Oxytocin (OXY) is a very abundant neuropeptide exerting a wide spectrum of central and peripheral effects as neurohormone, neurotransmitter, or neuromodulator. In the central nervous system (CNS), the OXY gene is predominantly expressed in magnocellular neurons in the hypothalamic paraventricular (PVN) and supraoptic (SON) nuclei. The magnocellular OXY neurons release their products into the general circulation in the neurohypophysis while the medio cellular OXY neurons secrete elsewhere in the CNS. OXY is also produced in peripheral tissues, e.g., uterus, placenta, amnion, corpus luteum, testis, and heart. OXY is a potent stimulator of spontaneous erections in rats and is involved in ejaculation. The typical actions of peripheral OXY are stimulation of uterine smooth muscle contraction during labor and milk ejection during lactation. OXY acts via the receptor which is a typical class of G protein-coupled receptor. OXY receptors have also been identified in other tissues, including the kidney, heart, thymus, pancreas, and adipocytes.

For details see <www.elis.sk>.

Key words: Oxytocin – Anatomy – Function – Minireview

General outline

Oxytocin (OXY) is a nine amino acid peptide structurally similar to closely related peptide arginine vasopressin (AVP), an antidiuretic hormone, which differs from OXY in two of the nine amino acid residues. These two neurohypophysial hormones, in most bony vertebrate species, exhibit in its structure a great evolutionary stability (Murphy et al., 1998). Thus two molecular lines, isotocin-mesotocin-oxytocin and vasotocin-vasopressin, can be followed from bony fishes and amphibians to mammals, respectively (Murphy et al. 1998; Achter et al. 1999).

Centrally acting OXY. Although OXY has an established role as a circulating hormone, it can also act as a “neurotransmitter and as a neuromodulator” by interacting with its central OXY receptor within the brain (Gould and Zingg 2003). Central OXY may have more sources of origin and multifarious encompassment in different anatomical and functional circuits. Experimental data indicate that:

1. Certain OXY-ergic magnocellular axons that together with vasopressinergic axons are the principal constituents of the “hypothalamo-neurohypophysial system”, i.e. the major peptidergic neurosecretory system with perikarya located in the hypothalamic paraventricular (PVN) and supraoptic (SON) nuclei (Swanson and Kuypers 1980; Rhodes et al. 1981; Hou-Yu et al. 1986) through which the brain controls peripheral organs (Burbach et al. 2001), terminate in the neural lobe of the pituitary and give off collaterals to the median eminence (ME), the medial amygdaloid nucleus, the lateral septum, and the arcuate nucleus (Pittman et al. 1981). In the arcuate nucleus, for instance, OXY nerve collaterals were shown to make synaptic connections with beta-endorphin synthesizing neurons (Csiffary et al. 1992). Other OXY neurons of the PVN give rise to axons that branch in the perifornical and more ventral lateral hypothalamus, and that some of their collaterals probably terminate on neurons close to the PVN (Hutton et al. 1985).
2. In the magnocellular SON and PVN nuclei, OXY is released locally from neuron dendrites or perikarya and functioning as an intrinsic (presumably by both the autocrine and paracrine fashions) self neuromodulator involved, for instance, in the synchronization of the firing of OXY cells during lactation. A receptor-mediated positive feedback action, i.e. an autoregulatory loop mechanism, of OXY on its own dendritic release within the SON during parturition has been described (Neumann et al. 1996). This indicate that intrinsic OXY release may be important for the coordinated activation of OXY neurons and for the synergistic central and peripheral OXY effects involved in the regulation of parturition-related events necessary for the survival of the newborn, including the onset of lactation. It is interesting that unilateral oxytocin release, either in the PVN and SON, may facilitate the occurrence of bursts of the oxytocin cells in both the contralateral PVN and SON (Moos and Richard 1989). This is probably one of the ways how to achieve a coordinated action of the OXY system.

3. Vast majority of OXY neurons with central axonal projections occupy the dorsal-caudal portion of the PVN and are called “mediocellular” (Kiss et al. 1991) or “parvicellular” (A MICO et al., 1990) because they are smaller than the magnocellular neurons that innervate the posterior lobe of the pituitary gland. Although these OXY neurons do form intrahypothalamic projections, their axons terminate primarily outside the hypothalamus. OXY, along with other neuropeptides including corticotrophin releasing hormone (CRH), AVP, somatostatin, enkephalin, and proopiomelanocortin, is a part of the descending fibers tract directed from the PVN to caudal autonomic centers (PALKOVITS 1999). This is probably one of the ways how to achieve a coordinated action of the OXY system.

