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The role of oxytocin in male and female reproductive behavior

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ABSTRACT

Oxytocin (OT) is a nonapeptide with an impressive variety of physiological functions. Among them, the 'prosocial' effects have been discussed in several recent reviews, but the direct effects on male and female sexual behavior did receive much less attention so far. As our contribution to honor the lifelong interest of Berend Olivier in the control mechanisms of sexual behavior, we decided to explore the role of OT in the present review. In the successive sections, some physiological mechanisms and the 'pair-bonding' effects of OT will be discussed, followed by sections about desire, female appetitive and copulatory behavior, including lordosis and orgasm. At the male side, the effects on erection and ejaculation are reviewed, followed by a section about 'premature ejaculation' and a possible role of OT in its treatment. In addition to OT, serotonin receives some attention as one of the main mechanisms controlling the effects of OT. In the succeeding sections, the importance of OT for 'the fruits of labor' is discussed, as it plays an important role in both maternal and paternal behavior. Finally, we pay attention to an intriguing brain area, the ventrolateral part of the ventromedial hypothalamic nucleus (VMHvl), apparently functioning in both sexual and aggressive behavior, which are at first view completely opposite behavioral systems.

1. Introduction

"There is no simple correspondence between an adaptive behavior and any single peptide" and " there is no necessary unitary relation between a limbic peptide and a single pattern of behavior" (Herbert, 1993). These statements were applied on a wide range of neuropeptides, including oxytocin (OT), and remain just as true as they were about two decades ago. Despite our considerably increased knowledge about locations and mechanisms of OT-release, the physiological and behavioral effects of OT on reproductive behavior in mammals (including humans) remain a complex matter of "whispered secrets and public announcements" (Leng and Ludwig, 2008).

Oxytocin (OT) is a nonapeptide with a molecular weight of 1007 Da, isolated and characterized in 1953 (Du Vigneaud et al., 1953). OT is produced in magno- and parvocellular neurons of the paraventricular hypothalamic nucleus (PVH), in the supraoptic hypothalamic nucleus (SON) as well as in accessory hypothalamic neurons, located in between these nuclei as well as in the bed nucleus of the stria terminalis (BNST) and medial preoptic area (MPOA) and mostly surrounding hypothalamic blood vessels (Armstrong and Hatton, 1980; Armstrong et al., 1980; Bealer et al., 2010; Kelly and Swanson, 1980; Sawchenko and Swanson, 1982b; Swanson, 1987; Swanson and McKellar, 1979a). The magnocellular neurons of PVH and SON send their fibers to the posterior pituitary, where the content is released in the vasculature to enter the general circulation to get access to all receptive peripheral organs (Bargmann, 1949; Kelly and Swanson, 1980; Swanson, 1987). The magnocellular projections form the hypothalamo-neurohypophysial tract, which bends laterally and ventrally around the fornix and ventromedial hypothalamic nucleus

Abbreviations: 5-HT, serotonin; 8-OH-DPAT, Dipropylamino-5,6,7,8-tetrahydro-naphthalen-1-ol; AOB, accessory olfactory bulb; AVP, vasopressin; BNST, bed nucleus of the stria terminalis; CNS, central nervous system; EB, estradiol benzoate; ERα-IR, estrogen receptor-α immuno-reactive; Fos-IR, Fos immuno-reactive; GABA, gamma aminobutyric acid; GnRH, gonadotropin-releasing-hormone; HAA, 'hypothalamic attack area'; HPA-axis, hypothalamus-pituitary-adrenal-axis; ICV, intra-cerebro-ventricular; IST, isotocin; LG, 'licking-and-grooming'; MEApd, medial amygdaloid nucleus, posterodorsal part; MEApv, medial amygdaloid nucleus, posteroventral part; MPOA, medial preoptic area; mRNA, messenger ribonucleic acid; OT, oxytocin; P, progesterone; PAG, periaqueductal gray; PAGdl, periaqueductal gray, dorsolateral part; PAGvl, periaqueductal gray, ventrolateral part; PE, premature ejaculation; PVH, paraventricular hypothalamic nucleus; SON, supraoptic hypothalamic nucleus; SNP, single nucleotide polymorphism; VCS, vaginocervical stimulation; VMH, ventromedial hypothalamic nucleus; VMHdl, ventromedial hypothalamic nucleus, dorsolateral part; VMHdm, ventromedial hypothalamic nucleus, dorsomedial part; VMHvl, ventromedial hypothalamic nucleus, ventrolateral part

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(VMH) before entering the internal lamina of the median eminence. The PVH, the SON and the accessory groups each contribute about one third of the fibers entering the posterior pituitary (Rhodes et al., 1981; Swanson, 1987). In addition to the pituitary-directed projections, the PVH projects to target areas within the central nervous system (CNS). It was long thought that these projections originated exclusively from parvocellular OT-neurons located in the dorsal PVH, however, some recent studies showed that magnocellular OT-neurons project to CNS-target areas as well (Knobloch et al., 2012; Ross et al., 2009; Ross and Young, 2009). The destinations of central OT-projections vary from the olfactory bulbs to the lumbosacral spinal cord and involves numerous limbic and brainstem regions (Buijs, 1978b; Buijs et al., 1978; Knobloch et al., 2012; Ono et al., 1978; Ross et al., 2009; Ross and Young, 2009; Sawchenko and Swanson, 1982b; Swanson and McKellar, 1979a; Yu et al., 1996b).

Concerning the functional aspects of the OT-neurons in PVH and SON, many studies have shown their involvement in a variety of physiological and behavioral functions. A major challenge in this field of research is the difficulty to manipulate central oxytocin neurotransmission, since both OT and the currently available OT-receptor antagonists do not readily cross the blood–brain barrier. A currently ongoing debate centers around the question as to whether peripherally or intranasally administered OT can affect central neurotransmission and thereby influence behavior. Recent studies and reviews have come to an affirmative conclusion and intranasally administered OT is currently applied in humans for the treatment of mental illness (Churchland and Winkielman, 2012; Kagerbauer et al., 2013; Neumann et al., 2013; Veening and Olivier, 2013).

Originally most applications for humans were in the clinical realm, in the form of treatments induce uterine contractions during labor or the milk flow in the lactation period, frequently by intranasal administration (Hendricks and Gabel, 1960; Huntingford, 1961). Later on OT was also applied for the treatment of other diseases and over the last decade the effects of OT in social interactions in humans ('mind-reading', trust, 'face-processing', autism and fear-reduction) are being extensively explored (Behnia et al., 2014; Koch et al., 2014), see (Veening and Olivier, 2013) for a recent review. In animal experiments the effects of OT on social and affiliative behavior were also evident (Insel, 1992) as were the effects on parental behavior, food intake, grooming behavior and pain relief (Lee et al., 2009; Neumann and Landgraf, 2012; Veening et al., 2010; Veening and Olivier, 2013). The behavioral effects of OT are 'prosocial' (Lukas et al., 2011; Shelley et al., 2006) and are not typical for humans and rodents, since similar 'nonapeptide-effects' have been observed in a variety of other species, from mollusks via teleosts and birds to primates, including man (Churchland and Winkielman, 2012; Insel, 2010; Knobloch and Grinevich, 2014; Snowdon et al., 2010).

From the obvious 'prosocial' effects of OT it is not a major step to study the effects of OT on male and female social behavior. A remarkable effect of OT was observed in voles and other rodents where monogamously living species were clearly different from the polygamous species in the density and distribution of OT-fibers and -receptors (Carter, 2014; Carter et al., 1995; Carter and Porges, 2013; Gimpl and Fahrenholz, 2001; Insel, 2010; Insel and Shapiro, 1992; Knobloch and Grinevich, 2014; Lee et al., 2009; Manning et al., 2012; Neumann, 2008; Neumann and Landgraf, 2012; Pedersen and Tomaszycki, 2012; Veenema and Neumann, 2008; Weisman et al., 2012; Witt et al., 1990; Young et al., 2005).

In our present review we will present an overview of the known effects of OT on male and female reproductive behavior. Concerning the physiological and pharmacological details of the neuronal circuitry, a large amount of additional information has become available over the last decades but many questions remain to be answered. For some recent reviews, see (Snoeren et al., 2013a, 2013b; Veening and Coolen, 2013; Veening et al., 2013).

2. Getting together: role of OT in pair bonding

In monogamous pairs, either 'romantic' human couples (Borrow and Cameron, 2012; Carter, 2014; Carter and Porges, 2013; Grewen et al., 2005; Light et al., 2005) or long-term attached pairs of rodents like prairie voles (Cho et al., 1999; Williams et al., 1992a; Williams et al., 1992b), the affiliative effects of OT have been extensively documented (Carter, 2014; Carter et al., 1995; Insel, 2010; Insel and Shapiro, 1992; Lukas et al., 2011; Neumann, 2008; Ross et al., 2009; Snowdon et al., 2010; Young et al., 2005). Specific differences in the distribution of OT-receptors have been observed between the monogamous prairie voles and polygamous species like montane voles (Lee et al., 2009; Lee et al., 2010; Ross et al., 2009; Ross and Young, 2009; Young et al., 2005) and analogous differences in the 'OT-systems' have been observed in other animals, including primates (Crockford et al., 2013; Lee et al., 2009; Moscovice and Ziegler, 2012; Pedersen and Tomaszycki, 2012; Schneiderman et al., 2012; Snowdon et al., 2010). Pair bonds can be very strong and losing the preferred partner may have detrimental effects on the surviving animal or human individual (Carter and Porges, 2013; Insel, 2010; Young et al., 2005; Zellner et al., 2011). Calling it 'love', either directed to a young or to a partner of the opposite sex, appears to be the most appropriate description (Komisaruk and Whipple, 1998). "Love is deeply biological … and has a profound effect on our mental and physical state" (Carter and Porges, 2013), and OT is strongly involved in these feelings (balanced by AVP (Neumann and Landgraf, 2012; Pedersen and Boccia, 2006; Veenema and Neumann, 2008)). Panksepp included a role of OT in two of his 'Basic Emotional systems' (Panksepp, 2011) and noted the remarkable similarities between social attachment and addiction. "Attachment is a primary form of addiction, or perhaps more accurately, addiction is a deranged form of attachment" (Zellner et al., 2011).

