OXYTOCIN: AN OLD HORMONE FOR NEW AVENUES

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Summary

Oxytocin is a nonapeptide synthesized in the paraventricular and supraoptic nuclei of the hypothalamus. Although other similar substances are present in lower animals, oxytocin has been found only in mammals and probably have developed in parallel with typical mammalian behaviours, such as labour and lactation. In the last decade, several data have highlighted the key role of this neuropeptide in the formation of infant attachment, maternal behaviour and pair-bonding and, more generally, in linking social signals with cognition, behaviours and reward.

The aim of this paper is to examine the physiological role of oxytocin in the regulation of different functions and complex behaviours, as well as its possible involvement in various pathological conditions. MEDLINE and PubMed (1972-2006) databases were searched for English language articles using the keywords oxytocin, attachment, psychopathology, psychiatric disorders. We reviewed papers that addressed the following aspects of the oxytocin system 1) synthesis and localization, 2) receptors, 3) peripheral localization and activities, 4) physiology, 5) psychopathology. Oxytocin has been demonstrated to be altered in several psychiatric disorders and seems to have a potential role in the onset of psychopathology. Future researches are needed to better understand the psychopathological implication of the dysregulation of the oxytocin system and the possible use of oxytocin or its analogues and/or antagonists in the treatment of psychiatric disorders.

Key Words: Oxytocin – Physiology – Psychopathology – Psychiatric Disorders

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Introduction

The neuropeptide research has its roots at the end of the 19th century, when earlier investigators identified a neural pathway from the supraoptic nucleus of the hypothalamus to the posterior pituitary (Ramon and Cajal 1894). Scharrer and Scharrer (1940) provided the first evidence that certain hypothalamic neurons secreted substances via exocytosis of cytoplasmic vesicles, and, about two decades later, Du Vigneaud (1953) isolated, in pituitary extracts, oxytocin (OT) that was the first peptide hormone to have its amino acid sequences identified and to be synthesized in its active form: the aim of this paper is to provide a comprehensive review of OT and of its physiological role in the regulation of different functions and complex behaviours, as well as of its possible involvement in various pathological conditions.

Synthesis and localization

The nonapeptide neurohypophisial hormones are classified into the vasopressin (AVP) and OT families in relation to the presence of a basic (AVP family) or a neutral (OT family) amino acid at the position 8. The different polarity of this amino acid residue enable AVP and OT peptides to bind to the respective receptors (Barberis et al. 1998). OT is a very abundant neurohypophysial nonapeptide constituted by cyclic part of six-amino acid with a disulfide bridge between Cys 1 and 6 and a three-residue tail alfa-amidated at the COOH-terminal.

In all vertebrates at least a OT-like and a AVP-like peptide are present, while suggesting two evolutionary molecular lineages: the isotocin-mesotocin-OT line, involved in reproductive functions, and the vasotocin-vasopressin line, involved in the water homeostasis. On

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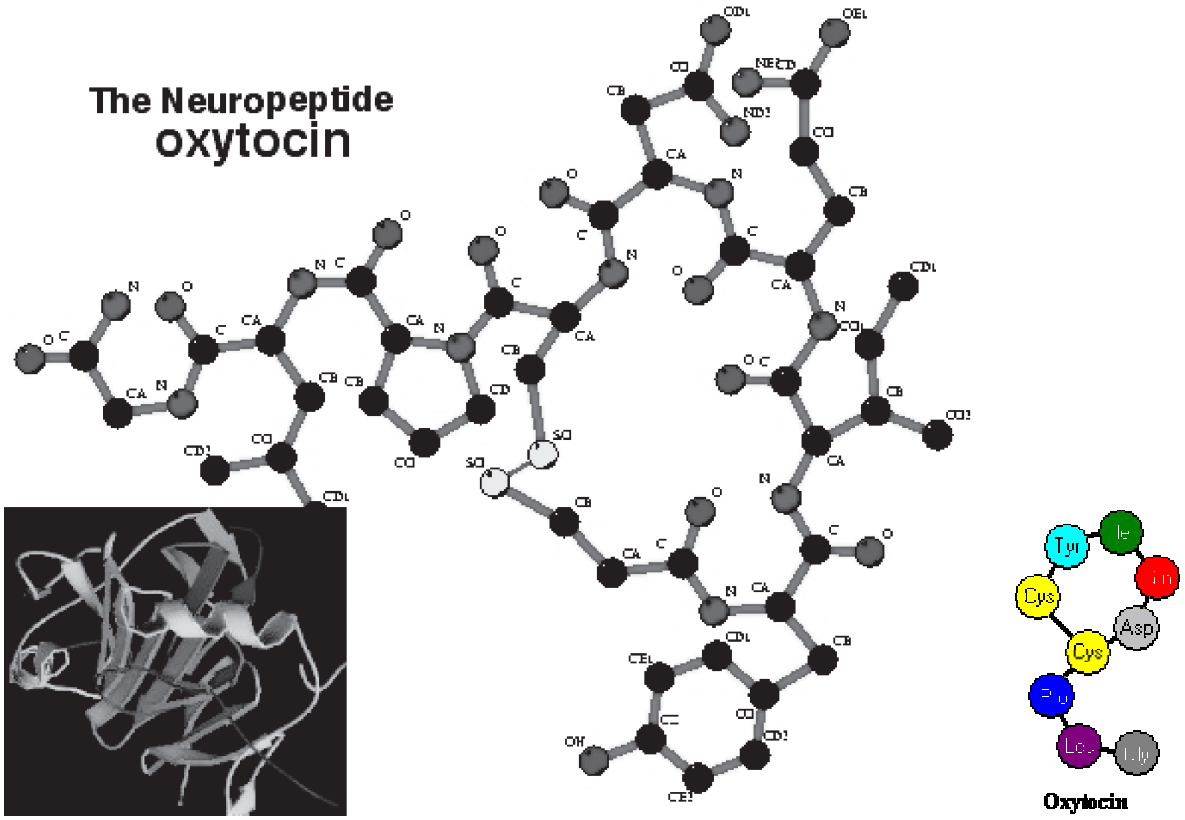

Figure. *Chemical structure of oxytocin*

the contrary, OT and AVP, that differ from each other in terms of two amino acids (Ile vs Phe at position 3 and Leu vs Arg at position 8, respectively), were only found in mammals and probably have developed in parallel with typical mammalian behaviours, such as uterine contraction during labour and milk ejection essential for lactation.

The majority of both OT and AVP are synthesized in the magnocellular neurons of the supraoptic (SON) and paraventricular (PVN) nuclei of the hypothalamus that are the principal costituents of the hypothalamo-neurohypophisial system (Swaab et al. 1975). OT and AVP are assembled on ribosomes in the soma of the neurons as precursors that are, subsequently, processed in the neurosecretory vesicles into which they are packaged by the Golgi apparatus. OT is first synthesized as preprooxytocin, that represents its largest precursor and comprises three components: a signal sequence of about 16–30 amino acid residues at the neuropeptide terminal, the neuropeptide sequence and the space parts. The signal and the space parts, that allow the precursor to deal with the endoplasmatic reticulum, are rapidly cleaved and splitted after the storage into the vescicles (Holmgren and Jensen 2001). During the intravescicular post-translational processing, OT precursor undergoes sequential proteolytic cleavage and other enzimatic modification (glycosylation, phosphorylation, acetylation, amidation) that generate the final products, such as OT, neurophysin and a carboxy-terminal glycoprotein. While undergoing this complex maturation process, OT is targeted along the axon to the posterior pituitary (Arvan and Castle 1998). Within the neurohypophisis each axon branches into an exceptional number of nerve terminals that are estimated to represent about 50% of the total volume of this neural lobe. When the magnocellular neurons are excited, OT and its transporting proteins are released into the blood and can act on the receptors located in distant target organs, such as mammary gland, kidney and others.

However, oxytonergic magnocellular axons do not terminate only in the neural lobe of the pituitary, but also in the arcuate nucleus, the lateral septum, the medial amygdaloid nucleus and the median eminence with not well-known functions. For instance, in the arcuate nucleus they make synapses with beta-endorphin synthesizing neurons (Pittman et al. 1981; Csiffary et al. 1992). In the magnocellular SON and PVN nuclei, OT is also locally released from neuron dendrites or perikarya with a function of self neuromodulator involved, for example, in the synchronization of the depolarization of OT neurons during lactation or in the autoregolatory positive feed-back of OT on its dendritic release in the SON during parturition (Neumann et al.

1996). Although the amount of somatodendritic release is small, as compared with the amount released from the neurohypophysis, the concentration of OT and VP in the extracellular fluid of the supraoptic nuclei resulting from this somatodendritic release has been calculated to be 100- to 1,000-fold higher than the basal plasma concentration. Intranuclear release of these peptides occurs in response to a wide variety of stimuli, including suckling, parturation, hemorrhage, certain kinds of stress such as fever, physical restraint, and pain, mating and territorial marking behaviours, dehydratation, administration of hypertonic solutions, and a range of pharmacological stimuli.

