European Journal of Pharmacology ∎ (∎∎∎∎) ∎∎∎–∎∎∎

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Behavioural pharmacology

The role of oxytocin in male and female reproductive behavior

J.G. Veening [a,c,*], T.R. de Jong [b], M.D. Waldinger [a], S.M. Korte [a], B. Olivier [a]

[a] Department of Psychopharmacology, Division of Pharmacology, University of Utrecht, Utrecht, The Netherlands
[b] Department of Behavioral and Molecular Neurobiology, University of Regensburg, 93053 Regensburg, Germany
[c] Department of Anatomy, Radboud University Medical Center, Nijmegen, The Netherlands

ARTICLE INFO

Article history:
Accepted 24 July 2014

Keywords:
Oxytocin
Reproductive behavior
Maternal behavior
Paternal behavior
Ejaculation
Ventromedial hypothalamus

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

* Correspondence to: Department of Anatomy (109), Radboud University Medical Center, P.O. Box 9101, 6500 HB, Nijmegen, The Netherlands. Tel.: +31 263813742.
E-mail address: jan.veening@radboudumc.nl (J.G. Veening).

http://dx.doi.org/10.1016/j.ejphar.2014.07.045
0014-2999/

(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

Please cite this article as: Veening, J.G., et al., The role of oxytocin in male and female reproductive behavior. Eur J Pharmacol (2014), http://dx.doi.org/10.1016/j.ejphar.2014.07.045