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REVIEW ARTICLE

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Role of oxytocin in parental behaviour

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Both animal and human studies have provided conclusive evidence that oxytocin (OXT) acts in the brain (eg, medial preoptic area, ventral tegmental area, nucleus accumbens) to promote parental behaviour under different reproductive and physiological conditions. OXT appears to accelerate and strengthen the neural process that makes newborns attractive or rewarding. Furthermore, OXT reduces stress/anxiety and might improve mood and well being, resulting in indirect benefits for parents. However, OXT also plays a role in the development of species reproductive and social strategies, making some species or individuals more prone to display caring activities in nonreproductive contexts. There are important differences in the development of the OXT system and its regulation by gonadal hormones that can make individuals or species very different. Those intra- and interspecific differences in the OXT system have been associated with differences in parental behaviour. For example, differences in OXT levels in body fluids and genetic variants for the OXT and OXT receptor genes have been associated with variability in parental mood and behaviour in humans. Thus, OXT has received much attention as a potential therapeutic agent for affective, emotional and behavioural problems. Despite many preliminary studies indicating promising findings, several unknown aspects of the OXT system remain to be addressed before we can achieve a complete understanding of its function in the brain. The enormous interest that this area of study has attracted in the last decade will likely continually contribute to advancing our understanding of the role of OXT in parental behaviour and other behavioural and physiological functions.

KEYWORDS
accumbens, amygdala, development, hormones, polymorphism, preoptic area

1 | OXYTOCIN ACTION IN THE NEURAL SUBSTRATE THAT SUPPORTS PARENTAL BEHAVIOUR

Oxytocin (OXT) is a peptide of 9 aminoacids that exerts its effects acting at a single type of receptor coupled to G-proteins.[1] The OXT receptor (OXTR) is widely distributed in the organism and participates in diverse processes related to behavioural, cardiovascular, immunological and reproductive functions, amongst others.[1] At the physiological and behavioural level, OXT is currently known to reduce stress responses and facilitate parental and affiliative behaviour, amongst other functions.[2-7] Sixty years ago, it was well known that OXT stimulated uterus contraction during parturition and milk ejection during nursing.[8,9] However, early studies,[10-12] carried out mainly in rats and sheep, also suggested that the rise in OXT that occurred around parturition not only stimulated the contraction of uterus and mammary myoepithelial cells, but also facilitated the onset of maternal behaviour.

The most familiar or common situation in which parental behaviour occurs is at parturition, when females display several

behavioural components typical of their species to nurse, protect and stimulate the newborns. Mother-newborn interaction and the sensory experience that results from smelling, touching and hearing the pups also strengthen that behavioural state and generate long-term neural changes, including learning and memory of those experiences.[2–15] Several studies show that maternal behaviour in most mammals is induced by hormonal changes that occur at the end of pregnancy and around parturition, which generally include increases in oestrogen, lactogens and OXT in specific sites of the brain.[2,13] For example, those hormonal changes are responsible for reducing odour mediated aversion toward newborns in rats[16-18] and promoting, only during a short temporal window, the acceptance of lambs in sheep.[19]

The first series of studies that explored OXT function in parental behaviour found that blocking the action of OXT with i.c.v. injections of OXTR antagonists, or OXT antiserum, delayed, whereas OXT administration facilitated, the onset of maternal behaviour in rats and sheep.[11,12,20-22] In the case of rats, OXT was only effective in anosmic animals, suggesting that OXT was not involved in the reversal of pup odour aversion.[23] Later, researchers focused their investigation on identifying the areas of the brain in which OXT could be acting to promote those changes. Several brain sites, which were part of the neural substrate that supported parental behaviour, emerged as natural candidates. One of those regions was the medial preoptic area and adjoining ventral bed nucleus of the stria terminalis (MPOA/vBST). The administration of oestrogens into the MPOA/vBST facilitated parental behaviour, whereas lesions impaired the active components of parental behaviour in most of the species and conditions studied.[2,24,25] However, researchers also knew that the MPOA sent projections to the ventral tegmental are (VTA), a brain region rich in dopaminergic neurones and projecting to the nucleus accumbens (NAc).[26] The NAc and the VTA-NAc projections were already related to the processing of rewarding stimuli.[2,25] Thus, the MPOA and VTA were considered as good candidate sites for where OXT acts and promotes parental behaviour. Indeed, OXT administration into the VTA facilitated maternal behaviour, whereas OXTR antagonists into the MPOA or VTA delayed its onset in rats.[20,27] Kendrick et al.[28-30] also found that OXT was released in the olfactory bulb of the sheep, at the time of parturition, likely facilitating the onset of maternal behaviour and the establishment of the selective bonding between mother and lamb.[28-30] This group of researchers also found that local infusions of OXT into the MPOA and olfactory bulb reduced rejection of lambs.[28] Interestingly, the medial amygdala processes this olfactory information and, in some species, could be a site of action for OXT to remove the aversion to the odours of newborns or to establish olfactory memories.[31-34]