From these data it is clear that the 'prosocial' effects of OT stimulate physical contacts and inter-individual interactions (Carter, 1992). These changes are also reflected in diminished fear and anxiety behavior (Lukas et al., 2011; McCarthy et al., 1992; Neumann and Landgraf, 2012), increased trust (Alvares et al., 2010; Baumgartner et al., 2008; Lukas et al., 2011) and at least in male individuals in increased risk-taking behavior (Kavaliers et al., 2012; Waldherr and Neumann, 2007).

3. Doing the deed: role of OT in female sexual behavior

Whereas the level of pair-bonding and affiliate behavior varies widely among mammalian species (and the associated neuroanatomy and dynamics of the OT system as well), male and female sexual behavior is much more stereotyped. Although the temporal pattern of copulation differs between species and even within rodent species (for example, rats are much faster to initiate and complete copulation than mice), all mammals display a similar list of sexual behaviors (for example mounts and intromissions), postures (for example lordosis) and physiological reflexes (for example erection and ejaculation). OT has been found to play a role in many aspects of these stereotyped sexual parameters.

3.1. Role of OT in desire and appetitive behavior

In the appetitive, precopulatory phase of the sexual sequence the male and female rodent start their interactions (Emery, 1986; Pfaus et al., 2000; Pfaus et al., 1999; Veening, 1975; Veening and Coolen, 2013; Veening et al., 2013). An estrous female will rapidly start to display soliciting or proceptive behavior, 'hopping' and 'darting', to attract the attention of the male, to induce erection and to elicit a successful ejaculatory series in the copulatory phase

(Emery, 1986; Pedersen and Boccia, 2006; Pfaus et al., 1999; Veening et al., 2013).

The precopulatory phase is characterized by the phenomenon of 'desire' (Giraldi et al., 2004; Giraldi et al., 2013; Pfaus, 2009). OT contributes to 'sexual desire' and expectancy of future reward (Bancroft, 2005; Borrow and Cameron, 2012; Pfaus, 2009) and in the human this desire is temporarily suppressed after parturition, affected by OT and amygdaloid influences (Rupp et al., 2013). Pfaus (Pfaus, 2009) developed a dual control-model of inhibitory and excitatory effects on sexual behavior, and showed that dopamine functions at the excitatory side of the balance, together with OT and the melanocortins, while 5-HT (mostly, see (Mendelson and Gorzalka, 1985)), opioids and endocannabinoids work at the inhibitory side of the model (Pfaus, 2009). Sexual arousal (Bancroft, 2005) and desire are naturally related to the 'rewards' expected later in the behavioral sequence and therefore the important role of dopamine does not come as a surprise (Baskerville and Douglas, 2010; Frohmader et al., 2010; Hull, 2011; Hull et al., 2004; Pfaus, 2009; Pfaus et al., 1995; Pfaus et al., 2012). In this behavioral phase learning and conditioning processes play a very important role (Pfaus et al., 2012) and providing the female with the opportunity to 'pace' the succeeding copulatory events, enhances the 'reward value' of the copulatory phase (Emery, 1986; Nyuyki et al., 2011; Pfaus et al., 2000; Pfaus et al., 1999).

In the precopulatory phase the peripheral levels of OT start rising in both sexes, which may contribute to the preparation of the genital organs for the coming ejaculation or 'orgasm' (Borrow and Cameron, 2012; Giraldi et al., 2004; Giraldi et al., 2013; Komisaruk and Sansone, 2003). The presence of OT is not necessary for the coordination and performance of sexual behavior of male and female rodents. Transgenic OT-knockout as well OT receptor-knockout mice showed normal patterns of sexual behavior and pregnancy. Only after parturition problems arose, because lactation was heavily disturbed and all young animals would have died within 24 h, without proper precautions (Lee et al., 2010; Nishimori et al., 1996; Young et al., 1996). Do we have to conclude then that OT does not play a role in sexual activities? No, certainly not!

3.2. Role of OT in female copulation – anatomical substrate

Lordosis is specific dorsiflexed posture, observed in rodents and many other mammals, displayed by the female during successive mounts, intromissions and ejaculation by the male. The female keeps a fixed standing position, for a variable time-period, usually with additional details like lateroflexion of the tail. For additional details: see (Veening et al., 2013). The behavior can be observed only when the female is in estrus, under the proper hormonal conditions (Coirini et al., 1989; McEwen, 1988; Schumacher et al., 1989). In other circumstances she will actively reject a male companion trying sexual interactions.

In the female, the pelvic organs involved in (pre-)copulatory behavior are provided with OT receptors and OT fibers descending into the lumbosacral parts of the spinal cord (Buijs, 1978a; Normandin and Murphy, 2011; Swanson and McKellar, 1979b). By this combination of peripheral and central effects the pelvic organs can be prepared for the copulatory activities with regard to lubrication, muscular contractility and pain suppression for the coming vagino-cervical distension (Devost et al., 2008; Gelez et al., 2010; Giraldi et al., 2004; Magon and Kalra, 2011; Moos and Richard, 1975; Peters et al., 1987; Sansone and Komisaruk, 2001; Wilson et al., 2009).

In addition to the pelvic nerve (Moody et al., 1994), the vagal nerve and the 'dorsal vagal complex' appear to play an important role in the release of OT (Borrow and Cameron, 2012; Komisaruk and Sansone, 2003; Komisaruk et al., 2004; Moos and Richard, 1975; Whipple and Komisaruk, 2002) while complex autonomic adaptations occur in the copulatory phase (Wilson et al., 2009).

For a recent overview of the spinal and brain structures involved in the control of the lordosis posture, see (Veening et al., 2013). For the moment, we will focus on a few 'main' areas in which OT is known to play a significant role: the PVH, the VMH, especially its ventrolateral part (VMHvl), the periaqueductal gray (PAG) region and the medial preoptic area (MPOA).

The PVH is one of the main sources of OT with projections to numerous peripheral and central destinations. Neuronal activation after sexual activities has been observed in females occasionally in both parvo- and magnocellular neurons (Cameron and Erskine, 2003; Flanagan et al., 1993; Pfaus and Heeb, 1997; Witt and Insel, 1994; Yang and Voogt, 2002). In rat pups, the parvocellular PVH neurons were activated by perineal stimulation and their activation produced a transient 89% increase in OT-levels in the lumbosacral spinal cord (Lenz and Sengelaub, 2010), which suggests that oxytocin is involved in the development and sensitization of the perineal part of the body, potentially supporting future copulatory activities in the male and female rat.

Concerning the VMH, this hypothalamic brain region is a crucial part of the motor circuitry producing the lordotic posture (Calizo and Flanagan-Cato, 2002; Flanagan-Cato, 2011; Mathews and Edwards, 1977a; Pfaff and Sakuma, 1979a; Veening et al., 2013). The VMH has been subdivided in several parts, a dorsomedial part (VMHdm) and a ventrolateral part (VMHvl), separated by a cell-poor intermediate area, and surrounded by cell-poor zone, especially prominent along its ventrolateral side (Canteras et al., 1994; Fahrbach et al., 1989; Flanagan-Cato, 2011; Millhouse, 1973a, 1973b, 1978; Van Houten and Brawer, 1978a, 1978b). In male rats the VMHvl is at least 25% larger than in females (Dugger et al., 2007; Madeira et al., 2001; Matsumoto and Arai, 1983). Millhouse (1973b, 1978) observed different kinds of neurons and most of them show about 3 primary dendrites and a few secondary ones (Ferri and Flanagan-Cato, 2012). The longest primary dendrite extends into the ventrolateral zone surrounding the VMHvl (Ferri and Flanagan-Cato, 2012; Flanagan-Cato, 2011). The longest dendrites, extending into the lateral cell-poor zone, are contacted by ascending and descending components of the medial forebrain bundle, traversing the intermediate hypothalamic area (Geeraedts et al., 1990a, b; Nieuwenhuys et al., 1982; Veening et al., 1982). OT-containing fibers are especially numerous in this area, along the VMHvl, which play an essential role in the estrus related behavioral changes and plasticity observed in this part of the VMH (Flanagan-Cato, 2011).

In the VMHvl at least 3 different cell types have been described: PAG-projecting neurons, ERα-IR neurons and neurons showing Fos-IR after mating, with only minimal functional overlap (Flanagan-Cato, 2011). The epaxial muscles (involved in the execution the lordosis response), have been injected with a retrograde (pseudorabies) virus and the pattern of labeling showed that the 'core' of the VMH and the estrogen-receptive neurons are hardly involved in these spinal projections and that by far the majority of the labeled neurons were observed in VMHvl (Daniels and Flanagan-Cato, 2000; Daniels et al., 1999).

