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Comparative Perspectives on Oxytocin and Vasopressin Receptor Research in Rodents and Primates: Translational Implications

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Abstract

In the last several decades, sophisticated experimental techniques have been used to determine the neurobiology of the oxytocin and vasopressin systems in rodents. Using a suite of methodologies, including electrophysiology, site-specific selective pharmacology, receptor autoradiography, *in vivo* microdialysis, and genetic and optogenetic manipulations, we have gained unprecedented knowledge about how these neuropeptides engage neural circuits to regulate behaviour, particularly social behaviour. Based on this foundation of information from rodent studies, we have started generating new hypotheses and frameworks about how the oxytocin and vasopressin systems could be acting in humans to influence social cognition. However, despite the recent inundation of publications using intranasal oxytocin in humans, we still know very little about the neurophysiology of the oxytocin system in primates more broadly. Furthermore, the design and analysis of these human studies have remained largely uninformed of the potential neurobiological mechanisms underlying their findings. Although the methods available for studying the oxytocin and vasopressin systems in humans are incredibly limited as a result of practical and ethical considerations, there is great potential to fill the gaps in our knowledge by developing better nonhuman primate models of social functioning. Behavioural pharmacology and receptor autoradiography have been used to study the oxytocin and vasopressin systems in nonhuman primates, and there is now great potential to broaden our understanding of the neurobiology of these systems. In this review, we discuss comparative findings in receptor distributions in rodents and primates, with perspectives on the functionality of conserved regions of expression in these distinct mammalian clades. We also identify specific ways that established technologies can be used to answer basic research questions in primates. Finally, we highlight areas of future research in nonhuman primates that are experimentally poised to yield critical insights into the anatomy, physiology and behavioural effects of the oxytocin system, given its remarkable translational potential.

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Research on the neuropeptides oxytocin (OT) and arginine vasopressin (AVP) using various rodent species has provided a wealth of information about the role these peptides play in the expression of species-specific social behaviours. Work in rats has demonstrated that central OT signalling is crucial for the onset of maternal nurturing behaviour (^{1,2}).

Intracerebroventricular (i.c.v.) infusion of OT facilitates the onset of maternal nurturing in virgin female rats, whereas i.c.v. infusion of oxytocin receptor (OXTR) antagonists delays the onset of maternal responsiveness in parturient dams. Mice with impaired OT release or signalling display impairments in maternal responsiveness (^{3,4}). Central OT and AVP signalling also modulate the expression of maternal aggression in defence of pups (⁵). In monogamous prairie voles (*Microtus ochrogaster*), OT and AVP interact with the dopamine system to facilitate the formation of pair bonds between mates (^{2,6}). AVP also facilitates the expression of selective aggression, or mate guarding behaviour, in male prairie voles (⁷).

The OT and AVP systems are also involved in more subtle aspects of social cognition, including recognising individuals as familiar (^{8,9}). OXTR and AVP receptor 1a (AVPR1a) knockout mice both have social amnesia and are thus incapable of remembering previously encountered individuals as familiar. Taken together, these studies across several rodent species demonstrate an important modulatory role for OT and AVP in social behaviours, such as maternal responsiveness and defence, social bond formation, and social memory.

Without these and other foundational studies in rodents, it is unlikely that the growth rate in the number of studies examining the OT system in humans and nonhuman primates (NHP) would be as high as it is currently (¹⁰). However, this rapid expansion of research into the behavioural consequences of OT manipulations in humans and NHP has outpaced our fundamental understanding of primate OT neurobiology. Specifically, there has been a significant gap in the understanding of the neural systems responsive to OT and AVP in primates, and the use of intranasal OT (IN-OT) in humans, in particular, has advanced rapidly despite a lack of knowledge of the mechanism or neurological targets engaged by this manipulation (¹¹⁻¹³). Here, we review recent progress in the neuroanatomical mapping of OXTR and AVPR1a in NHP species, which has improved our understanding of the function of these neuropeptides in NHP models of social cognition. We also provide a comparative overview of the evolutionary implications of species- and clade-differences in neurohypophyseal peptide receptor binding in the brains of mammals, with a focus on the clinical implications of conserved areas of OXTR expression in the brains of primates. This review concludes with suggestions for future research in NHP that will enhance our general understanding of neurohypophyseal peptide function in humans.