The current consensus is that the action of OXT in the VTA might increase the release of dopamine (DA) into the NAc and prefrontal cortex (PFC) to promote parental behaviour and process newborns as rewarding stimuli.[2,35-37] DA release would permit NAc-ventral pallidum (VP) circuitry to process pup-related sensory stimuli coming from basolateral amygdala and prefrontal cortex as rewarding. However, although the VTA neurones have OXTR, there is evidence that only a 10% of those neurones with OXTR are dopaminergic.[38] Therefore, the action of OXT on VTA glutamatergic neurones might also have still unknown effects with respect to promoting parental behaviour. Furthermore, OXT might act directly on the NAc or the PFC to facilitate parental behaviour. For example, i.c.v. injections of OXT increases the mean firing rate of neurones in the NAc shell,[39] suggesting a direct mechanism of action in the NAc rather than one mediated by DA release from VTA. Indeed, Moaddab et al.[39] propose that OXT might act on GABA medium spiny neurones that are efferent projections from the NAc. However, it should be noted that the current neural models discussed in several reviews[2,37] propose that OXT and DA release into the NAc would inhibit, rather than excite, medium spiny projecting neurones to the VP. This inhibitory effect could be mediated by presynaptic inhibition of glutamatergic inputs to NAc.[37] Medium spiny neurones in the NAc form a heterogeneous population of neurones with different projections sites, dopaminergic receptor subtypes and neurochemical innervations. Therefore, the action of OXT on different subpopulations of neurones might result in inhibitory or excitatory effects (Figure 1). Perhaps the release of OXT into the PFC, NAc, MPOA and VTA reduces the inhibitory output of the NAc to the VP only for certain specific parental behaviour motor components at the same time as it transiently increases inhibitory output from the NAc to the VP related to other interfering or nonspecific behavioural components.[40] Furthermore, a temporal dimension is also needed to understand DA and OXT function in the neural processing that occurs in the NAc to promote maternal motivation. Continuous switching between inhibitory and excitatory inputs from the PFC and BLA to the NAc could be modulated by the action of OXT in these areas. This information could be integrated in the NAc with respect to selecting the optimum behavioural motor patterns to better achieve the specific parental goals in that context; for example, adopting a quiescent nursing posture or to search and retrieve the pups to the nest. This is clearly an area that deserves more research.

In the last decade, new non-invasive techniques such as functional magnetic resonance imaging (MRI) have provided evidence that suckling-stimulated release of OXT in lactating rats activates most of those areas of the brain where OXT has been hypothesised to act to facilitate maternal behaviour and/or reduce stress/anxiety.[35,41] Moreover, several studies have provided evidence indicating that OXT also plays a role in the maintenance of some components of parental behaviour, such as the intensity of licking and grooming, quality of nursing postures and maternal aggression in rats.[4,42,43] Therefore, the possibility that OXT plays a role beyond the onset of parental behaviour has recently gained significant relevance.

2 | EFFECTS OF OXYTOCIN ON PARENTAL BEHAVIOUR IN MICE REVEALED BY TRANSGENIC METHODS

Most of the initial studies that investigated the role of OXT in parental behaviour were conducted in rats and sheep, although

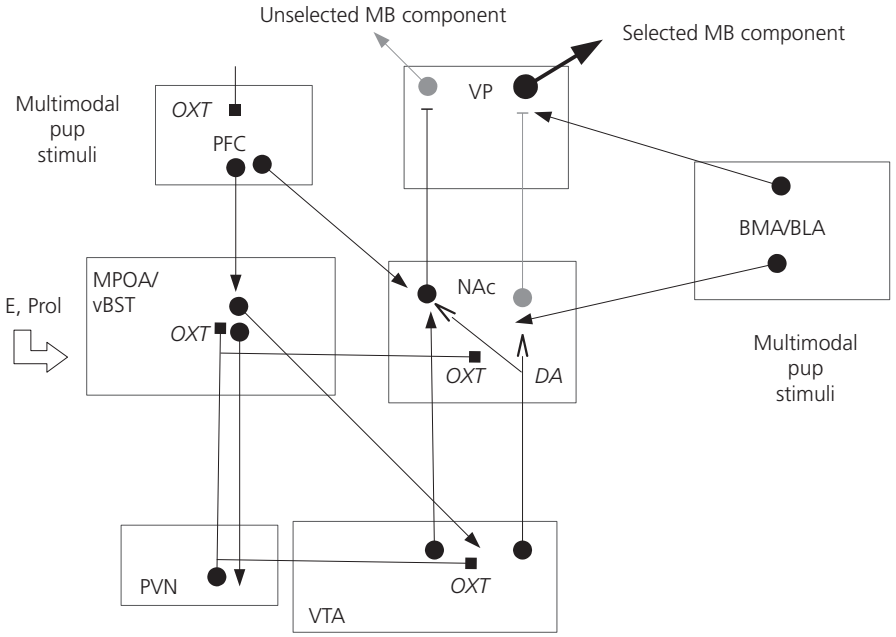

FIGURE 1 An adaptation from Michael Numan's model[37] shows how integration of glutamatergic, oxytocin (OXT) and dopaminergic (DA) inputs to the nucleus accumbens (NAc) could promote parental motivation and influence the selection of appropriate behavioural components required to take care of the newborns. The medial preoptic area and ventral bed nucleus of the stria terminalis (MPOA/vBST), the prefrontal cortex (PFC), the ventral tegmental area (VTA) and the NAc receive OXT inputs from the paraventricular nucleus of the hypothalamus (PVN) that can activate a latent, pup- or hormonally-induced (E, oestrogen; Prol, prolactin) parental neural circuitry that would result in active or passive parental motor components. The activation of the MPOA/vBST would stimulate glutamatergic and DA VTA efferents to the NAc that would modulate PFC and basomedial and basolateral amygdala (BMA/BLA) inputs to the NAc carrying pup-related sensory information. OXT and DA modulation of glutamatergic inputs to the NAc would inhibit a subpopulation of GABAergic medium spiny neurones to release a subpopulation of ventral pallidum (VP) neurones from its inhibition, allowing the expression of the appropriate behavioural component according to the information received from the BMA/BLA and PFC. Furthermore, a different subpopulation of NAc neurones would inhibit the VP to repress interfering behavioural components. Excitatory glutamatergic neuronal inputs end in a filled arrow; inhibitory glutamatergic neuronal inputs end in a bar; DA neuronal inputs end in an open arrow; OXT neuronal inputs end in a filled square. NAc inhibited neurones and inhibited VP behavioural output are shown in grey