Lordosis responses can be induced by electrical stimulation or disrupted by lesions of the VMHvl and this brain area has numerous relationships, among them a set of strong, mostly reciprocal, connections with the PAG (for a recent overview see (Veening et al., 2013)). In addition, the VMH receives olfactory, somatosensory and genitosensory stimuli from respectively the olfactory system, the flank region and the vagina and clitoris (Bennett et al., 2002; Bueno and Pfaff, 1976; Georgescu et al., 2009; Kirkpatrick and Merrill, 2011; Marson, 1995; Pfaus et al., 2006; Pfaus et al., 1996). In several studies neural activation was

observed in the female VMH after sexual activities, mostly but not exclusively in its ventrolateral part, the VMHvl (Blaustein et al., 1994; Coolen et al., 1996; Flanagan et al., 1993; Pfaus et al., 1993; Rowe and Erskine, 1993; Tetel et al., 1993; Wersinger et al., 1993).

Interestingly, epigenetic influences have been observed in the VMHvl when females reared by low-licking-and-grooming (LG) mothers were compared with females reared by high-LG mothers. In the latter group lordosis rating was lower and more defensive behaviors were observed during mating, a lower number of ERα-IR but more Fos-IR neurons were observed in the VMHvl after mating and the pseudo pregnancy rate after vaginocervical stimulation (VCS) was lower, compared to the high-LG group (Cameron et al., 2011). These differences may have effects on lordosis termination (see below) but generally favor the reproductive success of the low-LG-reared females.

Concerning the PAG, control of lordosis is among its most conspicuous functions (Arendash and Gorski, 1983; Harlan et al., 1983; Ogawa et al., 1991; Ogawa et al., 1992; Pfaff and Lewis, 1974; Sakuma and Pfaff, 1979). This control is performed in a close but complex cooperation with the ventromedial hypothalamic nucleus (VMH), especially its ventrolateral part (VMHvl) (Flanagan-Cato, 2011; Flanagan-Cato et al., 2006; Flanagan-Cato and McEwen, 1995; Pfaff and Sakuma, 1979a; Pfaff and Sakuma, 1979c).

Concerning the MPOA, this region shows neural activation (Fos-IR) in female rats after copulatory activities (Cameron and Erskine, 2003; Coolen et al., 1996; Coria-Avila and Pfaus, 2007; Flanagan-Cato and McEwen, 1995; Kirkpatrick and Merrill, 2011; Oboh et al., 1995; Parada et al., 2010; Pfaus et al., 1994; Pfaus et al., 2006; Polston and Erskine, 1995; Wersinger et al., 1993; Yang and Voogt, 2002), and the gonadotropin-releasing hormone (GnRH) neurons seem to be included in this activation pattern (Pfaus et al., 1994; Wu et al., 1992). The GnRH-fibers are descending along the mesencephalic aqueduct, where they are probably involved in the induction of lordosis via the surrounding PAG (Buma, 1989; Sakuma and Pfaff, 1980; Samson et al., 1980; Sirinathsinghji, 1985; Veening and Barendregt, 2010; Veening et al., 2012). The involvement of the MPOA in the hormonal control mechanisms was detected early (Freeman and Banks, 1980; Gray et al., 1978; Hayashi and Orimo, 1975; Leipheimer and Gallo, 1985; Moss and Foreman, 1976; Sirinathsinghji, 1986) and so were the stimulating effects of OT on lordosis, about a decade later (Arletti and Bertolini, 1985; Caldwell et al., 1989; Kow and Pfaff, 1988; Schulze and Gorzalka, 1991), (though this stimulation depended on the test situation chosen (Whitney, 1986)).

3.3. OT effects on lordosis and orgasm

OT injected in the cerebral ventricles (ICV) stimulates proceptive behavior (and the lordosis posture) while AVP has the opposite effect and tends to increase agonistic reactions towards the male (Pedersen and Boccia, 2006). Icv-infusion of OT-antagonists had an inhibitory effects on female sexual behavior in rats (Pedersen and Boccia, 2002), similar to the effects of vasopressin (Pedersen and Boccia, 2006) as well as of peripheral administration in primates (Boccia et al., 2007).

In rodents, OT may be dispensable for the induction of lordosis in mice (Lee et al., 2010; Nishimori et al., 1996) but in rats clear facilitating effects have been observed after both systemic (Arletti and Bertolini, 1985) and central (Caldwell et al., 1986; Gorzalka and Lester, 1987; Schumacher et al., 1989) administration of OT. Since peripheral OT does hardly enter the CNS (Mens et al., 1983; Robinson and Jones, 1982), neural mechanisms must be involved in the coordination, and these have been explored by peripheral lesions like pelvic neurectomy (Moody et al., 1994) and hysterectomy (Moody and Adler, 1995) and by VCS in sheep (Kendrick et al., 1993) and rats (Coolen et al., 1996; Northrop and Erskine, 2008; Pfaus and Heeb, 1997; Veening and Coolen, 1998).

The generally facilitating effects of OT on lordosis (Arletti and Bertolini, 1985; Kow et al., 1991; Witt and Insel, 1992) need some additional comments, because they were not observed under all circumstances in rats (Caldwell et al., 1989; Schulze and Gorzalka, 1991; 1992; Schumacher et al., 1991) or prairie voles (Witt et al., 1990). These authors showed that the sensitivity of the neural substrate for ICV OT depends on the light/dark schedule, with the stronger responses in the dark period (Schumacher et al., 1991), that the exact hypothalamic location of the OT-infusion is important (Caldwell et al., 1989) and may influence lordosis frequency and lordosis duration separately (Schulze and Gorzalka, 1991), and that infusion of OT in a lateral ventricle may have an inhibitory effect on lordosis, not observed after an identical infusion into the 3rd ventricle (Schulze and Gorzalka, 1992). For recent overviews of the possible effects of OT in the CSF, see (Veening et al., 2010; Veening and Olivier, 2013).

In female human studies, it was observed that plasma OT levels are variable over the menstrual cycle (Salonia et al., 2005), with lowest levels during the luteal phase. During sexual arousal plasma levels increase (Blaicher et al., 1999) to reach peak levels at the moment of orgasm with, in multiorgasmic women, a clear correlation between OT-levels and subjective orgasm intensity (Carmichael et al., 1994). Concerning the arousal and orgasm-induced elevated levels of OT, it seems to be “still unclear whether OT increases sexual arousal or is a natural byproduct of it” (Borrow and Cameron, 2012). The presence of OT-receptors on multiple organs, especially on the male and female genital organs (Gimpl and Fahrenholz, 2001) suggests a possibly ‘preparatory role’ of OT for the later and final phases of the copulatory process, like ejaculation and orgasm, ‘preparing’ all necessary muscular contractions and lubrication effects. On the other hand, it has been suggested that the high levels of OT play a role in ‘sexual satiety’ following orgasm by flooding the OT-receptors and producing desensitization (Caldwell, 2002)

The physiological and behavioral effects of OT are strongly linked to other hormones like estrogen (Caldwell et al., 1988; Caldwell et al., 1986; Coirini et al., 1989; McCarthy, 1995; McEwen, 1988), progesterone (Caldwell et al., 1994; Gorzalka and Lester, 1987; Schumacher et al., 1989; Witt and Insel, 1991), prolactin (Donner and Neumann, 2009; Egli et al., 2010; Harlan et al., 1983; Northrop and Erskine, 2008; Sobrinho, 1993) as well as other factors (Beinfeld, 2001; Carter et al., 2003; Dellovade et al., 2000; Kow and Pfaff, 1988; Pedersen and Boccia, 2006). A discussion of their interactions would go far beyond the scope of the present review and unraveling these requires sophisticated experiments, for instance, concerning prolactin (Northrop and Erskine, 2008). Vaginocervical stimulation (VCS), induced by 15 intromissions, induces prolactin release and pseudopregnancy in control female rats. Local infusion of an OT-antagonist in the VMHvl prevented this pseudopregnancy, leading to the suggestion that “OT release in the VMHvl mediates the effects of VCS on the induction of the prolactin secretion needed to establish pseudopregnancy” (Northrop and Erskine, 2008). This experiment brings us from the peripheral sensory stimulation, the VCS, directly towards one of the main controlling brain areas, the VMHvl, involved in the induction of the lordosis posture (see above). A single treatment with OT or an OT-antagonist in the first postnatal week of young rats resulted in long-term changes in the expression of ERα and OT in the mediobasal hypothalamus (Perry et al., 2009).

OT has been shown to be strongly involved in the induction of lordosis, if estrogen and progesterone are present (Davis et al., 1979; Pleim and Barfield, 1988; Pleim et al., 1989; Rubin and Barfield, 1983). The facilitating effects of OT were especially prominent in the VMHvl (McCarthy et al., 1994; Schulze and

Gorzalka, 1991; Schumacher et al., 1989), and the physiological effects of OT on hypothalamic brain slices were clearly enhanced by the addition estradiol (Booth et al., 2010; Kow et al., 1991).