The value and challenges of characterising OXTR and AVPR1a distributions in the brain

As early as the 1980s, researchers were working to identify the location of OXTR in the brains of rodents. This work was made possible by the development of radiolabelled OXTR

ligands for receptor autoradiography. The earliest radioligand available for this purpose was a tritiated version of OT (¹⁴), although the cross-reactivity of this ligand with the closely-related AVPR1a, combined with long exposure times needed on film before results can be attained, caused it to be an unfavourable and generally inconvenient tool for autoradiographic analysis of the brain.

Later, highly selective radiolabelled peptide analogues for OXTR and AVPR1a binding were developed for use in rodent brain tissue (¹⁵, ¹⁶). The iodinated OXTR radioligand, ¹²⁵I-ornithine vasotocin analogue (¹²⁵I-OVTA), and AVPR1a radioligand, ¹²⁵I-linear vasopressin-1a antagonist (¹²⁵I-LVA), allowed researchers to quickly and reliably map the central distributions of both OXTR and AVPR1a. To our knowledge, rodent species with known OXTR and AVPR1a distributions include laboratory mice and rats, hamsters, guinea pigs, the socially monogamous California mouse and the promiscuous deer mouse, a social and a solitary species of tuco-tuco, two species of Central American singing mice, the eusocial naked mole-rat and the solitary Cape mole-rat, and the socially monogamous prairie and pine voles and the non-monogamous montane and meadow voles (¹⁷).

Once these receptor distributions were characterised in rats, mice and voles, it became possible to follow-up on earlier i.c.v. antagonist experiments by performing site-specific manipulations of the precise neural substrates where OT is acting (i.e. regions expressing OXTR). In prairie voles, site-specific infusion of an OXTR antagonist directly into the nucleus accumbens (NAcc) or the prefrontal cortex, two areas with dense OXTR binding, is sufficient to block the formation of a partner preference (¹⁸). Interestingly, OXTR binding in the NAcc, which is dense in monogamous prairie voles, is low to absent in the non-monogamous but closely-related meadow and montane voles (¹⁹), which suggests that species-specific differences in neural distributions of OXTR can reflect the social organisation of the species (^{20,21}). Furthermore, individual differences in the density of OXTR in the NAcc in prairie voles have now been shown to be mediated by a single nucleotide polymorphism (SNP) in a regulatory region of the *OXTR* gene (²²), and individuals with high NAcc OXTR show enhanced social attachment (²²) and resilience to early life stress (²³). Infusions of OT directly into the medial amygdala (MeA) of OT knockout mice rescues the social amnesia described above, and infusions of an OXTR antagonist into the MeA of wild-type mice recapitulates those deficits in social memory (²⁴). Recent research in mice has now shown that OT works in concert with the serotonin system in the NAcc of mice to modulate the rewarding aspects of social interaction (²⁵). Furthermore, an elegant study using a multidisciplinary approach demonstrated that OXTR signalling tunes the auditory cortex to maximally respond to pup vocalisations, which facilitates maternal responsiveness (²⁶). Thus, knowing the receptor distributions in the brains of these rodents made it possible to more precisely determine the neural circuits and genetics underlying species-specific social behaviours. However, it is unknown to what degree our knowledge of how OT and AVP work in the rodent brain may lead to an understanding of how these neuropeptides modulate social behaviour in humans.

Despite the progress in OT and AVP research in rodents, there has been a significant lag in the mapping of neurohypophyseal peptide receptors in the brains of primate species, particularly for OXTR. This knowledge gap can be attributed mainly to the loss of binding

selectivity when the radioligands ^{125}I -OVTA and ^{125}I -LVA are used in primate tissue. Although these compounds bind selectively to their respective receptors in rodents, they have now been shown to exhibit relatively high affinities for both OXTR and AVPR1a in primates (27,28). Nevertheless, before these pharmacological limitations were fully understood, these radioligands (as well as the older tritiated versions of the endogenous neuropeptides themselves) were used for receptor autoradiography in three primate species: in the common marmoset for OXTR and AVPR1a (29,30), in the rhesus macaque for AVPR1a (31), and in human for OXTR and AVPR1a (32,33). Although these efforts give us a preliminary view of the localisation of OXTR and AVPR1a across a few primate species, the results needed to be re-evaluated, confirmed and expanded, given the new knowledge of the lack of selectivity exhibited by the radioligands that were used.