a series of studies also investigated wild mice.[44] Wild house mice behave very differently from most mice strains bred and used under laboratory conditions (ie, BALB, C57BL/6, CBA, DBA). Although naïve females from most laboratory strains show a high propensity to display maternal behaviour, female wild house mice attack pups.[44-47] In those initial studies, McCarthy[44] found that s.c. or i.c.v. injections of OXT inhibited infanticidal behaviour in wild house mice. Later, several researchers developed and studied knockout (KO) mice to reveal OXT function in parental behaviour. Those transgenic animals were created using laboratory mouse strains (eg, CB57Bl/6) as background. Therefore, wild-type virgin unexperienced females from those transgenic animals were very prone to show maternal behaviour. By contrast, males, although somewhat variable, were generally infanticidal. Most studies that investigated these OXT or OXTR transgenic mice only found minor (increases in latency to retrieve pups) or no deficit in maternal behaviour. Originally Nishimori et al.[48] reported that no deficit in maternal behaviour was displayed by OXTKO virgin and postpartum females. Females could not nurse the pups (no milk ejection) but their behaviour was normal. Personal observations made at Emory University, Atlanta, GA (Olazabal DE, unpublished) with OXTKO and OXTRKO mice are also in agreement with that initial finding. However, a series of studies later found differences that, in some cases, are confusing and, in others, are only partially replicable. For example, Ragnauth et al.[49] found higher infanticidal responses in OXTKO females tested in a semi-natural environment. On the other hand, Pedersen et al.[50] found that less OXTKO virgin females retrieved pups and those that did it retrieved a lower number of pups. However, that deficit was found in one but not all days in which maternal behaviour was tested. Virgin and postpartum females of the KO mice for the gene Peg3, which had reduced OXT in hypothalamic neurones, also showed longer latencies to retrieve pups.[51] However, Champagne et al.[52] could only confirm those findings in Peg3KO females from a B6 (but not 129Sv) background, suggesting that the observed effects where not simply a consequence of the manipulation of the gene. More recently, Denizot et al.[53] found no deficit in maternal behaviour in Peg3KO mice generated using a different target site in the gene. It was concluded that a reduction in postnatal growth was not the result of reduced OXT or maternal behaviour. KO mice for the gene CD38, a transmembrane glycoprotein with ADP-ribosyl cyclase activity, which catalyses the formation of Ca^{2+} signaling, also showed

a lower concentration of OXT in plasma and cerbrospinal fluid (CSF), and some deficit in maternal behaviour. CD38KO females also took longer latencies to retrieve pups (reversed by OXT treatment). However, that behavioural deficit did not cause major effects on the survival of the offspring or the rate of weaning,[54] and multiparous CD38KO dams did not show any deficit.[55]

In relation to OXTRKO mice, Takayanagi et al.,[56] found that virgin and postpartum females displayed longer latencies to retrieve pups in some of the testing days, and they also presented a deficit in crouching over the pups. However, when the females were left untouched, no difference in crouching behaviour was found. Moreover, Macbeth et al.,[57] working with a conditional forebrain OXTRKO mouse, only found fewer females retrieving pups on the day 1 of sensitisation, with no difference by the third day. No difference was found in postpartum females, although there was an increase in mortality in the first litter, an effect that was not longer seen in the third litter.[57] Altogether, these findings support, at best, the idea that OXT facilitates and accelerates the onset of maternal behaviour in mice, making the animal more prone to be maternal, and perhaps also inhibits potentially infanticidal responses in wild mice. However, the evidence also suggests that the lack of OXT or OXTR in mice only causes a minor effect in the onset of maternal behaviour that does not affect pup survival and cannot be detected after repeated exposure to pups or after maternal experience; for a critical revision of KO studies, see also Yoshihara et al.[58]

3 | SPECIES DIFFERENCES IN OXT AND OXTR REGULATION BY GONADAL HORMONES AND THEIR RELEVANCE FOR PARENTAL BEHAVIOUR

Many studies found that oestrogen treatment increases OXT and OXTR production in the brain of several species.[1,59-62] However, sex differences and the effects of gonadal hormones on OXT and OXTR production differ among species and the areas of brain investigated.[63-68] For example, in contrast to rats and mice,[68,69] no sex differences in the density of OXTR in the brain have been reported in prairie voles and naked mole rats.[65,66] However, rats and mice also differ in the areas of the brain where sex differences are found. Although few sex differences in OXTR density have been found in mice (eg, males > OXTR density in ventral part of the lateral septum; and pro-oestrus females > OXTR density in ventromedial nucleus of the hypothalamus [VMH]), Smith et al.[70] found that male rats had higher OXTR density than female rats in several brain regions (eg, posterior-dorsal and posterior-ventral medial amygdala, as well as VMH), and lower OXTR density in others (eg, intermediate lateral septum and the posterior caudate putamen). Furthermore, female rats in the pro-oestrus stage of the oestrous cycle had higher OXTR density in the VMH (similar to mice) and the MPOA, although not in other brain regions, such as the anterior olfactory nucleus, central amygdala or paraventricular nucleus of the hypothalamus.[68]