For an extensive overview of the neurochemistry of the VMH, see Flanagan-Cato (2011). A few points have to be mentioned, however, to understand the plasticity of the VMHvl and certain behavioral transitions discussed in a later section. Many of the long, laterally extending dendrites of the ERα-IR neurons express OT-receptors (Ferri and Flanagan-Cato, 2012; Flanagan-Cato, 2011; Flanagan-Cato et al., 2001). As we have seen, both estrogen and OT have a facilitating effect on female sexual behavior and lordosis, but other factors play a role as well, like GABA-ergic interneurons and glutamate, present in the OT-fibers (Flanagan-Cato, 2011; Flanagan-Cato et al., 2001; McCarthy et al., 1995; McCarthy et al., 1990; McCarthy et al., 1991b). Estradiol treatment combined with OT-administration enhances neuronal firing in the VMHvl (Booth et al., 2010; Kow et al., 1991). "Ovarian hormones enhance OT production, the electrical activity of OT neurons, and up-regulate the level of OT receptors in the VMH" (Ferri and Flanagan-Cato, 2012; Theodosis, 2002). The fiber plexus lateral to the VMHvl plays an important role in these interactions, because there VMH-dendrites and OT-fibers actually meet (Griffin et al., 2010; Schumacher et al., 1990). Estradiol treatment in female rats increases spine density and axospinous synapses, while these parameters decrease in male rats after the same treatment (Carrer and Aoki, 1982; Frankfurt et al., 1990; Lewis et al., 1995; Sa and Madeira, 2005). Estradiol also caused a marked shortening of the laterally extending dendrites, which effect could be reversed by a sequential progesterone treatment (Griffin et al., 2010; Madeira et al., 2001). So, estradiol regulates the number of contact in the zone lateral to the VMHvl. Remarkably, however, the VMH-dendrites showing OT-labeling, probably as a result of OT-internalization, were excluded from this shortening effect and remained intact (Griffin et al., 2010). These OT-estradiol interactions appear to be clearly involved in the plasticity occurring during the estrous cycle (4 or 5 days in the female rat) with its concurrent changes in behavior, especially the performance of the lordotic posture. But there are more factors playing a role here e.g. glutamate. The OT-fibers co-release glutamate, also in the axon-terminals in the contact area, lateral to the VMHvl, and glutamate (-agonists) have an inhibiting effect on female sexual behavior (Georgescu and Pfaus, 2006a; Georgescu et al., 2009; McCarthy et al., 1991a; McCarthy et al., 1995). In addition, glutamatergic neurons are present in the VMH and glutamate-transporters have been observed in the short dendrites of the ERα-IR VMHvl neurons (Flanagan-Cato, 2011; Georgescu and Pfaus, 2006a; Georgescu et al., 2009; McCarthy et al., 1991a; McCarthy et al., 1995). The situation is apparently very complex, with a mix of excitatory and inhibitory factors released together, and additional research is absolutely necessary to clarify these complex anatomical and neurochemical relationships (Ferri and Flanagan-Cato, 2012; Flanagan-Cato, 2011; McCarthy et al., 1991a). These complex interactions are not always or necessarily 'pro-sexual' or 'pro-lordosis'! Some of the mechanisms working in the area lateral to the VMHvl may not promote lordosis, but prepare the female for the termination of the estrous period (see Section 5).

3.4. OT and male copulation – anatomical substrate

Oxytocin (OT) strongly affects male sexual behavior. Evidence from male rats and a few other species have indicated that sexual cues and behaviors stimulate central and peripheral OT neurotransmission which, in turn, facilitate copulation (Argiolas and Melis, 2013; Gil et al., 2013). The neurocircuitry responsible for these interactions has been investigated using various techniques, including tract-tracing studies and immunohistochemistry to identify how oxytocin neurons are connected with reproductive tissue and measurement of the activation of OT neurons and OT release in response to sexual interactions.

Parvocellular OT neurons project directly to the spinal cord (Gerendai et al., 2001). A series of tract-tracing studies, in which pseudorabies viruses were injected into the corpus cavernosum, penile muscles, epididymis and prostate of male rats, showed that the PVN was connected to each type of tissue (Gerendai et al., 2001; Marson and McKenna, 1996; Marson et al., 1993; Orr and Marson, 1998; Tang et al., 1998) putatively via the sacral parasympathetic nucleus (Tang et al., 1999). Varicosities containing OT or neurophysin (a carrier protein indicating the presence of either OT or AVP (Breslow and Burman, 1990)) have been found in close apposition to neurons in the sacral parasympathetic nucleus, ventral horn, and dorsal gray commissure that directly or indirectly control the genitals (Tang et al., 1998; Veronneau-Longueville et al., 1999; Wagner and Clemens, 1993). The (putatively OTergic) paraventricular neurons projecting to the spinal cord also provide collateral projections to the nucleus paragigantocellularis in the brainstem, which exerts a tonic serotonergic inhibition of penile reflexes (Bancila et al., 2002; Normandin and Murphy, 2011). Conversely, it was found that predominantly magnocellular OT neurons in the caudal portion of the PVN receive genitosensory input from the penis (Normandin and Murphy, 2011).

Indeed, Fos-expression is increased in both parvocellular and magnocellular oxytocinergic neurons of the PVH and SON in response to sexual behavior or sexual cues in rats (Caquineau et al., 2006; Nishitani et al., 2004; Pattij et al., 2005; Witt and Insel, 1994). Consistently, electrical stimulation of the dorsal penile nerve or glans penis produces excitation in OT cells in the PVH and SON of rats (Honda et al., 1999; Yanagimoto et al., 1996). Finally, sexual interaction with a female coincides with an increase in OT release in the PVH (measured by in vivo microdialysis) and in the cerebrospinal fluid (measured using cisterna magna sampling) in rats (Hughes et al., 1987; Waldherr and Neumann, 2007).

Taken together, a circuit emerges in which sensory information associated with sexual interactions reaches predominantly magnocellular neurons in the PVN and SON, which release OT locally as well as in the bloodstream. Local OT release activates nearby parvocellular OT neurons (Kita et al., 2006), which in turn facilitate genital reflexes via the sacral parasympathetic nucleus in the spinal cord. Of course this circuit is strongly influenced by other neuropeptides and neurotransmitters, and includes other brain areas besides the PVH, SON and spinal cord, which will be discussed (briefly) later in the review.

3.5. OT effects on erection and ejaculation

Infusions of OT (~1–90 ng) into the cerebral ventricles is generally known to facilitate copulatory reflexes by increasing non-contact erections (observed in sexually potent male rats in the presence of an inaccessible receptive female) and reducing ejaculation latencies and postejaculatory intervals (Argiolas et al., 1985; Arletti et al., 1985; Mizusawa et al., 2002). In squirrel monkeys, ICV OT (0.1 pg) increased the frequency of sexual interactions in dominant, but not subordinate squirrel monkeys (Winslow and Insel, 1991). However, ICV infusion of OT at doses higher than approximately 100–200 ng may not be effective or even inhibiting sexual reflexes, potentially by mimicking sexual satiety (Argiolas et al., 1989b; Mahalati et al., 1991; Stoneham et al., 1985). ICV administration of an OT receptor antagonist (2–1000 ng) shows inhibition of sexual behavior by increasing the intromission latency, decreasing copulatory activity and abolishing ejaculation in rats as well as inhibiting noncontact erections (Argiolas et al., 1989a; Argiolas et al., 1988; Arletti et al., 1992; Melis et al., 1999). It is of note here that the OT receptor antagonist used in these

studies showed an additional strong blockade of the vasopressin (AVP) V_{1A} receptor (Manning et al., 2012). Although the nonapeptide AVP has not been consistently implicated in male sexual behavior, at least one report described the significant role of peripheral V_{1A} receptors in the pro-ejaculatory effects of OT (Gupta et al., 2008).

Consistent with the inhibitory effects of OT receptor antagonists, reducing OT neurotransmission via selective lesions of the parvocellular neurons in the PVN, which reduce the number of OT-immunoreactive fibers in the lumbosacral spinal cord, causes a longer latency to noncontact erections, mounts and intromissions, and decreases seminal emission as well as the postejaculatory interval (Ackerman et al., 1997; Hughes et al., 1987; Liu et al., 1997). Lesions of both the magnocellular and parvocellular neurons in the PVH, which target both OT and AVP neurons (as well as other neurotransmitters and neuropeptides present in the PVH), inhibit noncontact erections and increase the mount frequency and latency to ejaculation during copulation (Liu et al., 1997).

The clear effects on male sexual behavior by changes in general OT neurotransmission have led to a search for projection areas in which OT exerts its effects. Intrathecal injection of OT at the lumbosacral, but not thoracolumbar, level of the spinal cord increased erection (Giuliano et al., 2001). In addition, local infusions of OT in the PVH, hippocampus, ventral tegmental area, and posteromedial amygdala all facilitate noncontact erections (Chen and Chang, 2001; Melis et al., 1986; Melis et al., 2007; Melis et al., 2009). Microinjection of OT into the medial preoptic area (MPOA) reduced the mount frequency and postejaculatory interval in sexually experienced rats, and reduced the ejaculation latency in naïve rats (Gil et al., 2011; 2013). Although local infusion of OT receptor antagonists could inhibit or block the effects of OT in these areas (Chen and Chang, 2001; Melis et al., 1986; Melis et al., 2007; Melis et al., 2009), and administration of an OT receptor antagonist to the spinal cord at the lumbosacral level reduced bulbospongiosus muscle contractions and ejaculation (Clement et al., 2008), the antagonists had no or very mild effects on sexual reflexes when administered in the MPOA or PVH alone (Gil et al., 2011; Melis et al., 1999).

As described above, the effects of OT on male sexual behavior are at least partly executed through central OT neurotransmission. However, a significant role of peripheral OT neurotransmission cannot be excluded. The considerable amount of OT that gets released into the bloodstream following sexual cues or interactions in rats, rabbits and humans (Carmichael et al., 1987; Hillegaart et al., 1998; Kruger et al., 2003; Murphy et al., 1987; Stoneham et al., 1985; Uckert et al., 2003) presumably has a function. Indeed, systemic (intravenous or intraperitoneal) injection of oxytocin facilitates ejaculation, as measured in rats, rabbits and bulls (Arletti et al., 1985; Arletti et al., 1990; 1992; Melin and Kihlstroem, 1963; Palmer et al., 2004; Stoneham et al., 1985). Interestingly, peripheral OT predominantly facilitates ejaculation whereas central OT predominantly affects erection. In fact, peripherally administered OT has been occasionally found to inhibit erection (Palmer et al., 2004; Zhang et al., 2005). Consistently, peripheral administration of OT receptor antagonists inhibited markers of ejaculation and facilitated markers of erection in anaesthetized rats (Clement et al., 2008; Zhang et al., 2005).