We have recently reported the design of a pharmacologically optimised method for competitive binding receptor autoradiography that can selectively and reliably reveal the distributions of OXTR and AVPR1a in primate tissue (27). With this method, which combines the use of the radioligands mentioned above with selective competitor ligands, we have now successfully mapped OXTR in the brain of the most common NHP model organism used in biomedical research: the rhesus macaque (*Macaca mulatta*) (27). The mapping of OXTR in the macaque brain was previously attempted in the 1990s but abandoned because of the apparent nonselectivity of ^{125}I -OVTA (34). Additionally, we have mapped OXTR and AVPR1a in the brain of the socially monogamous coppery titi monkey (*Callicebus cupreus*) (35). We have also independently confirmed the findings reported by Schorscher-Petcu *et al.* (2009) for OXTR and AVPR1a binding in the forebrain of the common marmoset (*Callithrix jacchus*) (S. M. Freeman, unpublished observations). These findings provide new insights into the diversity and conservation of OT and AVP function in the primate brain and contrast with findings from rodent studies.

Evolutionary perspectives on central OXTR distributions

OXTR in rodents is concentrated in brain regions involved in olfactory processing

In rodents, social interactions are driven mainly by chemical communication and olfactory investigations, such as scent marking and anogenital sniffing. Identification of individuals as either kin, a familiar conspecific or an unrelated potential mate of the opposite sex is based on olfactory processing of major urinary proteins (36). In laboratory experiments, the duration of olfactory investigation is a common measurement in social interaction tests. For example, in the studies in mice that demonstrated the requirement of OT in the MeA for social memory of a familiar conspecific, social memory was measured by the habituation of time spent in olfactory exploration of the stimulus animal after repeated presentations (8,24).

Accordingly, regions expressing OXTR in the rodent brain are most frequently found in areas of the olfactory pathway (Fig. 1A,B). OXTR expression across rodent species is observed in the olfactory bulb and accessory olfactory nucleus, as well as downstream regions that receive projections from this primary sensory area and are involved in olfactory processing, including the MeA, central amygdala, bed nucleus of stria terminalis and the piriform cortex. OXTR is often also expressed in areas that are not involved in olfactory processing but may be involved in the processing of social information, including the lateral

septum, hippocampus, NAcc and prefrontal cortex. Taken together, it is clear that areas that are involved in the processing of olfactory input and areas that are sensitive to OT are highly co-localised in the rodent brain, providing an ecologically relevant neural circuit for the processing of social information in rodents. Future studies of nonapeptide function and rodent social behaviour should focus on the use of olfactory stimuli and measures of olfactory exploration to hone our understanding of these highly co-localised systems.

OXTR in primates is concentrated in brain regions involved in visual processing and attention

Across the animal kingdom, but particularly in primates, the eyes are arguably one of the most salient stimuli in an animal's visual environment. Detecting and recognising eyes immediately gives an individual a great deal of information, which, in most cases, needs to be interpreted and acted on quickly for an animal to survive. In primates, the eyes, along with the other components of the face, have developed important functions in social communication⁽³⁷⁾. The location and orientation of the eyes in the face provides information about individual identity, and an individual's gaze direction can give clues to nearby conspecifics about potentially relevant stimuli in the environment, such as an incoming predator. Primates need to be able to quickly detect subtle shifts in gaze by nearby individuals (e.g. a flash of eye contact from the dominant male) to adequately navigate social environments. Not only do primates need to be able to detect subtle changes in the eyes of others to gain important socially relevant information, but also they need to adjust their own gaze direction in response. This reciprocal relationship between the gaze of two individuals is arguably one of the most important aspects of primate social communication.

In this context, it is not surprising that there is considerable overlap in OXTR expression among primate species in areas that are important for visual processing, shifts in gaze direction and the allocation of attention to visual stimuli (Fig. 1c,d and Table 1). In the primary visual path from the retina, OXTR has been detected in the superior colliculus (SC), pulvinar (Pv) and primary visual cortex (interestingly, AVPR1a binding has also been detected in many of these regions) (Table 1). Interesting support for the involvement of these subcortical structures in the detection of another's gaze direction comes from evidence from cortically blind patients with damage to the visual cortex^(38,39). Activity in the right amygdala was increased in these patients in response to presentation of images of faces with direct gaze compared to averted gaze^(38,39), and this activity co-varied in a condition-dependent way with activity in the SC and Pv⁽³⁸⁾. The Pv has also been implicated in the salience of visual stimuli⁽⁴⁰⁾. In areas involved in saccadic eye movements in response to visual stimuli, OXTR is expressed in the superficial grey layer of the SC (Fig. 2), as well as deeper layers, and in the oculomotor nucleus (III) and the nucleus prepositus, which are two brainstem motor nuclei that control the muscles of the eye and participate in the horizontal gaze stabilisation system, respectively⁽⁴¹⁻⁴³⁾.