Another way to see the differences in the regulation of OXTR expression in different species or brain regions is by analysing developmental changes in the oxytocinergic system. Several studies have shown that the expression of OXTR in the different areas of the brain could increase, decrease or remain unchanged throughout development.[69,71-73] For example, there is a reduction in the density of OXTR in the NAc from weanling to adult age in rats but not in mice. However, in both species, there is an increase in OXTR density in the VMH, whereas, in other areas (eg, central amygdala), no change has been found during that period.[69-73] These species- or site-specific patterns of changes that occur during development can be explained by differences in the susceptibility to the effect of gonadal hormones and/or programmed developmental changes independent of the rise of gonadal hormones. Thus, when discussing OXT and OXTR fluctuations and regulations in the brain, we must consider that different species or areas of the brain respond differently to internal or external stimuli, probably adapted to play a species- and site-specific function. This is particularly important for understanding the mechanism that might have evolved in different species to promote differences in reproductive or social strategies. For example, it might be interesting to explore the role of OXT in the VMH, an area where the expression of OXTR increases in several species by gonadal hormones fluctuations and/or after parturition.[69,74] The VMH has an inhibitory role in maternal behaviour according to Bridges et al.[75] and Sheehan et al.[76] Thus, changes in the density of OXTR in the VMH might play a role in the disinhibition of maternal behaviour in some species but not others. It should also be noted that regulation of the expression of OXTR in different areas of the brain at the same time might be necessary for the species or individuals to properly display their behaviour. How the pattern of release of OXT adapts to those transient or permanent changes in the expression of the receptor within or among species is still not well understood but remains an interesting topic of research. Below, a discussion is provided of how OXT brain release, as well as OXTR fluctuations and its different brain distribution, might contribute to paternal behaviour and the induction of caring activities in nonreproductive naïve animals.

4 | OXYTOCIN AND PARENTAL BEHAVIOUR IN REPRODUCTIVE AND NONREPRODUCTIVE CONTEXTS IN RODENTS

In many species, mothers share their caring activities with other members of the group or family. For example, in some species, a male (most commonly the progenitor) also participates in the caring activities.[77,78] Although paternal behaviour is considered to occur in only 5%-10% of the species,[77,78] these percentages could be underestimating the incidence of this behaviour in males. Division of work between mothers and fathers (guarding/defence

vs nursing, etc.) or differences in male and female investment in offspring have influenced researchers to consider many species as nonpaternal. Thus, it might be important to distinguish the actual display of paternal behaviour, as well as the mechanisms underlying that behaviour, from the most common (also flexible and variable) social or reproductive strategy observed in a species. As an example, in many strains of laboratory mice, males show paternal behaviour even towards alien pups.[79,80] Accordingly, why are they not considered a biparental or multiparental species? It is well known that "Promiscuous" species, such as striped mice, can also show high levels of paternal behaviour.[81] Therefore, it is clear that we still know little about the incidence of paternal behaviour in nature and the hormonal and cognitive changes that promote paternal behaviour in sires, human fathers or naïve inexperienced individuals who are also contributing to the caring activities. Parental behaviour is not only a reproductive, but also a social behaviour, likely the most prosocial behaviour if we consider the investment that even nongenetically related individuals make sometimes to rear offspring.

Thus, the contribution of nonreproductive animals (males and females) is important for the stability of social groups in several species. The fact that both naïve virgin males and females from some species can eventually display parental behaviour has been investigated for a long time.[17,45,66] Although some naive individuals show parental behaviour immediately or almost spontaneously, others require repeated exposure to pups (sensitisation) to show that behaviour.[2,82] The neural basis supporting nonreproductive parental behaviour is mostly like that described earlier in the present review, although the neuroendocrine or cognitive mechanisms underlying those behavioural changes are less well known. However, the evidence suggests that OXT release in specific sites of the brain might also be behind the onset of paternal behaviour and sensitised (repeated exposures) or spontaneous maternal behaviour in naïve animals.[78,83,84]

For example, CD38 KO sires with CD38 lentivirus infection in the NAc, and treated with s.c. OXT, recovered from the deficit in retrieval behaviour observed in CD38 KO females that were untreated.[83] Interestingly, a recent study in female mice also showed that OXT in the MPOA promoted sensitised-induced parental behaviour. Okabe et al.[84] found higher c-fos in OXTR expressing neurones in the MPOA of mice exposed to pups repeatedly vs those exposed to pups a single time.[84] This procedure is known to sensitise animals and reduce latency to retrieve pups. Okabe et al.[84] also found that OXTR antagonist injections into the MPOA before the initial exposure, but not after 4 days, blocked the shortening in latency observed after repeated exposures. Therefore, repeated interaction with the pups likely induced higher OXT release into the MPOA and increased activation of this brain region known to be critical to facilitate the onset of parental behaviour. However, what about OXT role in establishing an intrinsic or latent parental programme that makes individuals (males and females) more prone to display parental behaviour? This is discussed in the next section.