The pro-ejaculatory effects of systemic OT may be exerted via peripheral OT receptors that have been found in the testis, epididymis, ductus deferens, prostate and penis of rats, rams and humans, where they mediate the contractility of smooth muscle cells involved in ejaculation (Corona et al., 2012). However, systemic administration of OT also activated the ejaculatory motor pattern, which is exerted by motor neurons in the spinal cord (Carro-Juarez and Rodriguez-Manzo, 2005), suggesting that at least some of the effects of peripheral OT occur via central OT receptors. Consistently, the novel non-peptidergic OT receptor antagonist, GSK557296, which readily crosses the blood–brain barrier, showed inhibition of various markers of ejaculation, with the strongest effects obtained following ICV and intrathecal infusion at the lumbar level compared to IV and thoracic level infusions (Clement et al., 2013).

Although it is clear that OT strongly affects male sexual behavior, it is much less understood whether variability in the endogenous OT system may underlie innate or experience-induced variability in sexual parameters. When male rats were divided into stable rapid or sluggish ejaculators, it was shown that OT neurons in the SON (but not PVH) were more activated following copulation and ejaculation in the first group compared to the latter (Pattij et al., 2005). In addition, the pro-ejaculatory effects of systemic OT were stronger in sexually sluggish rats compared to sexually potent rats (although OT could not rescue sexual behavior in fully impotent rats) (Arletti et al., 1992). Furthermore, sexually potent rats had a higher expression of OT mRNA in the magnocellular PVN compared to impotent rats (Arletti et al., 1997). These studies suggest that endogenous release of OT in response to sexual cues is naturally inhibited in sluggish rats, or naturally facilitated in sexually efficient rats. Interestingly, sexually efficient male rats had lower levels of OT receptor binding in the MPOA compared to inefficient animals (Gil et al., 2011). The authors suggested that OT receptors might have been internalized or transcriptionally down-regulated in efficient copulators as a response to higher OT levels.

Copulation on the day of sacrifice stimulated OT receptor-mRNA expression in the MPOA, with the highest levels observed in first-time copulators. Sexually experienced males had higher levels of OT receptor protein in the MPOA than sexually naive males and first-time copulators (Gil et al., 2013). These studies indicate that sexual experience, either immediately or over time, changes the endogenous OT system.

3.6. OT and premature ejaculation in men

The ejaculation and erection facilitating effects of oxytocin, as found in animal studies, may contribute to explain a thus far rather unrecognized clinical phenomenon in men with lifelong premature ejaculation (PE): the acute hypertonic or hypererotic state, which occurs when a man with lifelong PE is engaged in an erotic situation. It is characterized by an early ejaculation (ejaculatio praecox), but also by an early or facilitated erection (erectio praecox) and an immediately occurring detumescence of the penis after ejaculation (detumescentia praecox) (Waldinger, 2014). It has been postulated that the facilitated erection, facilitated ejaculation and facilitated penile detumescence are associated with centrally and peripherally increased oxytocin release in association with involvement of the central serotonergic system and other neurotransmitter and endocrinologic systems (Waldinger, 2014). Research into this triade of symptoms will presumably contribute to a better neurobiological understanding of lifelong PE and its delineation to the three other PE subtypes (Waldinger, 2013; Waldinger, 2008).

In a large sample of men ($n=1517$), no effects were detected of twelve OT receptor gene SNPs on ejaculatory function. However, a heterozygote effect on one SNP in the oxytocin receptor gene (rs75775) was found, so that individuals heterozygous for this SNP had a significantly elevated risk for premature ejaculation symptoms compared with carriers of either homozygote (Jern et al., 2012)

3.7. Other neurotransmitters involved in the OT- male sexual behavior circuit

Recent reviews have extensively discussed the role of various neurotransmitters and neuropeptides (aside from OT) in the

control of male sexual behavior and genital reflexes (Argiolas and Melis, 2013; Corona et al., 2012; Melis and Argiolas, 2011). For example, it is known that the pro-erectile effects of OT are supported by dopamine, glutamate and nitric oxide within the PVH as well as in the hippocampus, amygdala and ventral tegmental area. On the other hand, gamma-aminobutyric acid (GABA), opioid peptides and endocannabinoids inhibit the pro-sexual activity of OT neurons.

Since these reviews did not include a description of the potential role of serotonin (5-HT)-OT interactions (de Jong et al., 2007), we discuss that in more detail here. The role of 5-HT in male sexual behavior is extensive and complex, but in general, increased extracellular 5-HT levels inhibit sexual behavior and increase the ejaculatory threshold through the activation of 5-$HT_{1B/2C}$ receptors (de Jong et al., 2006). Increased 5-HT levels appear to simultaneously counteract their own inhibition of sexual behavior via activation of 5-HT_{1A}-receptors, which facilitate ejaculation (Ahlenius et al., 1981; Snoeren et al., 2013b). Thus, high 5-HT levels (either caused by tonic endogenous release or artificially increased via SSRI administration) maintain a high ejaculatory threshold, and increased or decreased activation or sensitivity of 5-HT_{1A} receptors can adjust it up or downward (Ahlenius and Larsson, 1999; de Jong et al., 2005a; de Jong et al., 2005c; Giuliano and Clement, 2006; Looney et al., 2005). The current theory is that both 5-HT_{1A} autoreceptors (located on 5-HT neurons in the raphe nuclei) and 5-HT_{1A} heteroreceptors (located throughout the CNS) are involved in the facilitation of ejaculation (Snoeren et al., 2013b). Interestingly, 5-HT and OT interact with one another in various brain areas associated with male sexual behavior. In the PVH, 5-HT_{1A} receptors are expressed by oxytocinergic (OT) neurons in the hypothalamus (Zhang et al., 2004). Since 5-HT_{1A} receptor activation induces Fos-immunoreactivity in hypothalamic OT neurons (Coolen et al., 1997; de Jong et al., 2005b) and causes a strong peripheral (and potentially central) release of OT (Bjorkstrand et al., 1996; Van de Kar et al., 1998; Vicentic et al., 1998), this has been proposed as a possible pathway through which 5-HT_{1A} receptor agonists facilitate ejaculation (de Jong et al., 2007). Indeed, unpublished studies have indicated that the pro-ejaculatory effect of systemic injection with 8-OH-DPAT could be partly blocked by ICV administration of an OT receptor antagonist (unpublished observations dr. T.R. de Jong). Furthermore, in the nucleus paragigantocellularis in the brainstem, 5-HT neurons that project to the spinal cord tonically inhibit sexual reflexes and receive putatively inhibitory OT-ergic projections from the PVH (Bancila et al., 2002; Normandin and Murphy, 2011). The sacral parasympathetic nucleus in the spinal cord, which controls the smooth muscle cells in the genitals, receives projections from both inhibitory 5-HT-ergic and facilitatory OT-ergic neurons (Tang et al., 1998). Finally, in the medial preoptic area, OT release facilitates and 5-HT release inhibits male sexual behavior (Dominguez and Hull, 2010; Gil et al., 2011). Taken together, OT and 5-HT appear to counteract each other in various central nervous system regions involved in male sexual behavior, whereas OT appears to support the facilitation of ejaculation by 5-HT_{1A} receptor activation.

4. The fruits of labor: role of OT in parental care

The crucial role of OT in various physiological and behavioral aspects of the peri-partum period is well known. Most knowledge has been derived from female mammals, in particular rats and mice, but more recently other species have been investigated as well. There is an increasing interest in mammalian species in which the male plays a substantial role in the care for offspring. The role of OT in paternal behavior is therefore highlighted in this review.

4.1. Role of OT in maternal care

The most drastic effects of OT appear around parturition when OT supports the delivery of the fetus by stimulating the uterine contractions, and the myoepithelial cells of the mammary gland to induce milk ejection for the succeeding lactation period (Armstrong and Hatton, 2006; Crowley et al., 1992; Lincoln and Paisley, 1982; Summerlee, 1981; Summerlee and Lincoln, 1981). Afferent signals from the uterine cervix or from the nipples stimulate the magnocellular neurons of the PVH and the SON to start the secretion of OT via the posterior pituitary. However, the magnocellular neurons send their products not only into the peripheral circulation. Recently it was observed that the fibers, leaving the magnocellular PVH and SON, send collaterals to the nucleus accumbens region involved in reward mechanisms (Ross et al., 2009). In addition to the magnocellular neurons, the PVH contains numerous parvocellular OT neurons with projections widely dispersed throughout the CNS, expanding even into the lumbosacral parts of the spinal cord (Armstrong and Hatton, 1980; Armstrong et al., 1980; Buijs, 1978a; Buijs et al., 1983; Sawchenko and Swanson, 1982a; Swanson and Kuypers, 1980; Swanson and McKellar, 1979b). Since OT released in the peripheral circulation has virtually no access to the CNS (Mens et al., 1983; Robinson and Jones, 1982), the numerous behavioral changes occurring at the time around parturition must be the result of activation of the parvocellular OT-innervation, of course in cooperation with other hormonal -, transmitter- and peptidergic changes occurring in that period (Herbert, 1993; Rosenblatt et al., 1988). These changes can be labeled as 'maternal behavior' (Numan, 2007; Numan et al., 2005; Numan and Sheehan, 1997; Olazabal et al., 2013; Tsuneoka et al., 2013) and are more extensive and complex than just nursing the just born animals because they involve changes in the olfactory system, food intake, sexual behavior, (maternal) aggression and in cognitive and memory functions (Blevins et al., 2003; Blevins et al., 2004; Carter, 1992; 1998; Neumann, 2002; Uvnas-Moberg, 1998; Vaccari et al., 1998). The high CNS-levels of OT around parturition play a strong role in the 'behavioral transformation' occurring in the mother, in combination with other factors like estrogen levels and other neuromodulatory substances (McCarthy et al., 1992; Neumann, 2003; Neumann et al., 2003).