OXTR expression across primate species has also been found in two major cholinergic regions of the brain: in all four species, in the nucleus basalis of Meynert (NBM) (Fig. 2) and, in rhesus macaques, in the pedunculo-pontine tegmental nucleus (PPT). These nuclei are major sources of cholinergic input to the rest of the brain⁽⁴⁴⁻⁴⁶⁾ and are important

regulators of selective attention and motivation (^{47,52}). Furthermore, cholinergic input from the PPT strongly innervates the macaque SC (⁵³), and neurones in the PPT have also been shown to be active in monkeys during saccade tasks (⁵⁴) and to directly stimulate SC neurones and facilitate the initiation of saccadic eye movements (⁵⁵). Furthermore, NBM projects to the amygdala and is the primary source of cholinergic input to the basolateral amygdala (^{44,46,56,57}). This cholinergic input is required for memory consolidation (^{58,59}), possibly promoting the encoding of memory during sustained attention to visual stimuli. Thus, it is possible that these OT-sensitive cholinergic areas could be mediating some aspects of the changes in eye movements and shifts in visual attention in response to changing social cues in the environment.

Although these areas of conserved OXTR expression reflect an overall abundance in visual processing and attention circuits, there are some notable species differences, which could be used to inform the selection of an appropriate NHP model species for future research goals. For example, all of the primate species investigated to date have OXTR in the NBM, and so any of these species may be useful to study the basic physiology of visual social attention. However, the dense OXTR binding seen in the NAcc of the common marmoset (³⁰) makes marmosets a particularly appropriate choice for exploring the role of OT in social reward, which would complement recent discoveries in mice (²⁵). In monogamous titi monkeys, there is remarkably dense OXTR binding in the dentate gyrus of the hippocampus (³⁵), although the function of this population of OXTR is unknown. The distribution of OXTR (and AVPR1a) is now being investigated in monogamous prairie voles with the aim of understanding how patterns of receptor expression may contribute to sociospatial memory (⁶⁰). Titi monkeys, similar to prairie voles, form lasting pair bonds and are highly territorial, which renders this species an excellent primate model for similar questions of nonapeptide function in social and spatial memory. Thus, marmosets and titi monkeys may be useful models for the study of more complex forms of social behaviour, such as social reward, social memory and pair bonding, whereas the rhesus macaque provides a robust model for investigations of social visual attention.

Clinical relevance of OXTR expression in primate visual circuits

It has been shown that infants, toddlers and adolescents with autism spectrum disorder (ASD) all show disrupted patterns of eye movements in response to images/videos of human faces or naturalistic social scenes, including avoidance of the eye region of faces, atypical fixation targets to the nonsocial aspects of social scenes and a lack of attentional bias toward faces, as measured by faster saccadic disengagement from images of faces (⁶¹⁻⁶⁴). More severe disruptions in eye movements and social visual attention in ASD patients correlate with the intensity of social dysfunction (^{63,64}). Thus, it has been hypothesised that intervention at an early age in these patients to increase gaze to faces may be able to ameliorate later life social outcomes. Indeed, IN-OT has been shown to acutely increase gaze to the eye region of human faces in autistic populations (^{65,66}), although the benefit of chronic or developmental OT exposure is only beginning to be explored (^{67,68}). Clinical trials are in progress that aim to explore the therapeutic potential of OT in ASD (^{67,69}), and considerable work is being carried out to examine its potential use to treat schizophrenia as well (⁷⁰). There is also growing evidence from genetic studies that specific SNPs in the

human *OXTR* gene are associated with an ASD diagnosis (⁷¹). One SNP (rs2254298) has also been linked to smaller amygdala volume (⁷²), which is a neural phenotype that has also been found in ASD populations and predicts ASD symptom severity (⁷³).