The magnocellular neurons display particular secretion patterns for the peptide. For example, OT neurons respond to hyperosmolarity with small increases in spontaneous firing rate, whereas during lactation the same cells display explosive synchronized bursts of activity associated with a pulsatile release of OT into the circulation to cause contraction of mammary smooth muscle and milk let-down. PVN neurons can be identified as either AVP or OT secreting on the basis of their spontaneous discharge patterns. Interestingly, in most cases, central release patterns of OT are accompanied by peripheral ones, whereas release of AVP is not. All the physiological situations during which large amounts of OT are released into the blood are characterized by ultrastructural changes in the magnocellular nuclei, e.g., reduced astrocytic coverage of oxytocinergic somata and dendrites, increases in GABAergic synapses, increases in the juxtaposition of the membranes of the perikarya and of the dendrites between adjacents neurons, and increases in the contact area between neurosecretory terminals and the perivascular space. These morphological changes are reversible with cessation of stimulation, affect exclusively oxytocinergic neurons, and may serve to facilitate and maintain the characteristic synchronized electrical activity of these neurons at milk ejection (Theodosis 1995). Neuronal network rearrangement may also occur after behavioral experience.

Some hypothalamic OT reaches the anterior pituitary lobe via the hypothalamopituitary portal vascular system. OT might thus be able to influence anterior pituitary hormones as a hypothalamic regulating factor. OT was found to be released into the portal vessels, and specific OT receptors are present in the rat adenohypopophysis. Another pathway for OT delivery to the adenohypophysis might be the short portal vessels connecting the posterior and anterior lobes. OT may participate in the physiological regulation of the adenohypophysial hormones prolactin, ACTH, and the gonadotropins.

There was a long controversy on whether OT released in response to suckling was responsible for the concomitant secretion of prolactin from the adenohypophysis. During suckling and under stress, both hormones are quantitatively predominant among the factors released. OT could only act as prolactin releasing factor when the dopamine levels are low, e.g., during the brief periods of dopamine withdrawal that characterizes the onset of prolactin secretion under various physiological stimuli. It was demonstrated that the pituitary OT receptor gene expression is restricted to lactotrophs and dramatically increases at the end of gestation or after estrogen treatment (Breton 1995). These findings suggest that OT might exert its full potential as a physiological prolactin-releasing factor only toward the end of gestation.

The major endocrine response to stress is via activation of the hypothalamic-pituitary-adrenal axis. ACTH secretion from the anterior pituitary is primarily regulated by CRH and AVP synthesized in neurons of the PVN. Unlike ACTH, plasma OT does not increase in response to all kinds of stress. In rats, OT can potentiate the release of ACTH induced by CRH. CRH is responsible for the immediate secretion of ACTH in response to stress. However, when the CRH levels are decreased following prolonged stress, the persistent level of OT in the median eminence could become important for the delayed ACTH response and for the generation of pulsatile ACTH secretory bursts (Boyle 1997). In contrast, OT infusion into human volunteers actually inhibited the plasma ACTH responses to CRH. Suckling and breast stimulation in humans produced an increase in plasma OT and a decrease in plasma ACTH level. The observed negative correlation of both hormones indicates an inhibitory influence of OT on ACTH/cortisol secretion under a certain physiological condition in humans. In conclusion, OT might control ACTH release under some physiological conditions in a species-specific manner.

Gonadotropes in the adenohypophysis synthesize and secrete the two gonadotropin hormones, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Although gonadotropin-releasing hormone (GnRH) is believed to be the primary secretagogue for LH, OT has also been shown to stimulate LH release. OT administered to proestrous rats caused advancement of the LH surge and earlier ovulation. OT has been observed to synergistically enhance GnRH-stimulated LH release. OT may sensitize the pituitary before full GnRH stimulation. In human females, preovulatory OT administration promoted the onset of the mid-cycle LH surge (Hull 1995). Overall, the physiological connection between OT and LH release has yet to be definitively established (Evans 1996).

The magnocellular neurons also contain a number of biologically active substances such as neuropeptide Y, tirosine hydroxylase, dynorphin, thyrotropin-releasing hormone, atrial natriuretic factor, galanin, nitric oxide synthase. Some of these substances may be co-released with OT and AVP and seems to modulate the release of OT and AVP (Pretel and Piekut 1990, Xiao et al. 2005). Dynorphin seems to acts on nerural lobe kappa-opiate receptors and inhibit the electrally stimulated secretion of oxytocin, while cholecystokinin and CRH stimulates secretion of both OT and AVP (Bondy et al. 1989).

Another group of OT neurons is localized in the dorsal-caudal part of PVN and may be implicated in the autonomic responses. The axons of these neurons, called parvicellular because of their smaller size compared to the one of the magnocellular neurons that innervate the neurohypophisis, are part of the descending tract directed to the preganglionic neurons of parasympathetic caudal autonomic centers including the dorsal motor nucleus of the vagus and the nucleus tractus solitarii, and to the sympathetic centers in the spinal cord (Amico et al. 1990, Palkovits 1999). OT is

also synthesized in peripheral tissues, e.g., placenta, uterus, corpus luteum, amnion, testis and heart.

Oxytocin receptors

There is a single population of OT receptors, which are expressed in both the brain and peripheral organs (Gimpl and Fahrenholz 2001). OT receptor is a member of the class I G protein-coupled receptor family and is primarly coupled via G(q) proteins to phospholipase C-beta. The activation of phospholipase C-beta leads to the generation of 1,2-diacyl-glycerol and inositol trisphosphate that, in turn, produce an increase of intracellular Ca^{2+} by the stimulation of protein kinase C and the Ca^{2+} release from the intracellular stores. The final increase of intracellular Ca^{2+} initiates a number of cellular events such as smooth cell contraction, modulation of cellular excitability, gene trascription and protein synthesis. Cholesterol and Mg^{2+} or Mn^{2+} have been demonstrated to act as positive allosteric modulators. On the contrary, progesterone, essential to manteinance of uterine quiescence, seems to be able to bind the rat OT receptors, thus inhibiting their function; in humans, the 5beta-pregnane-3,20-dione, a progesterone metabolite, seems to be able to inhibit the receptor acting as a negative modulator.

As far as the regional distribution of OT receptors in the brain is concerned, a high diversity between different species has been observed. In rats, OT binding sites have been demonstrated in the olfactory system, basal ganglia, thalamus, lymbic system (bed nucleus of the stria terminalis, central amygdaloid nucleus, ventral subiculum), hypothalamus (ventromedial nucleus), brain stem and spinal cord with great changes in the density during development. In the rabbit, no receptors have been detected in the ventral subiculum of the hippocampus or in the hypothalamic ventromedial nucleus. In human brain, they are mainly distributed in the pars compacta of substantia nigra and globus pallidus, areas which have been linked to attachment, as well as in the anterior cingulate and medial insula (Brown et al. 2005). Conversely, OT binding sites were absent in hippocampus, amygdala, entorinal cortex and olfactory bulb. At peripheral level they have been demonstrated to be localized in kidney, heart, thymus, pancreas and adipocytes. These receptors are stimulated by the OT released into the blood by the neurohypophisis and carry on several important physiological function.

Peripheral localization and activities of oxytocin

A. Kidney

In animals the influence of OT on renal function is influenced by the species used, the hormone's dosage, the degree of hydration and the metabolic status of the animal. In humans, despite conflicting data, the weight of evidence favours some antidiuretic effect of OT. Case reports of water intoxication complicating the infusion of OT to pregnant women support its antidiuretic action (Borg et al. 1983). Therefore, OT seems to be involved in normal osmolar regulation, which is presumably different from the volume regulatory components of Na homeostasis, although it is still unclear the exact mechanism (Meister et al. 1990). The kidney is one of the peripheral target tissues for the OT and AVP neurons released into the blood by stimulations, such as hypovolemia or hyperosmolarity. When plasma sodium concentration exceeds 130 mM, the levels of both hormones increase as an exponential function of plasma sodium concentration (Zhang et al. 2001)**.** Acute administration of OT to conscious rats produced a modest increase in the glomerular filtration rate and effective filtration fraction. The natriuretic effect of OT is principally caused by a reduction in tubular Na reabsorption, perhaps in the terminal distal tubule or the collecting duct (Conrad et al. 1993). Autoradiographical analysis exhibited the existence and exact localization of OT receptors in the rat kidney. Interestingly, the distribution of OT binding sites undergoes reshaping during postnatal development as it was similarly observed in the rat brain during maturation (Chan et al. 1988).

Different data suggest that the antidiuretic action of OT is not mediated by its receptor but by the V2 receptor, and probably similar mechanisms may be operative in humans. Oxytocin has an affinity for the V2 receptor two orders of magnitude lower that that of dDAVP (Conrad et al. 1993).

