also for the DA D2 receptor, whereas antagonists block odour-induced partner preferences in the monogamous species. The extended courtship period that males undertake to bring monogamous female prairie voles into oestrus provides a means of imprinting olfactory recognition of conspecifics. These sensory cues acquire behaviourally rewarding properties through connections with the NAcc, which further serves as a template for conditioning other secondary sensory cues. Hence, the expansion of features that become familiar and rewarding consolidates selective individual recognition for conspecifics with many common features and few differences.

Large brained primates, including humans, also form extensive and complex social bonds, but these species have poorly developed olfactory systems. The extent to which the ventral striatal reward system is common to primate social behaviour and what makes this sustained and complex are important questions for the future. Is the distribution of V1aRs similar to that in monogamous voles? Is it the complexity of social cues that access the NAcc through the frontal cortex that has taken over from olfactory cues? In primates, these relationships are not just restricted to prominent biological events like mating or parturition, so what other aspects of social organization have acquired this prospensity to 'imprint' the brain's reward system?

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