OT is present in the olfactory bulbs of the rat because fiber projections from the PVH innervate the bulbs as well as other parts of the olfactory system (Gimpl and Fahrenholz, 2001; Vaccari et al., 1998). There is evidence that some of the OT does not reach the bulbs directly via these neural projections (Yu et al., 1996a; Yu et al., 1996b), and transport of OT via the cerebrospinal fluid is possibly one of the mechanisms involved (Veening et al., 2010; Veening and Olivier, 2013). OT can directly affect neuronal processing in the bulb itself and in addition many amygdaloid and other limbic brain areas contain OT-receptors (Ghosh et al., 2011; Gimpl and Fahrenholz, 2001; Kang et al., 2009; 2011; Miyamichi et al., 2011; Nagayama et al., 2010; Sosulski et al., 2011) and may be influenced by a local release of OT. Similar mechanisms have been studied extensively in sheep (Kendrick, 2000; Kendrick et al., 1997; Kendrick et al., 1986; Kendrick et al., 1991). Functionally, the changes in 'olfactory sensitivity' and the succeeding changes in the 'olfactory memory systems' appear to serve two important functions: (1) to memorize who mated the female, important for ' pair-bonding', see Section 2; (2) to recognize her offspring which deserves her maternal care. Variations in maternal care may affect their offspring directly, including the activity of specific hypothalamic brain areas (Cameron et al., 2011; Champagne, 2008).

The behavioral changes occurring at parturition are complex because for properly feeding the young, adaptations in food intake maybe necessary. In addition specific protective postures are adopted during nursing and milk ejection. At the same time, however, occasional intruders interested in either reproduction

or the young animals themselves have to be kept at a distance to protect the young and a strong reaction in the form of 'maternal aggression' may be temporarily necessary. This list of behavioral changes occurring at parturition can be extended but suffices to show the complexity of the changes, involving not only interaction with the pups but also adaptation to additional nutritional requirements and even clear-cut 'antisocial' reactions to unwanted companionship. OT seems to play a role in each of these changes.

For nursing the young, OT plays an important role in the milk-ejection reflex, induced by the suction of the nipples (Armstrong, 2007). The number of suckling rat pups determines the amount of OT released in the peripheral blood and the amplitude of the milk ejection burst, but not the frequency of the milk ejections, about once per 5 min (Armstrong, 2007; Hatton and Wang, 2008; Lincoln and Wakerley, 1975a, b; Rossoni et al., 2008). Apparently, a central pattern generator is involved in the effects of continuous suckling stimuli, generating a massive synchronization of OT- neurons across the SON and PVH (Armstrong, 2007; Moos and Richard, 1989). The neural mechanisms behind the synchronization of OT-release turned out to be complex, involving coordinated somato-dendritic release of OT in the PVH and SON (Ludwig and Leng, 2006; Moos et al., 1989), effects of local glial cells (Brown et al., 2013; Wang and Hamilton, 2009; Wang and Hatton, 2009) as well as subcellular mechanisms (Brown et al., 2013; Zhang et al., 2010). Other hypothalamic areas participate in the synchronization mechanisms, like the mammillary region (Wang et al., 2013) and the dorsomedial hypothalamic nucleus (Honda and Higuchi, 2010a, b). The effects of the suckling-induced massive OT-release were also observed in the spinal cord (Ramos et al., 2008). This limited overview may suffice to indicate the extreme importance of OT for nursing the young.

Providing the young with nutrition for an extensive period of time implies that the mother has to take care of her own nutritional status, and OT appears to play a role in that respect as well, be it indirectly.

Lactation, as well as pregnancy itself, induces temporary hyperphagia in mother rats and other mammals, to increase caloric intake with adaptive changes in energy expenditure (Douglas et al., 2007; Fleming, 1976; Leng et al., 2008; Svennersten-Sjaunja and Olsson, 2005; Woodside et al., 2012). Interestingly, both central and peripheral administration of OT suppress food intake (Arletti et al., 1989; Blevins and Ho, 2013; Deblon et al., 2011; Douglas et al., 2007; Leng et al., 2008) with differentiated effects on carbohydrate and fat intake (Olszewski et al., 2010; Sabatier et al., 2013). In the human, OT may induce anorexia (Chaves et al., 2013; Demitrack et al., 1989; Maguire et al., 2013; Sabatier et al., 2013) and is of clinical interest for the treatment of obesity (Blevins and Ho, 2013; Maguire et al., 2013; Sabatier et al., 2013). Suppression of these negative OT-effects on food intake is apparently necessary during the lactation period. The mechanisms for this suppression are complex, as they involve a range of neuronal interactions, for instance related to the ventromedial hypothalamic nucleus and the 'dorsal vagal complex' in the caudal brainstem (Douglas et al., 2007; Eriksson et al., 1994; Mullis et al., 2013; Romano et al., 2013; Sabatier et al., 2013; Uvnas-Moberg, 1994). Actually, a large variety of hormonal and peptidergic factors is involved in the temporary suppression of the anorectic effects of OT (Atasoy et al., 2012; Brogan et al., 2000; Ghosh and Sladek, 1995; Linden, 1989; Menzies et al., 2012; Parker and Bloom, 2012; Perello and Raingo, 2013; Woodside et al., 2012; Zagoory-Sharon et al., 2008). The complexity of these control mechanisms makes it impossible to discuss them in more detail, but the evidence provided may suffice to make it clear that for the necessary maternal hyperphagia the regular effects of OT on food intake have to be suppressed temporarily.

In addition to the changes in food intake, the lactation period is characterized by the temporary suppression of ovulation and reproductive activities. The underlying mechanisms have been investigated extensively in humans, cows, ewes and mares (Bishop, 2013; Gee et al., 2012; Liu et al., 1983; Lunn, 1992; Mann and Lamming, 2001; McNeilly, 2001; Tallam et al., 2000) and appear to involve factors like GnRH and prolactin. There is no reason to suppose that the mechanisms in rats are fundamentally different (Fukushima et al., 2006; Grattan, 2001; Russell et al., 2001).

'Maternal aggression' is another, and for the present purpose final example of temporary behavioral changes occurring in the dam at the time of parturition and lactation (Erskine et al., 1978; Gandelman and Simon, 1980; Takahashi and Lore, 1982). It took some time before the involvement of OT was consistently reported (Consiglio and Lucion, 1996; Ferris et al., 1992; Giovenardi et al., 1997; McCarthy et al., 1986; Rosenblatt et al., 1988) because most of the early investigations were aiming at sensory or other hormonal factors (Albert et al., 1992a, b, c; Fleming and Rosenblatt, 1974a, b; Kolunie and Stern, 1990; Mayer and Rosenblatt, 1987; Stern and Kolunie, 1993). OT is currently known as a 'prosocial' factor (Lukas et al., 2011), which means that again some of its regular effects have to be suppressed temporarily. It appeared that OT and lactation also have a clear effect on fear behavior (Bosch et al., 2005; Ferreira et al., 2002; Hansen and Ferreira, 1986; Hard and Hansen, 1985; Lonstein et al., 1998; Neumann et al., 2001). Later investigations showed that vasopressin and OT are actually involved in complex and extensive interactions and control together many aspects of 'social' behavior, including fear, anxiety and aggression (Beiderbeck et al., 2007; Bosch et al., 2005; Bosch and Neumann, 2012; Ferreira et al., 2002; Neumann, 2008; Neumann et al., 2001; Veenema and Neumann, 2008) and these effects have to be studied in each brain area involved separately (Veenema and Neumann, 2008). No surprise then that the 'hypothalamo-pituitary-adrenal- (HPA-) axis' is also involved in these interactions (Caldwell, 1992; Giovenardi et al., 2005; Klampfl et al., 2013; Neumann, 2001; Neumann et al., 2001; Vilela and Giusti-Paiva, 2011).

The 'hypothalamic-attack-area' (HAA) (Kruk, 1991; Kruk et al., 1984a; Roeling et al., 1994; Siegel et al., 1999), located in the intermediate hypothalamus and along the ventrolateral part of the ventromedial hypothalamic nucleus (VMHvl) (Geeraedts et al., 1990a, b; Nieuwenhuys et al., 1982; Veening et al., 1982) is apparently involved in maternal aggression (Motta et al., 2013; Hansen, 1989). Pregnancy and lactation had no effect on the effective thresholds of electrical brain stimulation in the HAA (Mos et al., 1987). However, the HAA (Roeling et al., 1994) and the PVH have a widely distributed network of neuronal connections and therefore the neuronal adaptations occurring in the period of maternal aggression may occur outside the HAA. Lesioning the PVH is effective (Consiglio and Lucion, 1996; Giovenardi et al., 1997; Olazabal and Ferreira, 1997) but many additional brain areas have been indicated in the literature, too many for the present discussion. We intend to make an exception, however, for a single brain area: the VMHvl. This particular part of the VMH plays an important role in lordosis behavior, as discussed in Section 3.3, (Chung et al., 1990; Flanagan-Cato, 2011; Flanagan-Cato et al., 2001; Pfaff and Sakuma, 1979d; Romano et al., 1988; Sakuma and Pfaff, 1981; Sakuma and Pfaff, 1982; Schwanzel-Fukuda et al., 1984). At the same time, however, this region of the hypothalamus forms part of the HAA, mentioned above. It has been observed that under certain circumstances mother rats show ambivalent behavior towards a male intruder (Agrati et al., 2011). Recently, this brain area has been investigated in the mouse (Anderson, 2012; Lin et al., 2011; Saper, 2011), with quite remarkable results for which the reader is referred to Section 5 for further details.