B. Heart and cardiovascular system

Peripherally injected OT in rats decreases mean arterial pressure and even in the absence of a central control mechanism, OT is able to reduce the heart rate and the force of atrial contractions in isolated atria from perfused rat hearts. An OT antagonist reversed the bradycardia caused by the action of OT. However, OT at high concentrations (1 mM) leads to the stimulation of Antinatriuretic peptide (ANP) release (Favaretto et al. 1997). An OT antagonist primary inhibited this ANP release, and after prolonged perfusion, it finally decreased the OT-induced ANP release below that of control hearts. This observation suggested that intracardial OT stimulates ANP release in the heart (Gutkowska et al. 1997).

Gutkowska et al. (1998) proposed that OT and ANP act in concert in the control of body fluid and cardiovascular homeostasis. In fact, OT receptor transcripts and OT binding sites were shown to be present on atrial and ventricular sections as detected by in situ hybridization and autoradiograpy, respectively. Furthermore, the OT receptor gene is expressed in all chambers of the rat heart (Jankowski et al. 1998). The OT receptor mRNA levels in the atria were found to be higher than in the ventricles, but the OT receptor mRNA levels were calculated to be at least 10 times lower than the OT receptor mRNA level present in the uterus of a nonpregnant rat (Miller et al. 2002). OT concentrations were found to be higher in the atria than in the ventricles. In the right atrium, OT concentrations were 20-fold higher than those in the rat uterus although the OT mRNA level in the heart tissues was lower than that in the rat uterus. This discrepancy argues against the postulated abundant biosynthesis of cardiac OT (Jankowski et al. 1998). The relatively low concentrations of OT in the heart chambers and the high

OT doses required for ANP release would be more compatible with paracrine or autocrine effects of cardiac OT, particularly in the right atrium. Moreover, the OT quantities released from the perfused heart are not sufficient to substantially change the plasma concentrations of OT, but they may contribute to the natriuretic action by stimulation of ANP release (Gutkowska et al. 1997). Probably, blood volume expansion via baroreceptor input to the brain causes the release of OT that circulates to the heart. OT-induced ANP release in the heart may be achieved after activation of OT receptors and subsequent elevation of intracellular, which in turn could stimulate exocytosis and ANP secretion. ANP then exerts a negative chrono- and inotropic effect via activation of guanylyl cyclase and release of cGMP (Soares et al. 1999). Finally, a rapid reduction in the effective circulating blood volume is produced by an acute reduction in cardiac output, coupled with ANP's peripheral vasodilating actions. The ANP released would also act on the kidneys to cause natriuresis, and ANP acts within the brain to inhibit water and salt intake, leading to a gradual recovery of circulating blood volume to normal. Since the plasma concentration of both OT and ANP were found to be increased after parturition, the OT-stimulated ANP release might be at least partly responsible for the massive diuresis observed postpartum (Mukaddam-Daher et al. 2002). The effects of repeated subcutaneous OT injections on blood pressure and heart rate were investigated in spontaneously hypertensive rats. Surprisingly, when OT was given for 5 days, a sustained decrease in blood pressure was observed in male but not female rats, whereas the heart rate was unaffected (Petersson et al. 1997). Moreover, acute versus chronic OT treatments caused opposite effects on blood pressure, and these effects were modified by female sex hormones (Petersson et al. 1999). It appears that the complete OT system is present in the vasculature of the rat (Jankowski et al. 2000). The OT concentrations in the aorta and vena cava were reported to be even higher than those in the right atrium of the heart (Stam et al. 1998). Thus OT might play a direct role in volume and pressure regulation in a paracrine/autocrine manner (Gutkowska et al. 2000). A uterine-type OT receptor could also mediate vasodilatory responses in human vascularendothelical cells. Several experiments in various species have reported the existence of vascular endothelial arginine-vasopressin/oxytocin receptors that mediate vasodilatator effects, although a high concentration of oxytocin results in vasoconstrictor action (Thibonnier et al. 1999).

Therefore, the molecular mechanisms that activate myometrial contractions by OT-induced nonphosphorylation of MLC remain to be clarified . On the other hand, in cardiac tissue, the OT receptor mediates the action of OT to release a potent cardiac hormone, ANP, which slows the heart beat and reduces the force of contraction to produce a rapid reduction in circulating blood volume. In fact ANP has a vasodilatation action by cGMP that exerts negative chronotropic and inotropic effects on atria *in vivo* (Favaretto et al. 1997). Nitric oxide (NO), a diffusible lipophilic gas that is rapidly oxidized to an inactive form, is an important intracellular signal agent, which plays a role in activities such as vasodilatation and neuronal synaptic transmission (Oyama et al. 1993; Ventura et al. 2002).

Recently, it was hypothesized that OT would generate NO that might activate guanylyl cyclase, leading to production of cGMP that elaxes cardiac tissue and blood vessels; NO production has been suggested to be necessary to maintain basal OT secretion as well as arterial blood pressure, because NO selectively inhibited the OT release. The regulation of OT signaling by NO may represent feedback for determining the frequency and amplitude of signals being transmitted. However, the mechanism by which NO influences neuronal activity and cardiovascular function is not clearly understood (Vacher et al. 2003)

C. Thymus

OT is present in the thymus in surprisingly large amounts and is found to be colocalized with the cytokeratin network of thymic epithelial cells and not within secretory granules (Geenen et al. 1986). Because of its higher expression level in the thymic epithelium, OT was proposed as the self-antigen of the neurohypophysial family (Moll et al. 1988). The peptide is therefore not secreted but behaves like an antigen presented at the outer surface of the cell. Thymic OT also behaves as a cryptocrine signal targeted at the epithelium membrane from where it is able to interact with neurohypophysialpeptide receptors expressed by pre-T cells. OT receptors are predominantly expressed by cytotoxic CD81 lymphocytes, and they transduce signals via the phosphoinositide pathway. In pre-T cells, OT was found to induce the phosphorylation of focal adhesion kinase (Hansenne et al. 2004). Thus it was suggested that OT actively is involved in the program of T-cell differentiation both as a neuroendocrine self-antigen and as a promoter of T-cell focal adhesion following a cryptocrine pathway (Martens et al. 1998). In human thymus extracts, the content of the OT immunoreactivity declined with increasing age, whereas in rat thymic extracts, it was reported to increase during aging. The age-dependent changes might be linked to thymic involution. Some immune pathologies in humans may be explained by thymic OT being involved in T-cell-positive selection and activation (Melis et al. 1995).

D. Fat Cells

In adipocytes, OT has a so-called "insulin-like activity" because it stimulates glucose oxidation and lipogenesis. Treatment of rat adipocytes with lipolytic stimuli such as glucagon or isoprenaline stimulated the conversion of choline into phosphatidylcholine, and this lipolytic effect was antagonized by OT (Kelly et al. 1988). Moreover, human fat cells possess a plasma membrane-bound H2O2-generating system that is sensitive to extracellular stimuli. OT as well as insulin were able to activate this system. It was suggested that the H2O2 produced might participate in the regulation of fat cell differentiation and/or maintenance of the differentiated state. Populations of low- and high-affinity OT receptors have been described in rat adipocytes (Krieger and Kather 1995).

E. Pancreas

OT and AVP have been identified in human and rat pancreatic extracts at higher concentrations than those found in the peripheral plasma (Amico et al. 1988). However, a local synthesis of these peptides within this organ has not yet been established. According to most studies in several species, the neurohypophysial hormones induce the release of glucagon and, to a lesser extent, insulin from the pancreas. During in situ perfusion of the rat pancreas with OT, a marked stimulation of glucagon release and a modest stimulation of insulin release were observed. Using isolated islets from rat pancreas, OT elicited glucagon release, but failed to influence insulin release in a culture medium with low glucose content. The glucagonotrophic action of OT was diminished in the presence of a higher concentration of glucose (Dunning et al. 1984a).

In humans, OT evoked a rapid surge in plasma glucose and glucagon levels followed by a later arouse in plasma insulin and epinephrine levels. Hypoglycemia potentiated the effects of OT on plasma glucagon and epinephrine levels. OT was also found to potentiate glucose-induced insulin secretion (Dunning et al. 1984b). In contrast, Page et al. (1990) observed in humans no effects of OT on the decline or recovery of blood glucose concentrations or on the plasma glucagon response to insulin-induced hypoglycemia. Impaired glucose tolerance and hyperinsulinemia are common features of obesity. Interestingly, the plasma levels of OT were fourfold higher in male and female obese subjects, as compared with control subjects. OT rises in hypoglycemia, and this response is partially inhibited by dexamethasone. The OT rise in response to insulin-induced hypoglycemia was reduced in obese men. Pretreatment with the opioid antagonist naloxone enhanced the OT response to hypoglycemia in obese males and suggested an abnormal activity of endogenous opioids in obesity. In women, unlike men, endogenous opioids did not modulate OT release during insulin-induced hypoglycemia (Coiro et al. 1990).