5 | OXTR DISTRIBUTION IN THE BRAIN INFLUENCES THE PROPENSITY OF NAÏVE INEXPERIENCED ANIMALS TO DISPLAY PARENTAL BEHAVIOUR

In early studies, Bridges et al.[85] had shown that weanling rats showed parental behaviour with very short latencies. Furthermore, there was one study that also suggested that OXT could facilitate parental behaviour in juvenile or preweanling animals.[86] For example, preweanling rats (approximately 20 days of age) that received i.c.v. OXT increased holding and licking of pups.[86] Other studies had shown a reduction in OXTR density in the NAc of rats from age 20 days, when naïve male and female rats are prone to display parental behaviour, to adulthood, when naïve male and female rats ignore or avoid newborns.[71,72,87] Therefore, it was hypothesised that the decline in NAc OXTR could be related to the decline in parental responsiveness observed throughout development in rats. Then, using a comparative approach, we investigated whether higher OXTR in the NAc was related to a higher propensity to show an immediate parental response in naïve juvenile females from different species exposed to pups for the first time.[87] We found that juvenile female prairie voles and rats, that had higher OXTR density in the NAc than meadow voles and mice, were more prone to display parental behaviour toward pups when exposed to them for the first time.[87] A correlation was also found between the amount of time spent in contact with pups and the density of NAc OXTR in juvenile female prairie voles,[87] a species with a high incidence of parental behaviour in virgin inexperienced animals and described as socially monogamous and biparental. Later, we found that intraspecific variability in NAc OXTR was also related to intraspecific variability in the maternal response toward pups in adult female prairie voles. Higher NAc OXTR was found in maternal than in nonmaternal females.[88] Furthermore, we found that infusions of an OXTR antagonist into the NAc blocked maternal behaviour in adult female prairie voles. Thus, it was hypothesised that OXT in the NAc might increase the attraction toward pups and then facilitate the rapid induction of parental behaviour. It remains unclear whether this effect is a consequence of acute release of OXT in the NAc and/or the result of developmental changes promoted by long-term stimulation of those receptors already present at preweanling age.[89]

After our first series of studies in 2006,[87,88] Schorscher-Petcu et al.[90] found that marmosets, a species that live in stable family groups, with cooperative caring of newborns and sexual flexibility (not strictly monogamous),[91] have a high OXTR density in the NAc. Kalamatianos et al.[66] also found a high NAc OXTR in naked but not cape mole rats. Naked mole rats are known to form colonies with 1 queen, 1 or 3 reproductive males and several subordinates that contribute to the maintenance of the colony and the care of newborns. By contrast, cape mole rats are described as mainly a solitary species. Song et al.[92] has also shown that most naïve male mandarin voles (*Microtus mandarinus*) do not attack pups and instead show parental behaviour. This is a species that also presents high levels of OXTR in the NAc and is described as socially monogamous and

biparental. Higher NAc OXTR mRNA has also been associated in this species with a higher quality of parental behaviour. More recently, Wang et al.[93] found that the expression of OXTR mRNA in the NAc of mandarin voles was higher in new fathers compared to virgin or paired males. Therefore, in the last decade, the results of several studies have provided strong support for the role of NAc OXTR in the facilitation of parental behaviour in both males and females. The evidence also supports the idea that high density of NAc OXTR is associated with the presence of parental responses outside a reproductive context or as part of a cooperative group form of living (ie, helpers[66,90]).

However, several questions remain unanswered. Is OXTR NAc an adaptation to respond rapidly to newborns? Is it an adaptation to social monogamy and/or an adaptation to strengthen social groups? It is argued that OXTR NAc not only contributes to facilitating parental behaviour in male and female naïve individuals, but also is an adaptation to it.[94] Then, it is possible that OXTR NAc also contributes to the tolerance of other members of the group, including the presence of more than one adult male, and the maintenance of a stable social group (including stable partners), where other members can cooperate with the caring activities if necessary. Females could eventually copulate with more than one adult male but establish a stable group where their members cooperate in different activities, including caring activities. Furthermore, other studies[95] have proposed the interesting hypothesis that OXT promotes living in groups by selectively excluding other individuals (eg, alien males). Although that hypothesis could fit with the role of OXT in promoting parental behaviour and stronger bond within the social group, another hypothesis is that OXT in the NAc reduces antagonist behaviour within the group resulting in higher social stability and cooperative parental behaviour. Indeed, previous studies have found evidence of male-male prosocial effects for OXT in several species.[96,97] However, this does not exclude the possibility that OXT acting in other areas of the brain or contexts could play a role in the defence of the group from strange individuals (males or females) as shown by Du et al.[98] For example, some studies have shown that, in certain contexts, or under chronic administration of OXT, a reduction in social behaviour[96,99] or a loss of partner preference[97] can also be observed. There is a need for more research on the social or group behavioural dynamics of traditional and nontraditional species. Field and laboratory studies must complement each other in terms of understanding the most common social or reproductive associations among individuals within a species and its relationship with OXTR distribution in the brain. Furthermore, a more global analysis of brain OXTR distribution, adding to NAc OXTR other brain regions and neurochemical systems, needs to be made. OXT might be acting in the NAc to promote attraction toward pups and to strengthen bonds with other members of the group, whereas, in other brain regions, it might reduce stress/anxiety or increases aggressive behaviour against intruders.