4.2. Role of OT in paternal care

Although the majority of mammalian species display uniparental care, with mothers performing the great majority of parental

tasks such as feeding, sheltering, and grooming pups, in a small percentage (~5%) of mammalian species the fathers (and/or related males) demonstrate a considerable amount of caring behavior. In addition to humans, some alloparental primate species and biparental rodent species have been used as experimental animal models to investigate paternal behavior. The most widely used rodent species include the obligatory paternal prairie voles (Microtus ochrogaster), mandarin voles (Lasiopodomys mandarinus), and California mice (Peromyscus californicus) as well as the facultatively paternal meadow voles (Microtus pennsylvanicus) and various outbred strains of laboratory house mice (Mus musculus). Although there have been various findings suggesting that OT influences paternal care, and/or that paternal care is associated with changes in the OT system, the evidence is somewhat anecdotal and indicates species specificity. In addition, since most biparental species form monogamous pair bonds as well, see Section 2, it can be difficult to distinguish between the effects of becoming a father and the unavoidable simultaneous socio-sexual experience of cohabitation with a female, which affects the OT system as well (see Section 2).

In various species, it has been shown that OT levels or OT release is correlated with paternal behavior or paternal state. In human fathers, plasma and salivary OT levels are positively correlated with social engagement, affect synchrony, and positive communicative sequences with their 4–6-month-old infant (Feldman et al., 2011; Gordon et al., 2010). In paternally experienced males of a biparental primate, the common marmoset (Callithrix jacchus), the release of OT from cultured explants of the hypothalamus is increased compared with naïve, paternally inexperienced males (Woller et al., 2012). In juvenile and adult prairie voles, pup exposure causes transient elevations in plasma OT levels and increased Fos-immunoreactivity in OT neurons (Kenkel et al., 2012). However, aside from the acute pup-induced activation of the OT system, neither OT gene expression in the hypothalamus nor OT receptor binding in a number of brain regions differs between sexually naïve and paternally experienced male prairie voles (Wang et al., 2000). In male California mice, males cohabitating with a pregnant female show increased plasma OT levels compared with virgin males, but OT levels decline prior to parturition, remain low throughout the postpartum period, and do not correlate with the level of paternal behavior (Gubernick et al., 1995). Mandarin vole fathers show increased OT-immunoreactivity in the PVH and SON compared with virgin males, but brief exposure to pups or cohabitation with a female without pups have the same effects (Song et al., 2010). In meadow voles, sexually and paternally experienced, paternally behaving males have significantly higher OT receptor binding in several brain regions (accessory olfactory nucleus, lateral septum, BNST, and lateral amygdala) compared to sexually and paternally inexperienced, non-paternally behaving males; however, it is possible that these differences are caused by sexual rather than paternal experience (Gil et al., 2013; Parker and Lee, 2001). In addition, male California mice with various levels of sexual and paternal experience do not show increases in Fos-immunoreactivity in response to auditory, olfactory and visual cues from an inaccessible newborn pup (de Jong et al., 2009). In one non-mammalian species, the monogamous and biparental Central American convict cichlid (Amatitlania nigrofasciata), males displaying most paternal care show (Gil et al., 2013) increased Fos-immunoreactivity induction in parvocellular preoptic isotocin (IST) neurons, IST being the homolog of OT in fish (O'Connell et al., 2012).

Taken together, pup exposure and paternal experience appear to coincide with changes in the OT system that differ in strength among species. Conversely, artificially increasing or decreasing OT neurotransmission affects paternal care in various species. Intranasal OT administration improves social-paternal interactions between human fathers and their infant- or toddler-aged children (Naber et al., 2010; Weisman et al., 2012). In male common marmosets, ICV administration of OT increases food transfer from fathers to offspring (Saito and Nakamura, 2011). Conversely, in the Central American convict cichlid, systemic injection of an IST receptor antagonist blocks paternal care (O'Connell et al., 2012) and ICV administration of a combination of OT and AVP receptor antagonists (but not either antagonist alone) inhibits paternal behavior in paternally naïve prairie voles (Bales et al., 2004). In the same experiment, ICV administration of OT did not further increase the high levels of paternal care and impaired kyphosis (nursing posture).

In both humans and mice, genetic associations between the OT system and paternal behavior have been demonstrated. In human fathers (and mothers) genotyped with risk alleles for the OT receptor and for CD38, a membrane glycoprotein that facilitates OT secretion, plasma OT is reduced and the fathers show less parental touch. On the other hand, low-risk CD38 alleles and high plasma OT predict longer durations of parent-infant gaze synchrony (Feldman et al., 2012). Consistently, in facultatively paternal ICR-strain mice, paternal care is reduced following knockout of the CD38 gene, and ICV OT can rescue this impaired behavior. ICV OT further improves paternal care following reinstatement of the CD38 gene in the nucleus accumbens of CD38−/− sires (Akther et al., 2013).

Taken together, it appears that increased activity in the OT system is associated with increased or improved paternal care, and decreased activity in the OT system with the opposite, which is similar to the association between OT and maternal care. However, much more than maternal care, the influence of the OT system in paternal care is highly variable and species-specific and appears to depend on a) the natural level of paternal care displayed, and b) the basal neurobiology of the OT system, in males of a given species.

5. The VMHvl: a puzzling brain region ...!

In the experiments of Cameron et al. (Cameron et al., 2011) it was observed that the less receptive high-LG females showed the greatest neural activation in the VMHvl after mating. Since less than 50% of the activated neurons show ERα-immunoreactivity (Calizo and Flanagan-Cato, 2003; Tetel et al., 1994a; Tetel et al., 1993; 1994b), it is possible that some of the mechanisms working in the area lateral to the VMHvl do not promote lordosis, but prepare the female for the termination of the estrous period. As studied in detail by Georgescu and Pfaus (Georgescu and Pfaus, 2006a, b; Georgescu et al., 2009), VCS induced a considerable number of activated glutamatergic neurons in the VMHvl, and these numbers decreased under influence of estradiol and/or progesterone. The authors concluded that "the effect of EB and P to blunt the activation of the inhibitory glutamate neurons in the VMH by VCS may therefore be a mechanism by which females can experience a requisite amount of VCS before estrus termination is engaged" (Georgescu et al., 2009) and "it may well be the case that glutamate release in the VMH increases active rejection responses, consistent with our previous findings for the effect of glutamate agonist and antagonist infusions to the VMH" (Georgescu and Pfaus, 2006a, b).

'Estrous termination' can be described as a temporary form of 'sexual satiety' starting when a certain amount of VCS has been obtained in a given period of time. It lies at the basis of the rewarding aspects of 'pacing behavior' (Pfaus et al., 2012; Pfaus et al., 2000). The female starts to reject the anogenital investigations of the male, normally occurring in the early precopulatory phase, as well as all copulatory activities. When the female gets

pregnant and starts feeding her young, in the lactation period, the female not only rejects the male but her behavior becomes openly aggressive, 'maternal aggression', as discussed before. Apparently, the 'neural substrate' for this aggressive behavior is present in the female brain as well and can be temporarily released from its regular constraints. From our preceding discussion, it is almost inevitable to conclude that the plastic neuronal changes occurring in the VMHvl, in the lateral extensions of long dendrites into the intermediate hypothalamic zone and the OT-fibers contacting them, are involved in the behavioral changes from lordosis, via rejection to aggression.

The male-female similarities in the neural substrate are also evident if we pay attention to the induction of lordosis in male rodents. Defeminization- and masculinization processes follow their own specific patterns, concerning timing and hormonal control mechanisms (Gladue and Clemens, 1982; Kalcheim et al., 1981; Ward, 1972). Prenatal stress induces lordosis in adult male rats (Ward, 1972). The defeminization-process is under control of a variety of factors like androgens (Diaz et al., 1995; Segovia et al., 2009; Vega Matuszczyk et al., 1988; Ward, 1977; Weisz and Ward, 1980; Whalen et al., 1986), estrogen and progesterone (Dohanich and Ward, 1980; Olster and Blaustein, 1991; Ward et al., 1977) and various brain areas like anterior hypothalamic and preoptic regions, lateral septum and PAG (Gordon et al., 1979; Kondo et al., 1993; Kondo et al., 1990; Tsukahara et al., 2003; Tsukahara and Yamanouchi, 2001; 2002; Whitney and Herrenkohl, 1977). No surprise, then, to find the VMHvl involved also in these processes (Romano et al., 1990; Segovia et al., 2009). We can safely conclude that the neural substrate involved in lordosis behavior is not only present in the female, but in the male rat brain as well, where it can be uncovered by experiments leading to only a partial defeminization.

But if 'lordosis behavior' is represented in the male brain, what about 'aggressive behavior' in the male and female brains? The question rises if they are also represented in identical brain areas.