F. Adrenal Gland

Ang and Jenkins (1984) first identified immunoreactive OT and AVP in human and rat adrenal glands where they were localized in the cortex and in the medulla. In the cortex, the OT immunoreactivity was higher in the zona glomerulosa than in the medulla.

From the few studies that have addressed the role of OT in the adrenal gland, no clear data have emerged. Perfusion of the isolated rat adrenal gland with OT at 100 nM inhibited the acetylcholine-stimulated aldosterone secretion but smaller doses of OT given as a bolus stimulated aldosterone secretion in the intact perfused rat adrenal gland, but not in superfused adrenal cells. Legros et al. (1988) hypothesized that OT acts also at the adrenal gland level to decrease cortisol release and/or synthesis in humans.

G. Osteoblasts

Recently, functional OT receptors have also been discovered in primary cultures of human osteoblasts and in a human epithelial osteosarcoma cell line (Saos-2) (Copland et al. 1999). Moreover, the expression of the receptor in pre-osteoclasts is lower compared with mature osteoclasts, indicating that OTR expression levels could be related to the different stages of osteoclast differentiation (Colucci et al. 2002). All these findings, together with the recent demostration of OT receptors in human osteoblasts, the bone forming cells, suggest the bone as a new target tissue for OT and support the increasing evidences, suggesting the presence of a central neuroendocrine control of bone remodeling. However, further experiments are necessary to better clarify the biological role of OT on the different kind of bone cells and, more generally, on the skeletal metabolism (Petersson et al. 2002).

Physiology of oxytocin

A. Centrally mediated autonomic and somatic effects

1. Cardiovascular system

OT and OT receptors are present in the vascular system, hearth and kidney, and OT has effects on blood pressure, renal function, and salt intake. OT terminals in the solitary vagal complex modulate reflex control of the heart, acting to facilitate vagal outflow and the slowdown of the heart (Higa et al. 2002). Cardiovascular centers in the hindbrain and the spinal cord activated by OT mediate the increases in blood pressure and heart rate. Oxytocinergic neurons also innervate other brain regions important in cardiovascular control, such as the locus coeruleus, dorsal motor nucleus of the vagus, and intermediolateral cell column in the spinal cord. Generally, in humans and rats, the bolus intravenous administration of OT is often associated with a decrease in blood pressure (Petersson 1996).

Isosmotic hypovolemia and isovoloemic, isosmotic hypotension activate a very similar population of OT cells in the PVN and SON (Smith and Day 2003). This OT release inhibits salt intake. Under condition of experimental hypovolemia OT gene-knockout mice consumed 3 times the amount of NaCl than controls. OT plays a role in the regulation of blood pressure and salt appetite, specifically as mediated by volume receptors, and that the renin-angiotensin system is not involved in these changes (Rigatto et al. 2003).

Osmoreceptors located in systemic viscera and in central structures stimulate the nucleus of the solitary tract (NTS) and the lateral parabrachial nucleus and are responsible for inhibiting the ingestion of fluids under conditions of increased volume and pressure and for stimulating thirst under conditions of hypovolemia and hypotension (Johnson and Thunhorst 1997). There is also evidence for an OT-specific response to increased osmolality, rather than sodium (Blackburn et al. 1993). A role for central angiotensin (ANG) II in mediating the OT responses has been suggested, because OT antagonists potentiated the salt intake induced by ANG II. In addition, central administration of ANG II provoked systemic release of OT in rats.

Nitric oxide has important functions in modulat-

ing OT secretion from the hypothalamo-neurohypophyseal system. It appears that NO, tonically produced in the forebrain, inhibits OT secretion during normovolemic, isosmotic conditions. During osmotic stimulation, dehydratation, hypovolemia and hemorrhage, as well as high plasma levels of ANG II, NO inhibition of AVP neurons is removed, while that of OT neurons is enhanced. This produces a preferential release of AVP over OT important for correction of fluid imbalance (Kadekaro 2004).

Haemorrhage decreased the hypothalamic and neurohypophysial OT storage but increased the neurohormones plasma level in animals injected with vehicle solution. During the haemorrhage, the increase in plasma OT was inhibited in rats previously treated with galanin. The hypothalamic and neurohypophysial OT content significantly increased in animals treated with galanin and subsequently haemorrhaged. These results suggest that galanin may have a regulatory role in the hypothalamo-neurohypophysial function especially under condition of hypovolemia (Ciosek et al. 2003).

Dehydration or salt-loading increase the transcription of the OT gene and the proportion of neurons expressing OT (Meister et al. 1990). Magnocellular neurons in the supraoptic nucleus (SON) increase cell size in response to hyperosmolar conditions and decrease cell size in case of hypoosmolality. OT released from the neural lobe may reach the heart by circulation to induce ANP release, but the intacardiac OT might also play a paracrine role in stimulating ANP release. On the other hand, endogenous hypothalamic ANP seems necessary to stimulate OT release in the hyperosmolality condition (Chriguer et al. 2001).

Central pretreatment of rats with an OT antisense oligodeoxynucleotide attenuated the mean arterial pressure and heart rate responses induced by substance P. This suggests that OT neurons in the PVN mediate the increases in blood pressure and heart rate induced by stimulation of substance P receptors in the forebrain (Maier et al. 1998).

An OT anti-sense oligonucleotide injected into the PVN abolished the tachycardia produced by shaker stress in rats, indicating that OT may act as mediator of stress-induced tachycardia.The oxytocinergic system has also been shown to interact with the central vasopressinergic system in cardiovascular control. So, central injection of AVP (1–10 pmol) increased the mean arterial pressure and heart rate, and both responses were found to be enhanced in rats pretreated with OT (Poulin et al. 1994).

2. Analgesia

Some findings suggest that analgesic effects induced by non-noxious sensory stimulation may, in part, be mediated through activation of oxytocinergic mechanisms (Uvnås-Moberg 1993).

Analgesic effects of OT have been reported in most but not all studies in mice, rats, dogs, and humans (Brown 1998, Crowley 1977). Certain stimulations such as vaginal dilatation led not only to a rise in plasma OT concentrations, but also to an increase of the pain threshold. Analgesia was observed in rats after injecting OT into the lateral ventricles; on the other hand, systemic OT did not produce analgesia in rats.

In humans, intrathecal injection of OT was effective in treating low back pain for up to 5 h. An OT antagonist and the opiate receptor-blocker naloxone could reverse OT-induced analgesia. OT also increased b-endorphin and L-encephalin contents in the spinal cord, whereas an OT antagonist caused a decrease in the concentration of these opioids. Moreover, OT levels were elevated in the CSF of patients with chronic low back pain, perhaps a compensatory response to the painful condition (Yang 1994).

In a clinical case study, a high concentration (300 mg) of OT injected intravenously was reported to evoke strong analgesic effects lasting more than 70 min in a patient with intractable cancer pain at a time when opiates were no longer effective (Madrazo 1987).

3. Motor activity

Centrally administered OT can induce or modify several forms of behaviour together with the associated motor sequences. OT increased general motor activity (Petersson 2005) and OT antisera decreased this hyperactivity and seizures in a complementary fashion (Bodnar et al. 1984).

In this context, OT may possibly act at the spinal level. In rats, treatment with low OT doses led to a decrease in peripheral locomotor activity, whereas increasing doses of OT provoked sedative effects as indicated by a suppression of locomotor activity and rearing (Uvnås-Moberg et al. 1994). No studies are however available in humans.

4. Thermoregulation

In contrast to centrally administered AVP, for which antipyretic actions have been well documented, OT evoked mostly weak antipyretic effects at higher concentrations. In rabbits, intracerebroventricular administered OT produced small but long-lasting hyperthermias (Lipton et al. 1980). Intracisternally injected OT to adult male mice significantly increased colic temperatures. OT antagonized the hypothermia produced by other peptides such as bombesin or neurotensin and could also modulate the antipyretic action of AVP in rats. Possibly, the effects of OT with respect to thermoregulation may be physiologically significant during parturition and lactation (Mason et al. 1986).

B. Behavioral effects

1. Social behavior

A growing body of evidence implicates OT in mediation of complex social behaviors. It may be no coincidence that this peptide has been implicated in prototypically mammalian functions, such as milk ejection during nursing (Wakerley and Lincoln 1973), uterine contraction during labor and in sexual behaviour (Carmichael 1987, Carter 1992). All these data suggest that OT could be strictly involved in the regulation of social relationships that will be analyzed according to Harlow's classification (1979) of social bounds (pair attachment, parental attachment, infant attachment).

I. Pair attachment

The development of adult-adult pair bonds is cer-

tainly the least studied form of attachment from a neurobiological perspective. The relative paucity of studies can be attributed to the absence of pair bonds in commonly used laboratory animals, such as rats and mice. By definition, pair bonds occur in monogamous animals, and approximately 3% of mammals currently are considered monogamous, where the percentage of primates that are monogamous is considerably higher (perhaps 15%) (Van Schaik et al. 1990).