Despite the growing literature linking the OT system and ASD (⁷⁴), whether ASD is associated with an alteration in *OXTR* expression in the brain is unknown and is currently the subject of investigation. There is one report of decreased *OXTR* mRNA in cortical tissue in a very small sample of ASD subjects (⁷⁵). Although the central *OXTR* distribution in NHP may or may not be predictive of that of humans, given the remarkable species differences in receptor distribution, evidence is building from behavioural studies in both humans (⁷⁶) and NHP that IN-OT is capable of altering social visual attention. In rhesus macaques, three studies have found that treatment with IN-OT impacts social visual attention and looking behaviours in a variety of tasks (⁷⁷⁻⁷⁹). It has also recently been shown that treatment with IN-OT in macaques can alter neural responses to emotional faces (⁸⁰). This ability of IN-OT to modulate the social attention of macaques is congruent with the *OXTR* distribution in areas of the brain that are important for gaze direction, eye movements and attention, such as the NBM or the SC. Future studies in macaques should use the locations of *OXTR* in the macaque brain to further clarify the neural mechanism underlying the behavioural changes to better understand how OT may be modulating social visual processing in healthy and clinical populations of humans.

Implications of knowing *OXTR* and *AVPR1a* distributions in NHP

Informing the design of experiments in NHP

The existence of *OXTR* in brain regions involved in visual attention and eye movements has several implications for future studies. First, the behavioural paradigms used to investigate the effects of OT in NHP should be designed to test for attention to social stimuli. We recommend that researchers in this field review the established paradigms from the literature on the neurobiology of attention and modify those existing paradigms to incorporate social elements. Similarly, we suggest that future studies of the OT system in NHP utilise techniques from the field of visual neuroscience, such as eye tracking, to incorporate fine measurements of subtle changes in eye movements and/or head direction in social viewing tasks. Furthermore, implementing electrophysiological recordings in relevant brain regions during behavioural tasks can contribute to a more complete understanding of the circuitry underlying complex social behaviour (⁸¹). Recent studies in NHP have begun using combinations of these approaches, such as eye tracking, social viewing tasks and site-specific neural recordings, to better understand nonhuman primate social cognition (⁸²) and the function of OT in the NHP brain (⁸³).

The expression of *OXTR* in two of the main cholinergic areas of the brain indicates a potential involvement of acetylcholine in the regulation of social behaviour in primates. Manipulations of the muscarinic cholinergic receptor or nicotinic cholinergic receptor have been suggested as a way of enhancing attention (⁴⁷). Even the authors of the human *OXTR* mapping paper from 1991, who first detected purported *OXTR* binding in the NBM, suggested that OT binding sites on cholinergic neurones in this area may manipulate cholinergic transmission to downstream regions such as the cerebral cortex or hippocampus

(³²). Current studies in progress in rhesus macaques have found that OT delivered directly to the NBM changed social looking behaviour, as well as neural activity, in the basolateral amygdala (⁸⁴), which is an area that lacks OXTR mRNA but receives strong cholinergic input from the NBM. The investigation of the possible functional relationships between OT and the acetylcholine system represents an exciting new direction for the study of social behaviour and neurophysiology more broadly.

Site-specific injections of OT-related compounds into the brain

This neuroanatomical information about receptor distributions is critical for informing the design and analysis of future experiments in primates and should be a renewed focus for NHP research on OT. One obvious issue in translating the research approaches that are commonly used in rodents (e.g. i.c.v. or site-specific infusions in the brain) into the design of experiments using NHP is that many of the techniques involve invasive manipulations of the brain in large cohorts of animals. Although we are aware that ethical, cost and animal welfare considerations may be prohibitive to the widespread use of invasive manipulations of the brains of NHP, we also feel that there is still great potential to gain important insights into the neural circuitry of the OT system in circumstances when these neurosurgical techniques are available and appropriate. With that said, now that receptor distributions are known in the brains of many of the NHP species used in biomedical research, it is possible to infuse OT or selective OXTR agonists or antagonists directly into the brain regions that have high OXTR densities. Recent work using site-specific infusions of OT into the macaque brain has targeted the amygdala (^{81,83}). However, we now know that this region of the macaque brain does not contain detectable levels of OXTR binding (²⁷), although OXTR may be present on NBM terminals in the amygdala. As mentioned above, research currently in progress has now targeted populations of OXTR in the NBM (⁸⁴). These studies can establish whether OXTR activation in specific brain regions is necessary and/or sufficient to mediate species-typical behaviours or other types of physiological functions.