For example, the density of OXTR in the lateral septum is very variable among species and might also be part of an adaptation for different behavioural responses toward pups or other social stimuli.[87] Perhaps the action of OXT in the lateral septum is directly or indirectly implicated in the regulation of approach behaviour towards newborns and/or other individuals during social interactions.[76] Furthermore, OXTR in the lateral septum might be implicated in the regulation of anxiety or defensive responses that can result in changes in parental behaviour or aggressiveness against intruders.[69,100,101]

The important role that vasopressin (AVP) plays in the regulation of these behaviours also cannot be ignored, as well as the known cross-talk between OXT and AVP systems.[102,103] The action of AVP has been associated with promoting parental and aggressive behaviour in several species[102,104-107] and a different distribution of V1A receptors in the brain is also associated with different reproductive and social strategies.[102] Despite the distribution of OXTR and AVP receptors in the brain being clearly different, peptide diffusion throughout the extracellular space or dendritic release could reach distant areas and have an effect on the receptors of other systems.[108,109] Given the important cross-talk of the OXT and AVP systems, it is necessary to study the possibility that the role played by OXT in a certain species could be replaced in another by AVP.

Independent of the cognitive, hormonal or neurotransmitter changes underlying parental behaviour in different species, as well as reproductive or social contexts, the areas of the brain implicated in the onset and maintenance of the maternal state and its associated behavioural components appear to be very well conserved among species.[2,18] However, human behaviour also might have some unique characteristics. For example, parental behaviour in humans is not restricted only to the period around parturition or lactation. Human parents continue showing caring activities beyond the weaning period.[2] Thus, parental behaviour is complex and requires flexibility and many forms of adaptation to the continuing changes of the offspring and the interaction of parents with them.[2,110] We can expect that cognitive aspects, rather than changes in gonadal hormones, will be critical for this adaptation, particularly in humans. However, the literature provides evidence that both cortical areas and hormonal changes participate in the onset and maintenance of parental behaviour both in humans and rodents.[2,18,82,110,111] Therefore, comparative studies can be very useful for understanding the human condition if we carefully consider similarities and differences among species.[2,18]

6 | IMPLICATIONS OF OXYTOCIN IN HUMAN PARENTAL BEHAVIOUR AND MOOD REGULATION

In the last decade, there has been an enormous proliferation of publications providing evidence of the involvement of OXT in different physiological and neural processes that result in parental responses and better well-being.[112-115] Most studies have correlated behavioural or psychological states with levels of OXT in plasma, saliva, urine or CSF. Although that evidence is promising and has been generated in multiple independent laboratories, it must be considered with caution. This is because there is an important controversy in

the scientific community about the need for extraction of the samples before OXT is measured by radioimmunoassay, enzyme-linked immunoabsorbent assay or mass spectrometry.[116,117] What exactly is measured with and without extraction of the samples has been discussed in depth by McCullough et al.[116] and is not covered here. Howver, briefly, many researchers consider that those studies using unextracted samples might have measured OXT, OXT/OXT metabolites/derivatives or just other proteins not related to OXT. Thus, basal levels of OXT in plasma and CSF have also been a focus of controversy. It is still unclear what levels should be considered normal or as signs of a dysfunctional system. We still do not know how an altered or dysfunctional oxytocinergic system would look like in terms of OXT levels in body fluids and its receptor density in tissues. An additional factor of complexity is that researchers have used either plasma, saliva or urine samples in their studies, and levels of OXT in those fluids not always correlate or do so just weakly.[118,119] Taking these comments into consideration, a brief description of the evidence on OXT role in human parental behaviour is provided below.

6.1 | OXT in body fluids and parental behaviour

Levine et al.[120] (unextracted samples) found an important variability in the pattern of changes of OXT along pregnancy and the early postpartum period. In their study, an increase of plasma OXT from early to late pregnancy correlated with higher maternal-foetal bonding. However, the difference in the levels of OXT among individuals is so important that it might reflect a technical problem. Whether those differences were the result of normal physiological variability or difficulties in the process of collecting the samples and measuring OXT need to be investigated better. Strathearn et al.[121] (extracted samples) also found that, at 7 months postpartum, secure mothers who interacted and played with their infant had higher peripheral OXT than insecure mothers. OXT levels in the plasma of mothers after interacting with their own baby were also associated with the activation of the ventral striatum and VTA in a MRI session where mothers could see the face of their own baby. Then, a series of studies[118,122,123] (unextracted samples) found that the interaction of mothers and fathers with their newborns was associated with an increase in OXT in plasma and saliva but with subtle sex differences.[118,122] Higher OXT was associated with affectionate touch in mother and stimulatory touch in fathers.[123,124] Furthermore, higher levels of OXT in parents and children were also related to greater affect synchrony and infant social engagement.[122–124] On the other hand, Bick and Dozier[125] (extracted sample) also looked at OXT levels in mothers who interacted with their own or unfamiliar children. In contrast to what was initially expected, they found higher OXT levels in the urine of mothers interacting with unfamiliar children, suggesting that OXT might also play a more general function in mediating behavioural interaction with infants, rather than specifically with their own child. In a later study, Bick and Dozier[126] (extracted samples) found that OXT levels in urine in foster mothers were associated with the expression of behavioural delight toward their foster infant and the average event related potential response to images of infant faces. Recently, Abraham et al.[127] also found that more collaborative parental behaviour by helper humans was associated with stronger caudate-ventromedial PFC connectivity, suggesting that those areas of the brain, where OXT is acting in other species to promote parental responses, could be potential sites of action for OXT in humans. Finally, a new study by Kohlhoff et al.[128] (extracted sample) also showed that a higher baseline OXT in plasma and higher response of OXT to mother-infant free play interaction were associated with higher maternal sensitivity.