Prairie (Microtus Ochrogaster) and montane voles (Microtus Montanus) provide an intriguing natural experiment for studying the neural substrates of pair bonding (Insel 1997): in facts, montane vole looks remarkably similar to the prairie vole and shares many features of its nonsocial behaviors but differs consistently on measures of social behavior. The prairie vole is a mousesized rodent that is usually found in multigenerational family groups with a single breeding pair (Carter et al. 1995). They show the classic features of monogamy: a breeding pair shares the same nest and territory where they are in frequent contact, males participate in parental care, and intruders of either sex are rejected. Following the death of one of the pair, a new mate is accepted only about 20% of the time. On the contrary montane voles are generally found in isolated burrows, show little interest in social contact, and are clearly not monogamous.

A lot of studies have investigated if those species differ for central pathways for OT. In fact, the species differ in the neural distribution of receptors for both peptides as much as they differ in behavior (Insel 1992) and the receptors are expressed within entirely different pathways.

In the prairie vole, OT receptors are found in brain regions associated with reward (the nucleus accumbens and prelimbic cortex), suggesting that OT might have reinforcing properties selectively in these species. Conversely, receptors in the lateral septum, found only in the montane vole, might be responsible for the effects of OT on self-grooming, an effect that is observed in the montane vole but not the prairie vole.

Furthermore, other vole species (pine voles and meadow voles) selected for analogous differences in social organization (i.e., monogamous versus nonmonogamous) manifest similar differences in receptor distribution for both OT and AVP (Insel 1994).

Finally, after parturition, when the female montane vole becomes briefly parental, the pattern of OT receptor binding changes to resemble the pattern observed in the highly parental prairie vole.

Moreover, many authors observed that a critical requirement for social behavior is the ability of animals to identify conspecifics (Insel and Fernald 2004). Neural pathways employing the nonapeptides AVP and OT play a particularly prominent role both in social learning and recognition ("social memory"): in rats, OT supports, on the basis of olfactory stimulus, the onset of a partner preference (Popik and Van Ree 1993). OT seems involved in acquisition rather than in consolidation of social bonds. It was found that OT knock-out mice fail to recognize previously encountered conspecifics and do not show any attachment behaviour; central administration before the first contact but not after restores normal attachment behaviours (Dantzer et al. 1987).

The regulation of social behavior not only requires the recognition of familiar conspecifics, but also modification of behaviors that may impact the likelihood and consequences of a social encounter. For example, anxiety and novelty avoidance might be expected to reduce the likelihood of approaching a conspecific. Learning and memory mechanisms may also affect social behavior by modifying the impact of prior social encounters on an individual's behavioral responses. It is interesting that, although AVP and OT are both required for social recognition, they differentially regulate anxiety-like behavior and avoidance learning, with AVP and V1aR activation increasing anxiety-like behaviors in males, while OT decreasing them (Bielsky and Young 2004). Recently, the amygdala has been proposed as a candidate site at which AVP and OT may exert their opposing affects on anxiety-like behavior and avoidance learning (Huber et al. 2005). V1aRs and OT receptors are expressed within distinct subregions of the central nucleus of the amygdala, and the two neuropeptides interact in a manner that could produce opposing effects on neuronal activity. The fact that AVP and OT facilitate social recognition, but produce distinct and sometimes opposite effects on behaviors, may be explained by the need to regulate gender differences in social behaviors that require differential modulation of anxiety-like behavior, avoidance learning, or aggression. For example, OT regulates sexual behavior and social interactions in both males and females, and maternal behavior in females (Gimpl and Fahrenholz 2001), which require an inhibition of novelty avoidance, suppression of prior social avoidance learning, and decreased aggression. In contrast, AVP promotes behavior modifications that would influence the formation of territories and dominance hierarchies, which are characteristic components of male social behaviour.

Interactions among OT, AVP and glucocorticoids could provide substrates for dynamic changes in social behaviors. Non-noxious sensory stimulation associated with friendly social interaction induces a response pattern involving sedation, relaxation, and decreased sympathoadrenal activity. It is suggested that OT released from parvocellular neurons in the PVN in response to non-noxious stimulation integrates this response pattern at the hypothalamic level. The health-promoting aspect of friendly and supportive relationships might be a consequence of repetitive exposure to nonnoxious sensory stimulation (Uvnås-Moberg 1998). The relaxing and anti-stress properties of OT are suggested by the results of a recent study showing a negative correlation between OT plasma level and the levels of anxiety linked to romantic attachment (Marazziti et al. 2006).

Curtis and Wang (2005) examined c-fos expression in brain areas implicated in social behaviour in voles. They hypothesized that the presence of the c-fos protein after a period of time sufficient for pair bonding to occur may indicate brain areas that are especially important in pair bond formation; elevated levels of fos immunoreactivity have been found in the medial and cortical amygdala, medial preoptic area, and bed nucleus of the stria terminalis in females that mated several times over a 6-h period as compared to a variety of unmated controls. Those results have been compared with data obtained in OT knock-out mice: wild-

type (WT) and OT knock-out mouse showed similar neuronal activation in olfactory bulbs, piriform cortex, cortical amygdala, and the lateral septum. Wild-type, but not OT knock-out mice exhibited an induction of c-fos in the medial amygdala. Projections sites of the medial amygdala also failed to show a c-fos induction in the OT knock-out mice. OT knock-out mice but not the WT ones, mice showed dramatic increases in c-fos in the somatosensory cortex and the hippocampus, suggesting alternative processing of social cues in these animals.

Another point of interest is the different role that OT plays in male and female vole. Central OT administration in female, but not in male prairie voles, facilitates the development of a partner preference in the absence of mating (Winslow et al. 1993). A selective OT antagonist given centrally before mating blocks formation of the partner preference without interfering with mating (Insel 1995).

Recently, OT administration in humans was shown to increase trust, again supporting the involvement of the amygdala, a central component of the neurocircuitry of fear and social cognition that has been linked to trust and highly expresses OT receptors (Kosfeld et al. 2005).

A recent double-blind study, using functional magnetic resonance imaging to visualize amygdala activation by fear-inducing visual stimuli, showed that human amygdala function is strongly modulated by OT: as compared with placebo, OT potently reduced activation of the amygdala and reduced coupling of the amygdala to brainstem regions implicated in autonomic and behavioral manifestations of fear (Kirsch et al. 2005). This effect was located on the level of the midbrain and encompassed both the region of the periaqueductal grey and of the reticular formation, which are prominent among the brainstem areas to which the central nucleus of the amygdala projects (LeDoux 2000) and which mediate fear behavior and arousal (LeDoux et al. 1988). In agreement with these findings, autonomic response to aversive pictures has been reported previously to be reduced under OT (Pitman et al. 1993)

It is of interest to note that OT administration did not affect self-report scales of psychological state. This result agrees with the observations of Kosfeld et al. (2005), who also did not find an effect of OT on measured calmness and mood and showed that at the level of behavior, actual social interaction was necessary to bring out the OT effect. Namely, the neural effect of the neuropeptide on behavior is evident in the social context but not when subjects rate themselves in isolation. Moreover, the reduction in amigdala activation was more significant for socially relevant stimuli (faces) than for the socially less relevant scenes; differential impairment of amygdala signaling related to the social relevance of the stimuli is in agreement with emerging primate lesion (Prather et al. 2001) and human data indicating that social and nonsocial fear may depend on dissociable neural systems (Meyer-Lindenberg et al. 2005).

II. Parental attachment

The laboratory rat has been an ideal subject for studies of maternal care (Numan 1994). Unlike many mammals, nulliparous female rats show little interest in infants of their own species and when presented with foster young will either avoid or cannibalize them.

At parturition, however, a dramatic shift in motivation occurs and maternal behaviors such as nest building and retrieval of pups became established. Pedersen and Prange (1979) first demonstrated that injection of OT into the lateral ventricles of nulliparous ovariectomized rats induces maternal behavior. Perhaps even more remarkable, blockade of OT neurotransmission by means of central injection of an antagonist or by lesions of OT-producing cells in the hypothalamus results in a significant inhibition of maternal behaviour. These various interventions appear to inhibit the onset, but not the maintenance, of maternal behaviour: when the females became maternal, an OT antagonist had no effect (Skutella et al. 1993).

The rapid onset of maternal behaviour in response to OT has been confirmed in several studies. However, it is important to note that OT is effective only to initiate the maternal behavior, but not for the performance of maternal behavior per se. Therefore, when the females become maternal, an OT antagonist had no effect. Sub-cutaneous injection of the NO donor sodium nitroprusside was shown to prolong parturition and to inhibit maternal behavior in rats. Because OT was able to restore intrapartum maternal behavior, NO was suggested to interfere with the initiation of maternal behavior via blocking or diminishing the release of OT.

Estrogen is critical to the regulation of OT neurotransmission. The physiological changes in gonadal steroids that occur during pregnancy induce an increase of OT receptors in two key limbic brain regions - the bed nucleus of the stria terminalis and the ventromedial nucleus of the hypothalamus - at or just before parturition, coincident with the onset of maternal behavior (Caldwell 1994).