For example, the highly social and selectively breeding marmoset has dense OXTR in the NAcc (Fig. 3A) similar to that of the prairie vole (^{30,85}). Thus, it would be interesting to perform an experiment in marmosets analogous to the ones described above in prairie voles (¹⁸) demonstrating the prevention of pair-bond formation via site-specific blockade of OXTR in the NAcc. Such an experiment in marmosets could determine whether OT acting at OXTR in the NAcc is necessary for pair-bond formation in marmosets as it is in voles. Similar experiments could also be performed in titi monkeys, which are socially monogamous but, unexpectedly, do not exhibit OXTR binding in the NAcc (Fig. 3B). Instead, titi monkeys have AVPR1a expression in the NAcc (Fig. 3C) and extremely dense OXTR binding in the dentate gyrus (Fig. 3D) of the hippocampus (³⁵). By combining our new knowledge of OXTR-expressing regions in NHP with site-specific antagonist/agonist infusion studies or site-specific microdialysis experiments, it now becomes possible to assess in NHP where OT and/or AVP is acting to modulate complex social behaviours.

The rhesus macaque brain in general exhibits extremely sparse OXTR expression relative to AVPR1a (^{27,31}), with the most dense OXTR binding seen in the NBM and superficial grey layer of the SC (Fig. 2C,F). It would be of great interest to perform electrophysiological

recordings in the rhesus NBM and amygdala in response to OT manipulation during a visual social task⁽⁸²⁾. Data from such experiments would be particularly exciting because the importance of OT in early stages of visual processing as well as in ‘other-oriented attention’ have been alluded to recently in two behavioural studies that administered IN-OT to rhesus macaques^(77,79). Similar to the studies conducted in rodents over the past few decades, it is now possible to perform targeted manipulations of the macaque brain to better clarify the function of OT in primate social cognition and yield critical insights into the regulation of social attention by OT.

Ligands for behavioural neuropharmacology of the OT system in primates

Previous studies have highlighted the importance of using selective ligands when probing the OXTR and AVPR1a systems in primates as a result of the high levels of homology between OT and AVP themselves, as well as their receptors. This issue brings to light several important considerations for future work in these systems in both humans and NHP more broadly. First, the mixed selectivity issue within the study of OT and AVP in primates suggests that many of the effects of OT could be mediated by AVPR1a, and vice versa. This concept is not new; several previous studies suggested that the effects of OT and AVP are a result of the activation of the ‘opposite’ receptor^(4,80,86-89). Thus, with the growing number of IN-OT studies in humans, rhesus and other primates, we need to consider the idea that the effects of intranasal OT may be mediated in part by activation of AVPR1a.

Second, as behavioural pharmacology experiments proceed in NHP, it is crucial to use highly selective OXTR or AVPR1a drugs whose binding affinities have been validated in primates. There are now several highly selective, low molecular weight, nonpeptide ligands that purportedly cross the blood-brain barrier, such as the selective human AVPR1a antagonist, SR49059⁽⁹⁰⁾, and the selective human OXTR antagonist, ALS-II-69^(91,92). ALS-II-69 was evaluated in previous studies and shown to effectively block OXTR radioligand binding to primate brain tissue⁽²⁷⁾. Behavioural pharmacology experiments are ongoing that aim to assess the effectiveness of this ligand *in vivo* in altering social behaviour in a rhesus macaque model. We have also developed other novel, small-molecule, highly selective OXTR antagonists as tools for behavioural pharmacology in NHP, as well as for potential tracers for *in vivo* positron emission tomography (PET) neuroimaging^(91,92). Unfortunately, these compounds have not been found useful for detecting OXTR binding sites *in vivo* using PET.

The Merck compound L-368,899 is another small molecule OXTR antagonist that has been used in NHP studies⁽⁹³⁾, has excellent bioavailability after oral administration⁽⁹⁴⁾ and has been also reported to accumulate in limbic structures of the brains of rhesus macaques after peripheral injection⁽⁹⁵⁾. This compound is already being used in behavioural pharmacological studies in marmosets, including investigations of pair bonding and adult sociosexual behaviour^(93,96,97), stress reactivity⁽⁹⁸⁾, and responsiveness to infant cues⁽⁹⁹⁾. However, after radiolabelling L-368,899 and performing *in vivo* PET imaging in macaques, we found that there is minimal uptake in the brain, and the compound appears to accumulate in the ventricles and not in neural tissue⁽¹⁰⁰⁾. It is still possible that this drug

may be capable of binding to OXTR in the brain after peripheral delivery, although in concentrations that are below the detectable limit of PET imaging.