Parallel to these studies, other studies also supported the hypothesis that OXT reduced stress responses and, in that way, could promote well-being and facilitate the interaction and bonding between mothers and newborns.[119,129,130]. In humans, OXT has also been associated with changes in maternal mood and stress. Skrundz et al.[131] found that low plasma OXT levels during mid-pregnancy predicted symptoms of postpartum depression 2 weeks following birth. It was proposed that OXT was implicated in stimulating mother's well-being and in reducing anxiety during mother–offspring interaction. Depressive symptoms were also associated with low levels of OXT in plasma in a subpopulation of African-American women[132] (unextracted samples). Yuen et al.[133] (extracted samples) also found lower plasma OXT in depressed vs nondepressed women. The hypothesis is that early chronic life stressors and certain OXT genetic variants might reduce OXT levels in body fluids and affect the bonding and seeking of social support. At the same time, those changes would alter the hypothalamic-pituitary-adrenal axis response to stressors, as well as other neurotransmitters, hormonal and inflammatory factors that increase social withdrawal and depressive symptoms.[5,134] Other studies have also found that nursing mothers with higher OXT levels are more likely to describe positive mood states and reduced anxiety[135] (plasma extracted samples). By contrast, women who were abused in childhood had lower OXT concentrations in CSF and higher anxiety scores.[129] Pratt et al.[136] (urine extracted samples) also found a relationship between basal or stimulated OXT in mothers and children before and after their interaction. Children from depressed mothers had lower baseline urine OXT and attenuated OXT response during mother-child interaction. Furthermore, depressed mothers with high levels of OXT had no effect on the levels of OXT of their children, suggesting that OXT buffered the effects of depression on the child. OXT has also been proposed to buffer the effect of psychosocial stress, protecting high-risk women from developing depressive symptoms[137] (plasma unextracted samples).

6.2 | OXT and OXTR genetic variants and parental behaviour

Another series of studies investigated whether genetic variants for OXT and OXTR genes could be associated with differences in parental behaviour and mood in humans.[112,138] For example, Bakermans-Kranenburg and van Ijzendoorn [112] looked at genetic variants of the OXTR gene and found a polymorphism (rs53576, variant AA/AG) related to lower levels of sensitive parenting. Riem et al.[138] also found that nulliparous adult females with the rs53576 GG genotype had

greater heart rate responses to infant cries, although only among women with low depression scores, with the opposite finding for depressive women.[138] Functional MRI studies show that haemodynamic responses to child stimulation in brain regions mediating affect, reward and social behaviours in women were significantly correlated with observed positive parenting.[139] Furthermore, the OXTR single nucleotide polymprhisms (SNPs) rs53576 and rs1042778 were significantly associated with both positive parenting and haemodynamic responses to child stimuli in the orbitofrontal cortex.

Feldman et al.[113] also found that OXTR polymorphic variants (rs2254298 GG variant and rs1042778 TT variant) were associated with lower plasma OXT and less parental touch. A similar finding was reported for the CC variant of the rs379863 of the CD38 gene. Feldman et al.[113] also found that individuals carrying the low-risk A alleles for the CD38 rs3796863 and the OXTR rs2254298 SNPs had higher plasma OXT levels compared to those carrying other alleles. High plasma OXT and low-risk *CD38* alleles also predicted longer durations of parent-infant gaze synchrony and were associated with parents reporting greater parental care.

The MAVAN research group in Canada has also provided evidence indicating that genetic variants of this system are associated with maternal mood and behaviour. For example, Mileva-Seitz et al.[39,140] investigated the relationship and association of early experience, mothering and OXT or OXTR genotypes. Two separate OXT SNPs (rs2740210 CC genotype and rs4813627 GG genotype) were found to be significantly associated with higher maternal vocalising to the infant at postpartum month 2, regardless of early maternal environment. They also found a significant genotype-environment interaction between these 2 SNPs and maternal early-life experiences that contributed to predicting maternal instrumental grooming and maternal postpartum depression. However, postpartum depression did not mediate the gene-environment effects of the OXT SNPs on instrumental care. Their study also found a polymorphism of the OXTR gene (SNP rs237885) associated with prenatal (but not postnatal) depression scores.

Jonas et al.[114] also found that rs2740210 (SNP of the OXT gene) mediated the effect of early adversity on breastfeeding duration and depression. Women possessing the CC genotype were at higher risk of depression and shorten breastfeeding if they had early adversity during childhood. Finally, Tombeau-Cost et al.[141] have recently reported that the OXTR rs2254298 (A-carriers) had a complex effect suggesting increased positive parenting, as mediated by an improved performance of mothers on decision-making tasks performed when their children were 4 years old. Some other studies have also found and association between OXTR SNPs (rs139832701) and early stress and depression.[142] Unfortunately, except for the relationship found by Feldman et al.[113] for OXT levels and OXTR and CD38 genetic variants, the relationship between OXT/OXTR SNPs and OXT/OXTR levels in body fluids or human tissue is unknown. Meyers et al.[142] investigated the relationship between the expression of OXTR and several genetic variants of OXTR and found that variant CC/CC of the OXTR SNP rs3831817 was associated with a lower expression of OXTR in the brain. However, that SNP was not associated with any behavioural state. Therefore, it is important to replicate findings such as those described by Feldman et al.[113] and to continue looking for links between these genetic variants and changes in density or levels of OXTR and OXT, respectively, with the aim of understanding the biological mechanisms behind their associations with different behavioural states.