In humans, OT-related maternal behaviors have not been the subject of any systematic studies so far. In some reports it was shown that breast-feeding within 1 h of birth, when OT levels are very high, might support a long-lasting mother-infant bond and has a beneficial effect on the development of the child (Kennel et al. 1974).

III. Infant attachment

The formation of social attachments is a critical component of human relationships. Infants begin to bond to their caregivers from the moment of birth, and these social bonds continue to provide regulatory emotional functions throughout adulthood. It is difficult to examine the interactions between social experience and the biological origins of these complex behaviors because children undergo both brain development and accumulate social experience at the same time.

The AVP and OT neuropeptide systems are affected by early social experience**.** In mammals, the mother-infant interaction and other aspects of the early postnatal period may have profound behavioural effects; these effects in turn may produce long-lasting changes in neuroanatomy and neuroendocrinology. For instance, early life experiences seems to alter response of adult neurogenesis to stress and persistent changes in the corticotropin-releasing factor systems due to early life stress have been demontrated (Heim et al. 1997; Mirescu et al. 2004). OT may be a candidate substrate

for the transduction of early experiences (including birth process, breast-feeding and other aspects of parent-infant interactions) into both short-term and long-term behavioural changes and other physiological consequences, ranging from brain growth to later stress reactivity to ovarian disorders (Carter 2003).

The failure to receive species-typical care disrupts the normal development of the OT and AVP systems in young children. Perturbations in this system may interfere with the calming and comforting effects that typically emerge between young children and familiar adults who provide care and protection (Fries et al. 2005).

Indeed, OT and AVP levels are increased by socially pleasant sensory experiences, such as comforting touches and smells.

Studies with non-human animals have previously demonstrated that as levels of these hormones rise, animals increase their positive social interactions: they form social bonds, display selective infant–parent attachments, and form memories of these social interactions. Perhaps the most intriguing evidence implicating OT in the infant's attachment response comes from a recent study demonstrating that this peptide facilitates a rapid conditioned association to maternal odorcues but not to nonsocial stimuli (Nelson and Panksepp 1996). OT is found early in development, although in the rat, it does not show a fully processed transcript until the postnatal period (Whitnall et al. 1985). Receptors for this peptide is found in the developing brain (Tribollet et al. 1991, Shapiro and Insel 1989). Indeed, there is a transient but marked "overproduction" (relative to the adult) of OT receptors in limbic brain areas in the first 2 postnatal weeks (in both rodents and primates). Furthermore, exogenous administration of OT reduces the separation response of the rat pup, consistent with the possibility that this peptide has a role in either attachment or the separation response (Winslow et al. 1993, Insel 1991). OT receptors are part of the neural system of reward circuitry that includes the nucleus accumbens; a critical feature of this system for infant development is that it likely confers a sense of security and protection that makes social interactions rewarding.

2. Sexual Behavior

OT has been strictly correlated to sexual behavior and sexual function in mammalians, including humans.

In male rats, it is a powerful stimulant of penile erection (Argiolas et al. 1987); in female it is secreted during vaginal stimulation (Keverne 1983).

Recently, Withuhn et al. (2003) reported that neonatal exposure to exogenous OT can have long-term effects on the subsequent expression of adult behavior and physiology affecting the timing of sexual maturation in female rats, as indicated by the age of vaginal opening and the onset of first estrus.

It is well documented that levels of circulating OT increase during sexual stimulation and arousal and peak during orgasm in both men and women (Carmichael 1987, Carter 1992). Plasma OT and AVP concentrations were measured in men during sexual arousal and ejaculation and plasma AVP resulted to be significantly increased during arousal (Murphy 1987, Carter 1992). However, at ejaculation, mean plasma OT rose about five-fold and fell back to basal concentrations within 30 min, while AVP had already returned to basal levels at the time of ejaculation and remained stable thereafter. Men who took the opioid antagonist naloxone before self-stimulation had reductions in both OT secretion and the degree of arousal and orgasm. Also in women peak levels of serum OT were measured at or shortly after orgasm (Blaicher 1995). The intensity of muscular contractions during orgasm in both men and women were highly correlated with OT plasma levels, (Carmichael et al. 1987, 1994). This suggests that some of OT's effects may be related to its ability to stimulate the contraction of smooth muscles in the genital-pelvic area. Enhanced sexual arousal and orgasm intensity were reported in a woman during intranasal administration of OT. Anderson-Hunt and Dennerstein (1994, 1995), indeed, described the case of a woman who, about 2 h after the use of a synthetic OT spray, noticed copious vaginal transudate and a subsequent intense sexual desire. This response could be elicited only while she was taking daily doses of an oral contraceptive with estrogenic and progestogenic actions and might be caused through direct effects on sexual organs or sensory nerve sensitivity.

A few studies have already shown that OT fluctuates throughout the menstrual cycle (Altemus et al. 2001). A biological correlation between OT and the physiological processes of LH regulation in animal models has been previously described (Robinson and Evans 1990). Moreover, the suppression of endogenous OT activity in women has been shown to affect the ovulatory cycle (Evans et al. 2003).

A recent study confirmed that plasma OT fluctuates throughout the menstrual cycle in normally cycling healthy fertile women with adequate sexual activity but not taking any oral contraceptive pill, with plasma OT significantly lower during the luteal phase in comparison with both the follicular and ovulatory phases (Salonia et al. 2005). Moreover, plasma OT levels significantly correlate with selective components of the sexual response in both women taking and not taking oral contraceptives, namely the genital lubrication, apparently confirming the role of this neurohormone in in the arousal and peripheral activation of sexual function.

Overall, beyond its peripheral effects on reproductive organs, OT might affect or sensitize cerebral neurons responsible for the cognitive feelings of orgasm and could serve as a physiological substrate for both sexual behavior and performances in humans as well as in animals.

3. Stress-Related Behavior

OT is released from the pituitary gland in response to a variety of stressful stimuli which stimulate the HPA, including noxious stimuli, conditioned fear and exposure to novel environments. In many of these events noradrenergic neurones containing prolactin-releasing peptide are believed to stimulate oxytocin secretion into the circulation (Onaka 2004).

In rats OT exerts potent antistress effects such as decrease in blood pressure, corticosterone/cortisone level, and increase in insulin and CCK levels. Furthermore, acute exposure of rats to immobilization stress resulted in an increase in OT mRNA levels; both cen-

tral and plasma OT also increased by forced swimming and shaker stress. Thus, the stimulated release of OT could function to facilitate the activation of the hypothalamic-pituitary-adrenal axis and increase the glucocorticoid release. In contrast to most other OT-induced behavioral and physiological effects, the antistress effects could not be blocked by OT antagonists, suggesting that yet other unidentified OT receptors may exist.

It is also well documented that stress-induced central release of OT can ameliorate the stress-associated symptoms such as anxiety. OT displays anxiolytic properties in estrogen-treated females in mice and in rats. Estrogen-induced increases in OT binding density in the lateral septum may contribute to the facilitation of social interactions. Some of these effects may be mediated by an influence of OT on dopaminergic neurotransmission in limbic brain regions. Because stress and anxiety can impair maternal caretaking and reduce milk ejection, reduced stress responsiveness during lactation is adaptive for both mother and infant. Accordingly, lactating women had reduced hormonal responses to exercise stress when compared with postpartum women who bottle-feed their infants (Altemus 1995). In addition, women with panic disorder can experience a relief of symptoms during lactation (Klein 1995).

4. Feeding

OT acts as a "satiety hormone" in animals since both peripherally and centrally administered OT reduces feeding.

In addition, food and anorexia-inducing agents, such as CCK, lead to pituitary OT secretion and subsequently to reduced food intake. This suggests that both nausea and satiety activate a common hypothalamic oxytocinergic pathway that controls the inhibition of digestion (Olson 1991).

In fasted rats, OT given intraperitoneally or intracerebroventricularly, reduced food consumption and the time spent eating, and it increased the latency to the first meal. Pretreatment with an OT antagonist completely prevented the feeding inhibitory effect of OT, and per se increased food intake.

In particular, hyperosmolality is a very potent stimulus for OT release, and central OT was observed to mediate osmolality-related inhibition of salt appetite.

To explain how OT could mediate its influence on the ingestive behaviors, it was suggested that PVN neurons in general, and OT projections in particular, could either act to modulate the activity of intrinsic brain stem reflex arcs or exert a direct control over vagal efferents that project to the gut and inhibit the gastric motility.

5. Memory and Learning

OT and AVP are considered to play a pivotal role in various aspects of learned behavior. Overall, the concept emerged that AVP reinforces memory, whereas OT has just the opposite effect, namely, the attenuation of learning processes and memory. In particular, OT was shown to facilitate the extinction of avoidance reaction and to attenuate the storage of verbal memory (Dantzer et al. 1987). In cultured neurons, OT at concentrations over 1 mM reduces the activity of NMDA receptors, thus impairing one of the major substrates for the induction of learning and memory. Regarding its impairing effects on some memory-related tasks, OT could possibly be involved in the forgetting of delivery pain in mothers. On the other hand, studies on rodents indicated that socially relevant behaviors are controlled in a more complex way by both AVP and OT released intracerebrally (Engelmann et al. 1996).