In the male rat brain, aggressive behavior can be induced by low currents of intracranial brain stimulation and the location has been precisely defined (Kruk, 1991; Kruk et al., 1984a; Kruk and van der Poel, 1980; Kruk et al., 1979; Kruk et al., 1983; Kruk et al., 1998; Lammers et al., 1988; Roeling et al., 1994), in the intermediate hypothalamic region, rostral to and alongside the VMHvl (Geeraedts et al., 1990a, b; Kruk et al., 1983; Roeling et al., 1994; Veening, 1992). Of course additional brain areas are involved as well (septal regions, amygdala) but many of their fibers converge on this brain region, alongside the VMHvl. As discussed earlier, lactating mother rats show the same behavior, 'maternal aggression', arising from exactly the same brain regions (Kruk et al., 1984b; Mos et al., 1987). Apparently, the neural substrate for 'attack behavior' is organized also in the male and female rat brain in a very similar way, with hormonal changes being necessary to uncover this behavior in the female rat, see Section 4.1.

At first sight it is rather surprising that we have to conclude that two very different behaviors like lordosis and attack behavior, including their completely different postures, lordotic vs kyphotic respectively, may be induced by the same region of the hypothalamus. Very recently, however, new findings in the mouse brain were reported, shedding a completely new light on this puzzling situation. The findings will be discussed in the next section.

5.1. *The VMHvl as multi-modal hub for the control of sexual and aggressive behavior*

In female rats, stimulation of the VMH produces lordosis (Calizo and Flanagan-Cato, 2002; Flanagan-Cato, 2011; Mathews and Edwards, 1977b; Pfaff and Sakuma, 1979a). In contrast, damaging the VMH or the descending projections disrupts sexual behavior (Hennessey et al., 1990; Mathews and Edwards, 1977a; Pfaff and Sakuma, 1979b, d; Pfeifle et al., 1980; Rajendren et al., 1991). Neural activation of the female ventrolateral VMH (VMHvl) can be observed, but not exclusively, during and after sexual behavior (Blaustein et al., 1994; Coolen et al., 1996; Flanagan et al., 1993; Pfaus et al., 1993; Rowe and Erskine, 1993; Tetel et al., 1993; Wersinger et al., 1993). Interestingly, damaging the lateral side of the VMH affects female aggression (Hansen, 1989). In accordance, GABA (and glutamate) in or near the VMHvl is involved in maternal aggression (Hansen and Ferreira, 1986; Lee and Gammie, 2009). Recently, it was shown that during maternal aggression, c-Fos-staining can be especially observed in the VMHvl (Motta et al., 2013).

The hormones cq. neurotransmitters estrogen (Pfaff, 1980; Pfaff et al., 2008), progesterone (DeBold and Malsbury, 1989; Pleim et al., 1991) and oxytocin (Bale and Dorsa, 1995; Griffin et al., 2010) have a very stimulating effect on lordosis, when applied in the VMH, see Section 3.3. Interestingly, estrogens affect both the structure and function of the VMH (Flanagan-Cato, 2011; McCarthy and Konkle, 2005; Pfaff, 1980; 2011). Importantly, the estrogen-alpha receptors (ER-alpha) and oxytocin receptors are present in the VMHvl, but not in the VMHdm (Flanagan-Cato, 2011). Remarkably, under natural conditions, both the levels of estradiol and progesterone fluctuate across the estrous cycle, and during these fluctuations dendritic connections are reorganized and numbers of dendritic spines are increased (Carrer and Aoki, 1982; Frankfurt et al., 1990; Frankfurt and McEwen, 1991). In addition, these gonadal hormones turn on genes in the hypothalamus, thereby making sexual behavior possible (Ogawa et al., 1997; Pfaff, 2011).

For a long time it was puzzling how the same brain area, the VMH, could be involved in both (maternal) aggression and sexual behavior (Hansen, 1989; Hansen and Ferreira, 1986; Hrabovszky et al., 2005; Kruk et al., 1979; Kruk et al., 1983; Lammers et al., 1988; Luiten et al., 1985; Olivier and Wiepkema, 1974; Roeling et al., 1994; Veening et al., 2005). Recently, experiments in male mice from the research group of David Anderson at Caltech, have shed new light on the problem (Lin et al., 2011).

In male mice, optogenetic stimulation of the dorsomedial hypothalamus (VMHdm) causes flight and freezing behavior, while VMHvl causes aggressive attacks of opponent males, females and even inanimate objects (plastic glove). Pharmacogenetic silencing of VMHvl neurons reversibly inhibits this aggression (Lin et al., 2011). In agreement, it has been shown by pharmacogenetic neural inhibition in freely behaving male mice, that the VMHdl is involved in fear of a predator, while the VMHvl is involved in aggression and social fear, but not in fear of foot shock (Silva et al., 2013). Again, suggesting an important role for the VMHvl in social encounters.

The research group of Anderson also showed that electrophysiological recording of firing rate of VMHvl neurons resulted in 40% of the neurons being more activated by a male intruder, about 12% exclusively during attack, and about 25% by a female mating partner. About 50% of the recorded neurons responded initially to both a male and a female intruder, suggesting that the neurons share some common input, to differentiate between the male and female later during the encounters (Lin et al., 2011). Most intriguingly, VMHvl neurons are activated during attack and are inhibited during interactions with a female, suggesting that the VMHvl neurons mediating aggression are actively suppressed during mating. Special attention has to be paid to the fact that many VMHvl neurons are activated during both male-male and male-female encounters (Anderson, 2012). It was hypothesized that these dual-activated neurons could be involved in the organization of motor programs common to both attack and mating, such as approach behavior to a conspecific or ano-genital investigation as

part of appetitive sexual behavior (Anderson, 2012). In agreement, recently it was shown that predator cat odor induces approach behavior in parasite Toxoplasma gondii-infected male rats, whereas healthy rats show avoidance behavior (House et al., 2011). In detail, exposure to cat urine induces avoidance behavior associated with c-Fos-staining, reflecting neural activation, in the accessory olfactory bulb (AOB), posteroventral medial amygdala (MEApv), and VMHdm. Bizarrely, the brain parasite infected rats show approach behavior towards the predator cat odors, associated with c-Fos staining in AOB, posterodorsal medial amygdala (MEApd). A similar staining pattern can be seen, when healthy male rats approach female rat odor (House et al., 2011). Thus, during evolution the parasite has managed to change brain functioning after infection, thereby perturbing the "avoidance brain pathway", shifting neural activity to the nearby "approach brain pathway" (see above).

Apparently, sex and aggression in rodents not only share olfactory stimuli to 'chose' between the agonistic and mating patterns of behavior, but the VMHvl also appears to be a much more intricate point of sensory convergence before the decision 'either-or' can be taken. Altogether, it can be summarized that the VMH is a multimodal-hub for the control of social encounters. The projections from the VMHdm to the dorsolateral periaqueductal gray (PAGdl) serve the behavioral avoidance (flight) response with underlying physiology (increase in heart rate and blood pressure), while projections from the VMHvl to the ventrolateral periaqueductal gray (PAGvl) serve the behavioral approach response (Canteras, 2002; Keay and Bandler, 2001). Remarkably, in female rats this projection to the PAGvl may be very important during sexual behavior, when males grip the female tightly with their fore paws to enable intromission, because this pathway increases the nociceptive thresholds (Keay et al., 1994). Projections from the VMH to PAG are also important for the motor control of lordosis and vocalizations, including the ultrasounds used by rodents for courtship behavior (Floody and DeBold, 2004). Both neurons in the VMHvl and PAGvl contain high amounts of ER-alpha receptors, suggesting that both areas are under the control of gonadal hormones (Flanagan-Cato, 2011; Gerrits et al., 2009; Murphy and Hoffman, 2001).

In the seventies Millhouse (Millhouse, 1973b) showed with golgi-staining that a fiber capsule is entirely surrounding the VMH, which encompasses a dense terminal field. These fibers all have boutons en passant and short collaterals, which terminate in the capsule. Also oxytocin fibers descending from the magnocellular part of the PVH run along the VMHvl (Griffin et al., 2010). Furthermore, oxytocin-containing neurons are activated by sexual behavior (Arletti and Bertolini, 1985; Caldwell et al., 1994; Flanagan et al., 1993), their dendritic contacts are reorganized by ovarian hormones (Ferri and Flanagan-Cato, 2012; Griffin et al., 2010) and the effects of oxytocin are 'pro-social' (Macdonald and Macdonald, 2010; Meyer-Lindenberg, 2008; Striepens et al., 2011), including 'pro-sexual' for males and females (Flanagan-Cato, 2011) and 'anti-aggressive' (Calcagnoli et al., 2013; Caldwell et al., 1994; DeVries et al., 1997; Dhakar et al., 2012; Harmon et al., 2002; Neumann, 2008; Pedersen et al., 1994; Ragnauth et al., 2005). Thus, OT-fibers that are part of the VMHvl fiber capsule are in an excellent position to innervate long dendrites with OT receptors of interneurons in the VMHvl (Flanagan-Cato, 2011), thereby influencing the potential 'sex-aggression balance' towards appetitive sexual behavior.

6. Summary and conclusions

The conclusion seems warranted that under normal circumstances OT plays an important facilitating role during both male and female reproductive behavior, in rodents (Pedersen and Boccia, 2002) and other mammals including man and the 'unifying principle' of the OT action in the brain "is to facilitate social encounters by reducing the associated anxiety" (McCarthy, 1995). Much research is needed to further delineate the complex organization of the neural networks involved in reproductive and sexual behaviors in male and female mammals including man. OT seems to play an important role in many of these networks but its precise role needs further experimentation and hypotheses.

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