6.3 | OXT as a therapeutic agent

The series of studies described above, as well as many other studies suggesting that OXT might have antipsychotic-like, anti-addiction and antidepressant preclinical effects, amongst others,[143–145] have stimulated the idea that OXT could be used as a therapeutic agent. Thus, intranasal OXT has become an extensively used tool for human research. Several studies have shown that, in rodents, nonhuman primates and humans, intranasal OXT increased OXT in plasma and CSF. Increased OXT was found in microdialysates from both the hippocampus and amygdala, with peak levels occurring 30-60 minutes after nasal administration in mice and rats.[146] In that case, a central route of transport for OXT was proposed. Interestingly, Reim et al.[147] found that intranasal OXT decreased amygdala activation and increased activation of the insula and inferior frontal gyrus when women with insecure attachment representations heard infant cries. In addition, intranasal OXT also increased the BOLD (blood-oxygen-level dependent) functional MRI response in the caudate nucleus and dorsal anterior cingulate of human fathers who were viewing images of their children, suggesting that OXT enhanced the activation of brain regions involved in reward, empathy and attention.[148] In macaques, several studies also found increased CSF OXT around 30-40 minutes after intranasal OXT administration.[149] Lee et al.,[149] using deuterated OXT and its detection by mass spectrometry, found that peripheral administration of OXT did not lead to the central release of endogenous OXT in macaques, suggesting that measured OXT was the result of exogenous administration. By contrast, Striepens et al.[150] found that OXT CSF increased rapidly in human plasma (15 minutes) but took around 75 minutes to increase in the CSF, suggesting an indirect stimulation of the endogenous OXT system. Although many factors can induce variability in the efficiency of intranasal administration in primates, including variability in the anatomy of the area, doses or source of administration (nebulisers, nasal spray, aerosolised OXT, etc.),[147–150] the evidence supports the possibility of either a direct or indirect central effect of exogenous OXT. A few studies have found evidence to support the beneficial effects of intranasal OXT in paternal behaviour[151,152] and in promoting protective behaviour in mothers suffering from postpartum depression.[153] However, there is still some scepticism about the bias of some of the studies using intranasal OXT.[117,154] As in other pharmacological interventions, we can expect that, if OXT reaches the brain, it could have multiple effects, acting at different levels, and favouring one or other change depending on the site(s) of action and the context at which the individual is studied. At this point, it is worth noting that the distribution of OXTR in the human brain

remains unknown and it has not been possible to visualise the action of OXT in the human brain via positron emission tomography.[155]

7 | CONCLUSIONS AND PERSPECTIVES

In summary, OXT is a peptide that plays multiple physiological and neural functions in animals and humans. One of those functions includes promoting parental behaviour in multiple (direct and indirect) ways. OXT likely acts in the brain throughout development in a species-specific manner, shaping basic reproductive and social strategies in different species and generating sources of variability in behaviour and physiology within a species. OXT is also released acutely when the individual detects or interacts with a newborn facilitating the rapid approach and/or increasing the attraction toward pups, as well as reducing the anxiety or stress associated with such encounters. The action of OXT in the brain is also species-specific and can have an impact on different brain regions of the neural substrate that support parental behaviour (mainly the MPOA, VTA, NAc, amygdala and PFC) to promote those behavioural and affective changes. Although the neurophysiological mechanism that mediates the action of OXT in the brain is still not well understood, there is evidence that OXT can act at the different levels of the reward neural circuitry promoting or strengthening the reinforcing properties of pups. Evidence for age, species and individual differences in the OXT system converge to support the implication of OXT in the facilitation of parental behaviour in animals and humans. Interestingly, we can speculate a relationship between the shortening in latencies to respond to pups and the increases in contact with them promoted by OXT in animals with the higher maternal sensitivity and synchrony promoted in humans. Nonpharmacological therapeutic approaches or treatments that stimulate endogenous OXT release can perhaps improve mother-infant interaction, ameliorate or prevent mood disorders, and prevent maternal discomfort during the postpartum period. These promising studies must be continued so that we can fill the gaps in our current knowledge and establish a better relationship and connections among the existing evidence. New creative ways of assessing the neural and neurochemical basis of parental behaviour in humans should perhaps include the pre-screening of individuals, using several psychometric tools or questionnaires, to create extreme groups with known distinct parental styles or behavioural responses. Then, responses could be investigated not only to baby cries or images, but also to more complex scenarios where parental skills should be applied to resolve specific tasks.

Several questions should be addressed in the near future. One of these refers to the neural circuitry where OXT acts to promote their effects. In particular, studies in animals must continue to investigate the developmental and acute neural adaptations promoted by OXT, as well as its interaction with DA and other neurochemical systems (eg, AVP). Second, we need to investigate how to make exogenous or endogenous OXT access the brain regions of interest. Third, we still need to understand how OXT levels in body fluids relate to OXTR density in tissue and how OXT and OXTR genetic variants affect them. This will allow us to identify individuals with an atypical or dysfunctional OXT system that could be at risk for behavioural pathologies. Fourth, there is a need to know what factors are associated with a variable or dysfunctional OXT system and how to work to compensate or correct those alterations, or their behavioural or physiological consequences. The enormous interest that this area of study has attracted in the last decade will likely contribute to advancing our understanding of this system and its behavioural and physiological functions.

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