These selective antagonists, given centrally or peripherally, can be used in combination with IN-OT to parse apart the contribution of OXTR and AVPR1a in the brain or in the periphery to the behavioural effects observed after IN-OT treatment. As this area of research moves forward, it is critical to determine the relative contribution of each of these receptors to OT-dependent changes in behaviour. This issue is especially relevant with respect to the current drug development efforts to treat ASD with drugs targeting the OT system. If some of the beneficial prosocial effects of IN-OT are a result of activation of AVPR1a, then drug development efforts should also include selective targets for AVPR1a. Similarly, if some of the effects of IN-OT are mediated by peripheral OXTR activation, the brain penetration of agonists may not be essential for therapeutic effects.

Finally, research in NHP should consider alternative approaches to manipulate the OT system, including pharmacologically evoking endogenous OT release (¹⁰¹). For example, melanocortin receptor 4 (MC4R) signalling has been shown to evoke OT release in hypothalamic slices in the rat (¹⁰²). Melanotan-II, an MC4R agonist, given peripherally, activates OT neurones and potentiates central OT release following a physiological stimulus (¹⁰³). Peripheral MT-II administration also facilitates OT-dependent social bonding in prairie voles and eliminates the social behaviour deficits associated with neonatal social isolation in prairie voles (^{23, 103, 104}). Although MC4R agonists show promise for eliciting OT-mediated behaviours, they also interact with other behaviourally relevant neurochemical systems (²³) and thus are not useful tools for isolating OT function. Nevertheless, because they can be given peripherally and evoke central OT release, they could have important translational applications and are easily tested in NHP (¹⁰¹).

Conclusions

To conclude, we feel there are several important take-home points from this discussion of comparative primate OXTR and AVPR1a neuroanatomy and receptor pharmacology. First, knowledge of the distribution of OXTR and AVPR1a in a particular species of interest should be used to guide the rationale and outcome measures of NHP pharmacological studies. Neurohypophyseal receptor distributions in NHP display species differences, as well as a conserved core distribution related to the importance of visual processing of social stimuli. Those core conserved receptor populations may be most informative for translational studies that inform human OT neurobiology.

Second, NHP can be used to more precisely understand OT function in the brain than is currently possible using IN-OT in humans, which is useful for understanding the mechanisms by which IN-OT influences behaviour. Although intranasal delivery of OT in NHP more accurately models current human IN-OT studies, this approach does not provide information on whether the effects are mediated by central or peripheral receptors, or whether they are mediated by OXTR or AVPR1a (¹²). IN-OT studies even in humans are often underpowered given the modest effect sizes, making the interpretation of studies with few subjects unreliable (¹¹). NHP provide the opportunity to go far beyond what is possible

in humans, with direct central neuropeptide administration or with IN-OT in combination with central selective antagonist administration to identify the central mechanisms of action. Site-specific OT manipulations in receptor containing areas with selective agonists or antagonists can provide even greater precision for clarifying brain mechanisms. Finally, combining site-specific manipulations with electrophysiological recording and behavioural analysis has the potential to provide a level of understanding of OT function that is currently only available in rodents.

Given the lack of selectivity for some of the ligands developed for use in rodents, it is critical for NHP researchers to consider the pharmacological properties that their chosen ligands exhibit in their species of interest. Species differences in receptor binding characteristics vary widely, especially in light of recent discoveries in New World monkeys, which show genetic variations in both the OT and AVP peptide and receptor genes across species (105-110). Simply comparing the binding characteristics of the most common ligands for the human and rat OT and AVP receptors reveals considerable variation in pharmacological properties across species (28).

Research on the role of OT and AVP in regulating social behaviour and cognition in NHP is in its infancy, far behind the level of precision found in rodent research. OT and AVP research in NHP has been faced with challenges related to a lack of knowledge of receptor distributions and of selective pharmacological agents. New studies are now revealing receptor distributions and developing selective agents. This information, combined with standard NHP techniques such as electrophysiology, have poised NHP to provide novel, mechanistic insights into how the OT and AVP systems modulate social sensory systems. These advancements have remarkable implications not only for basic behavioural neurobiology and social neuroscience in NHP, but also for honing pharmacological therapies that may improve social cognition in psychiatric disorders, such as ASD and schizophrenia.

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Fig. 1.