6. Lactation and Parturition

OT is the most powerful galactokinetic hormone and milk production is the only irreplaceable role of OT; while, for instance, the role of OT in parturition can be assumed by other mechanisms that act in its absence in a reduntat way.

The decision, for a mother, to breast-feed or bottle-feed a child could have various implications: the degree to which bioactive compounds in milk, or changes in OT or other peptides, produced by the infant itself that are secondary to suckling and/or maternal contact, affect physiology or behavior has only recently become the subject of serious investigation, being a potential manipulation of the peptide experience of the newborn (Carter 2001). OT is present in breast milk and because tactile stimulation can induce its release (Uvnås-Moberg 1998), must be taken into account many aspects of maternal-child interactions including the amount of time spent holding the infant, to understand the potential to influence the OT system (Carter 2001). There are no definitive studies, to our knowledge, about the capacity of OT to pass from the mother's to the child's digestive system and to remain functionally intact or to maintain functional fragments.

Milk ejection occurs by the contractions of myoepithelial cells as a reflex response to the stimulation by suckling and kneading of the nipple, but other important factors interact to facilitate this reflex as the sight, smell and sound of the baby (Leng et al. 2005). During suckling dual mode of OT secretion occurs. OT neurons secrete large amount of neuropeptide from nerve terminals into the bloodstream to act in the mammary glands and parallely, they secrete OT by paracrine way from their dendrites in the SON to synchronize the generate bursts of OT release (Ludwig 1998).

The cascade of events that, at the time of delivery, causes the activation of OT, cells is not well studied in humans, therefore the hypotheses are based on data springing from studies in rats. During parturition, the first event is the mechanical stimulation of the uterus and cervix that leads, via the vagal and pelvic nerves, to the brainstem's relay -nucleus tractus solitarii, ventromedial medulla. These brainstem sites, in their turn, project directly to magnocellular cells and many of the projecting cells are noradrenergic (Day et al. 1988). The A2 noradrenergic cells of the NTS project mainly to OT cells (Raby and Renaud 1989). Noradrenaline depolarises OT cells mainly via á1 receptors (Yamashita et al. 1987) and á1 receptor mechanisms are believed to play a role in the bursting activity of OT cells during suckling (Crowley et al. 1992).

Electrophysiological evidences emphasize the presence of many changes in the properties of OT cells during parturition. There is a positive feedback mechanism, during delivery, similar to the high frequency

bursts recorded from OT cells during suckling in lactation (Fuchs et al. 1991).

Oxytocin and psychopatology

A. Autism

Autism and autism spectrum disorders are a complex, still poorly understood, wide spectrum of developmental disorders, characterized by impairments in three behavioral domains 1) social interactions; 2) language, communication and imaginative play; and 3) range of interests and activities (Muhle et al. 2004). A core feature of autism is impairment in social behaviors, including reciprocal social interaction and communication. Animal studies indicate that OT and VP can strongly influence social and cognitive functioning, playing a critical role in the processing of social cues, social recognition and social bonding, mainly affected in autistic patients (Insel 1992, Panskepp 1992, Lim et al. 2005). Several studies suggest that abnormalities in the neural pathways for either OT or VP might account for several aspects of autism: repetitive behaviors, early onset, cognitive and social deficits, alterations in neuronal development, predominance in boys and genetic loading (Insel and Young 2001, Insel et al. 1999).

Based on these data, and considering that family and twin studies indicate that the main causative determinants of autism are multiple interacting genetic factors (Muhle et al. 2004), OT and OT brain receptor may be candidate gene and protein that contribute to the social behavior deficits observed in autism. Animal models and linkage data from genome screen in humans indicate that OT receptor at 3p25-p26 is an excellent candidate for mediating genetic vulnerability to autism (Insel et al. 1999, Young 2001, Young et al. 2002), and recent genetic studies in human confirmed an involvement of OT receptor gene in the susceptibility to autism (Wu et al. 2005, Ylisaukko-oja et al. 2006).

Autistic subjects have also been reported to have lower serum levels of OT and to release an altered form of OT that is typically seen during only fetal life, showing deficits in OT peptide processing (Green et al. 2001). Hollander (1998) hypothesizes that an excess of OT, possibly through OT administration at birth, could contribute to the development of autistic spectrum disorders and related syndromes, by proposed downregulation of the OT receptor.

Considering the molecular evidence for OT receptors internalization by excess OT, the OT's effects on animal social behavior, the indications that OT's may cross the maternal placenta as well as an underdeveloped or stressed infantile blood brain barrier at birth, Wahl (2004) concludes that a causal connection between OT excess and behavioral disorders such as autism can be supported from a molecular perspective.

Patients with autism spectrum disorders have been recently shown to reduce their repetitive behaviors following OT infusion in comparison to placebo infusion, however these preliminary data need to be supported by controlled trials (Hollander et al. 2006).

B. Obsessive-compulsive disorder

Putative OT receptors have been identified in a variety of forebrain sites which have also been implicated in the neuroanatomical substrate of OCD (Rapoport and Wise 1988, Stahl 1988, Modell et al. 1989, Insel 1992). McDougle (1999) proposed that pathological doubting associated with the need to repeatedly carry out checking compulsions is a clinical manifestation of the cognitive effects of a dysregulated OT system in some forms of OCD. Attempts to systemically administer OT to OCD patients in the hope that it would facilitate the extinction of avoidance behaviors associated with the disorder have produced mixed results (Ansseau et al. 1987, Charles et al. 1989, den Boer and Westenberg 1992, Salzberg and Swedo 1992, Epperson et al. 1996). The general lack of a robust effect on OC symptoms is likely attributable to the fact that 0.003% of peripherally administered OT crosses the blood–brain barrier in many animal species (Mens et al. 1983). The central administration of OT to animals has been observed to markedly increase grooming behavior (van Wimersma Greidanus et al. 1990). Contamination obsessions and cleaning compulsions are prototypical symptoms in non-tic-related OCD patients (Holzer et al. 1994, Leckman et al. 1995) and parallel the OT-induced allogrooming behavior observed in a number of animal species. (McDougle 1999).

OT has also been proposed to contribute at several levels to sexual behavior (Carter 1992, Winslow and Insel 1991). Violent and horrific thoughts, images, and impulses are also common types of obsessions (Jenike et al. 1990) and central OT injections in animals is associated with increased aggression (Pedersen et al. 1992, Winslow and Insel 1991).

Pregnancy and the immediate postpartum period is a time of increased risk for the onset or exacerbation of OCD. Importantly, central OT concentrations peak during the third trimester and puerperium, and remain elevated in breast-feeding women. Some reports indicate that a significant number of women have the onset or exacerbation of OCD during pregnancy or the postpartum period (Jenike 1990, Neziroglu et al. 1992, Sichel et al. 1993, Epperson et al. 1995). Epperson et al. (1995) assessed all women in their OCD clinic to determine the association between pregnancy and the puerperium and the induction or exacerbation of their OC symptoms. Most of the women who had OCD prior to becoming pregnant reported a significant worsening of their OC symptoms during pregnancy or shortly after delivery. Women (18,6%) with onset of OCD during or immediately following pregnancy were significantly more likely to report contamination obsessions as the primary OC symptom compared with women with OCD prior to pregnancy. Given that concerns about cleanliness of the infant as well as the infant's environment are considered 'normal' for pregnant women and new mothers, these data suggest that contamination obsessions may be a pathological correlate of normal behavior. It may be that a subgroup of women are vulnerable to the induction or exacerbation of OCD upon exposure to elevated levels of OT during pregnancy and/or the puerperium. Further researches while showing that as many as 11% to 47% of women have

their first onset of OCD in the peripartum period (Leckman and Mayes 1999, Maina et al. 1999, Williams and Koran 1997). Leckman (1997, 1999) suggested that normally during the peripartum period there is a heightened sensitivity to threat and parents experience anxious intrusive thoughts and engage in compulsive-like harm avoidant behaviors, which bear a strikling reseamblance to several symptoms of OCD.

OT and AVP levels were measured in the CSF of adults with OCD and Tourette'syndrome and in healthy controls (Leckman et al. 1994) the results shawed similar concentrations of arginine VP in all three groups, but increased OT levels only in patients with OCD. Remarkably this increase was observed only in a subset of patients with OCD without a personal or family history of tic disorders, and in this group the CSF OT level correlates with current severity of OCD. It was, therefore, suggested a possible role for OT in the neurobiology of some subtypes of OCD, and the necessity to incorporate the tic-relatedeness as a variable in biological and behavioral studies of patients with OCD. A further report, however, did not confirm this result (Altemus 1999).