Oxytocin receptor (OXTR) expression in rodent and primate brain areas that modulate attention to relevant social stimuli. (A) OXTR expression in select areas of the rodent brain (17,111). (B) The olfactory information pathway in the rodent brain, including regions involved in social recognition (112,113). (C) OXTR expression in the nonhuman primate brain (27,30,35). (D) The pathways in the primate brain that process visual input, modulate visual attention and control of eye movements (41,43,44,46,49,52,54,114,116). III, oculomotor nucleus; Am, amygdala; AOB, accessory olfactory bulb; BNST, bed nucleus of stria terminalis; CoA, cortical nucleus of the amygdala; Hipp, hippocampus; LS, lateral septum; MeA, medial amygdala; MPOA, medial preoptic area; NA, nucleus accumbens; NAcc, nucleus accumbens; NBM, nucleus basalis of Meynert; NP, nucleus prepositus; OB, olfactory bulb; OE, olfactory epithelium; Pir, piriform cortex; PPT, pedunculopontine tegmental nucleus; Pv, pulvinar; PFC, prefrontal cortex; SC, superior colliculus; TB, trapezoid body; V1, primary visual cortex; VMH, ventromedial hypothalamus; VMO, vomeronasal organ.

Fig. 2.

Conserved regions of oxytocin receptor (OXTR) expression across the nonhuman primate species studied to date. (A–C) OXTR binding in the nucleus basalis of Meynert (NBM). (D–F) OXTR binding in the superficial gray layer of the superior colliculus (SuG). (A) Coronal sections from the brain of the common marmoset [S. M. Freeman, unpublished confirmation of the study by Schorscher-Petcu *et al.* (³⁰)]. (D) Coronal sections from the brain of the common marmoset (³⁰). (B, E) Coronal hemisphere sections from the brain of the coppery titi monkey (³⁵). (C, F) Coronal sections from the brain of the rhesus macaque (²⁷). O, inferior olivary nucleus. All images reproduced with permission.

Fig. 3. Comparative receptor expression in New World monkeys. (A) Oxytocin receptor (OXTR) binding in the nucleus accumbens (NAcc) of the common marmoset [S. M. Freeman, unpublished confirmation of the study by Schorscher-Petcu *et al.* ⁽³⁰⁾]. (B) Lack of OXTR binding in the NAcc of the coppery titi monkey ⁽³⁵⁾. (C) Arginine vasopressin receptor 1a (AVPR1a) binding in the NAcc of the coppery titi monkey ⁽³⁵⁾. (D) OXTR binding in the

dentate gyrus of the hippocampus (DG) and presubiculum (PSB) of the coppery titi monkey (35). All images reproduced with permission.

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Table 1

Comparison of Oxytocin Receptor (OXTR) and Arginine Vasopressin Receptor 1a (AVPR1a) Binding Sites Across Primate Species, Only in Areas of the Brain that Process Visual Input, Control Visuomotor Responses (Eye/Head Direction) and/or Mediate Visual Attention.

	<u>Common marmoset</u>		<u>Rhesus macaque</u>		<u>Titi monkey</u>		<u>Human</u>	
	OXTR ^a	AVPR1a ^a	OXTR ^b	AVPR1a ^c	OXTR ^d	AVPR1a ^d	OXTR ^{e,f}	AVPR1a ^f
Thalamic								
LG	–	–	–	–	–	+	–	–
Pv	–	–	–	–	+	+	–	–
Subcortical								
SC	–	+	–	–	+	+	+	–
SuG	+	+	+	–	–	+	+	–
Pt/NL	+	–	–	–	–	+	ND	ND
Cortical								
V1	ND	ND	–	+	+	+	ND	ND
V2	ND	ND	–	+	–	+	ND	ND
Occ	–	+	–	+	–	+	ND	ND
Visuomotor								
III	–	–	+	ND	–	–	ND	ND
NP	+	–	ND	ND	+	–	+	–
PSB	–	–	–	+	+	+	–	–
Attentional								
NBM	+	+	+	–	+	–	+	–
PPT	–	+	+	ND	–	–	ND	ND
CeA	–	–	–	+	–	+	–	–

+, binding detected; +*, Binding detected but not discussed; –, no binding detected; ND, binding not determined in this region.

III, oculomotor nucleus; CeA, central amygdala; LG, lateral geniculate nucleus of the thalamus; NBM, nucleus basalis of Meynert; NP, nucleus prepositus; PPT, pedunculopontine tegmental nucleus; PSB, presubiculum; Pt/NL, pretectum/nucleus limitans; Pv, pulvinar; SC, superior colliculus; SuG, superficial gray layer of the superior colliculus; V1, primary visual cortex; V2, secondary visual cortex.

^aSchorscher-Petcu *et al.* (30).

^bFreeman *et al.* (27).

^cYoung *et al.* (10).

^dFreeman *et al.* (35).

^eLoup *et al.* (32).

^fLoup *et al.* (33).