In 43 children and adolescents with OCD, CSF OT levels were positively correlated with comorbid depressive symptoms and anxiety (Swedo et al. 1992). Seventeen of the 43 children and adolescents received clomipramine treatment, and compared with baseline measures, CSF OT levels increased significantly after clomipramine treatment (Altemus et al. 1994).

C. Addiction

Abuse drugs are known to enhance brain reward mechanisms and the mesolimbic dopaminergic projections form a crucial drug-sensitive component of the reward circuitry. The drug-sensitive dopaminergic components of the reward circuitry are under the modulatory control of a wide variety of neuronal and hormonal systems (Koob 1992) including OT, which (Kovacs et al. 1998) plays a role in inhibiting learning and memory as already underlined. Because adaptation and learning are likely to be involved in the neural events leading to drug tolerance and dependence (De Wied et al. 1986), several studies were addressed to the hypotesis that OT may modulate the role of dopamine in the reward circuitry. Evidence regarding this hypothesis comes primarly from experimental drug addiction in rodents. Regarding opioid addiction, OT has been shown to inhibit the development of tolerance to morphine (Kovacs and Telegdy 1987) and to attenuate various symptoms of morphine withdrawl in mice (Kovacs et al. 1998). In rats, intravenous self-administration of heroin was decreased by OT treatment (Kovacs and Van Ree 1985).

Regarding cocaine abuse, OT attenuated dose-dependently cocaine-induced hyperactivity (Kovacs et al. 1990). In chronic cocaine administration, OT markedly inhibited behavioral tolerance to the sniffing-inducing effects of cocaine in mice, while facilitated the development of behavioral sensitization (Sarnay et al. 1992a, Sarnay et al. 1992b).

Regarding ethanol, OT blocked the development of tolerance to ethanol in mice (Szabò et al. 1989).

In parturitional animals cocaine disrupts OT activity and increases maternal neglect and aggression. In humans, the use of cocaine during pregnancy is associated with lower OT levels, greater hostility and depressed mood (Light et al. 2004). Acute alcohol administration inhibits OT secretions (Nemeroff and Loosen 1987), while chronic use stimolates it, possibly through elevation of plasma estrogens and reduced beta endorphin observed in alcoholics. (Marchesi et al. 1997). OT increase might be involved in the cognitive dysfunctions and alcohol-induced neuropsychological deficits observed in alcoholics. (Holden et al. 1988, Marchesi et al. 1997)

D. Eating disorders

Eating disorders are associated with aberrant eating behaviors, body image distorsions, impulse and mood disturbances, as well as characteristic temperament and personality traits, and various forms of hypotalamic-pituitary disfunctions. Subjects with eating disorders show a wide variety of neuroendocrine disturbances (Kaye et al. 1998) which could be a consequence of central nervous system neuropeptide dysregulation: in particular OT and VP are of interest in eating disorders because they influence feeding behavior (Olson et al. 1991) and have been implicated in obsessional behavior (Leckman et al. 1994). Alterations of these neuropeptides have been found in acutely ill patients, but it is not certain whether they are a consequence of pathological eating or malnutrition, or if they represent premorbid traits that contributes to a vulnerability to develop eating disorders (Baranowska 1990, Gold et al.1986, Kaye 1996).

Demitrack (1990) found that underweight restricting anorexics had reduced CSF OT levels, while other found impaired plasma OT response to challenging stimuli in the same type of patients. Such abnormalities tend to normalize after weight restoration, while suggesting that such changes may be secondary to malnutrition and/or abnormalities fluid balance (Chiodera 1991).

It was hypothesized that a low level of centrally directed OT could act in concert with a high level of CSF VP in underweight anorexics so as to enhance the retention of cognitive distortions of the aversive consequences of eating, exacerbating the tendency for restricting anorexics to have perseverative preoccupation with feeding.

More recently, recovered women with eating disorders were studied addressing for any persistent psychobiological abnormalities which might be trait-related and potentially contribute to the pathogenesis of the disorders. Elevated cerebrospinal fluid VP in recovered women with eating disorders, while OT levels were normal, proposes that elevated cerebrospinal fluid VP may be related to the pathophysiology of eating disorders (Frank 2000).

AutoAbs against OT have been also found in anorexia and bulimia nervosa, while suggesting that immunitary dysfunction may contribute to the development of these disorders (Fetissov et al. 2005).

E. Depression

The HPA-axis is considered the final common pathway of a major part of the depressive symptomatology, and a longlasting hyperactivity of the CRH neurons is commonly seen in depressed individuals (De Kloet et al. 1997, Pariante 2001).

The VP and OT neurons are activated in the paraventricular nucleus of patients with major depression or bipolar disorder. This may have functional consequences for HPA-axis reactivity, since both VP and OT are known to potentiate the effects of CRH (Newport et al. 2003, Purba 1996). Because of their central effects, the parallel activation of OT neurons in depression has been connected to eating disorders in depression (Purba 1996).

F. Post-traumatic stress disorder

OT plays an important role on memory: attenuates memory consolidation and retrieval (Bohus et al. 1978) and appears to facilitate the extinctions of an activate avoidance response and attenuates passive avoidance behavior (Amico and Robinson 1985). The intranasal somministration of OT inhibits effects on memory retrieval and conditioned responding in patients with PTSD (Pitman et al. 1993). The alterations of OT induced by severe early stress and maltreatment may alter brain devolpment and increase the risk of developing PTSD and other psychiatric disorders (Teicher 2002).

Prolyl endopeptidase (PEP) is an enzyme that cleavages many active behaviorally active neuropeptides, such as VP, TRH, substance P, OT, bradykinin, neurotensin and angiotensin (Welches et al. 1993). The activity of PEP was investigated in PTSD patients and found to be increased, in particular, in those with concurrent major depression (Maes et al. 1999). It was thus proposed that increased serum PEP, through increased degradation of neuropeptides, is a marker for predisposition to PTSD and may play a role in the neuroendocrine pathophysiology, behavioral and affective symptoms of PTSD (Maes et al. 1999).

G. Other anxiety disorders

In non-human mammals OT is a key mediator of complex emotional and social behaviors (Insel and Fernand 2004). Because of its established effects on affiliative behavior in non-human mammals, there are numerous speculations about its role in human emotions and relationships. OT levels in mothers of infants are positively correlated with sociality, calm and tolerance (Nissen et al, 1998) and with reductions in the incidence of stress and anxiety disorders (Altemus 1995). Pregnancy appears to be a protective period for some anxiety disorders, including panic. Hormonal changes during pregnancy, such as increased prolactin, OT and cortisol, may contribute to the suppression of stress response that occurs during this period (Leckman et al. 1994b). OT is released during stress (Jezova et al. 1995) and is an important modulator of anxiety and fear response, with anxyolitc effect (McCarthy et al. 1996, Marazziti et al. 2006). Amygdala function has been implicated in danger signal in social interaction, and dysfunction in disease such as anxiety disorders, depression and autism. Human amygdala function is strongly modulated by OT. Kirsch et al. (2005) showed that intranasal OT potently reduced activation of amygdala and reduced coupling of the amygdala to brainstem regions implicated in autonomic and behavioral manifestations of fear, while indicating potential therapeutic strategies in disorders in which amygdala function has been implicated. Mathew et al. (2001) suggested, that OT system downregulation might contribute to the neurobiology of social anxiety disorder while explaining some of cognitive misappraisals observed in patients, such as aberrant social affiliativeness.

H. Schizophrenia

OT levels were measured in patients with schizophrenia and were compared with healty controls. OT concentrations resulted to be increased in all patients, higher in those receiving neuroleptic treatment and increased after three weeks of neuroleptic treatment. Drug-induced increase in OT concentrations have been assioted to clinically observed amnestic syndrome and debilitation in schizophrenic treated with neuroleptics (Beckmann et al. 1985). The presence of alterated OT function in untreated schizophrenic patients is suggested by a morphometric evaluation of neurophysin-immunoreactivity on human brain (Mai et al. 1993).

I. Prader-Willy syndrome

Prader Willy syndrome is a genetic disorder characterized by mental retardation, hypogonadism, short stature and distinctive dysmorphic features. There are evidences for OT dysfunction in Prader Willy Syndrome (PWS).

In a postmortem study, a 42% reduction of OT-expressing neurons has been found in the paraventricular nucleus of PWS subjects compared with controls (Swaab et al. 1995). The findings of elevated OT (Leckman 1994) in the cerebrospinal fluid of patients with obsessive-compulsive disorder may be of particular relevance to PWS. OCD is estimated to occur in PWS with a prevalence rate of 45-50% (Dykens et al. 1996). Elevated levels of OT have been found in PWS subjects, compared with normal control subjects., lending additional support for hypotalamic and OTergic pathway dysfunction underlying part of the symptomatic cluster of the syndrome, and suggests a relationships between OT, PWS and OCD. Important limitations of this study is the lack of obsessive-compulsive and depressive symptoms quantification (Martin et al. 1998).

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