4. Not all centrally projecting OXY neurons are only located within the parvicellular PVN. OXY immunoreactivity in the locus coeruleus, the raphe nuclei, and the periaqueductal gray remains unaffected after lesion of the PVN in rats, suggesting that OXY fibers in these areas may have extrinsic origin, i.e., located outside of the PVN. Extrahypothalamic OXY synthesizing neurons have been found in the triangular nucleus of the septum, the medial posterior region of the bed nucleus of the stria terminalis and the medial preoptic area in rodents and primates (SOFRONIEW and WEINDL. 1978) and oxytocin-expressing neurons have been identified in the anterior commissural, periventricular, paraventricular, supraoptic, and perifornical nuclei as well as the bed nucleus of the stria terminalis and inter-supraoptical-paraventricular (internuclear) islands (Chung et al. 1991). However, to what extent the effect of these neurons might be similar to that one originating in the caudal-dorsal PVN is not understood.

5. Oxytocinergic magnocellular neurons of the PVN and SON display coexistence with a number of biologically active substances, in many cases of unknown physiological significance. Neuropeptide Y (NPY) co-exists with oxytocin in magnocellular neurons and adrenocorticotrophin and chronic osmotic stimulation can separately influence NPY gene transcription in these structures (Larsen et al. 1993). Double labeling immunohistochemical studies revealed coexistence of OXY with tyrosine hydroxylase (Scutella et al. 1993), dynorphin (Eriksson et al. 1996), CRH (Pretel and Pietk 1990), thyrotropin-releasing hormone (Tsuro et al. 1988), atrial natriuretic factor (Jirikowski et al. 1986), galanin (Landry et al.,1991), nitric oxide synthase (Xiao et al. 2005), and others. Even transient coexistence of oxytocin with vasopressin in hypothalamic magnocellular neurons of parturient (Jirikowski et al. 1991) or osmotically stressed rats has been described (Telle- ria-Diaz et al. 2001). As reviewed in the work of Bondy et al. (1989) a number of coexisting peptides co-release with the major magnocellular hormones: dynorphin is co-released with vasopressin from neural lobe nerve terminals and acts on neural lobe kappa-opiate receptors to inhibit the electrically stimulated secretion of oxytocin; cholecystokinin, via high-affinity receptors located in the neural lobe, stimulates secretion of both oxytocin and vasopressin; CRH is co-released with OXY from the neural lobe, has receptors in the intermediate lobe of the pituitary, but not in the neural lobe itself. CRH stimulates the secretion of oxytocin and vasopressin from combined neurointermediate lobes but not from isolated neural lobes.

6. Under normal physiological conditions OXY is present within the cerebrospinal fluid (CSF) in concentrations slightly higher than those in plasma, however, its remarkable elevation is observable, for example, in subjects suffering with psychotic diseases (Beck-
neurons expressing OXY in the third ventricular region suggests that nitric oxide is an important messenger in neurons. The widespread presence of nitric oxide synthase in cerebrospinal fluid-contacting cells, or the adjacent parenchyma, and their processes inserted into the ependymal lining of the third ventricle (Xiao et al. 2005). The widespread presence of nitric oxide synthase in cerebrospinal fluid-contacting neurons expressing OXY in the third ventricular region suggests that nitric oxide is an important messenger in the CSF-hypothalamo-hypophyseal neuroendocrine regulation that may in part act in concert with OXY (Xiao et al. 2005). However, neuronal pathways giving rise to OXY in the CSF and the periphery might be anatomically and functionally separate.

7. The distribution of OXY receptors in the brain is quite distinct from that of AVP receptors (De Wied et al., 1993). Whenever occurring in the same area, AVP and OXY binding sites seem to be present in different sublocalities of the targeted structure (Kremarik et al., 1993). For example, AVP binding sites in the rat hippocampus are observable mainly in the inner and outer part of the dentate gyrus and in a subregion of the CA1 field, whereas OXY binding sites are present in the subiculum and in a different part of the CA1 field. AVP binding sites in the rat dorsal vagal complex are accumulated in the NTS and the area postrema, while OXY binding sites are concentrated in the DMV. PVN neurons that contain OXY and project to the dorsal vagal complex apparently do not respond to suckling, but they do respond to dehydration, hemorrhage, and exogenous cholecystokinin, vice versa. OXY neurons projecting to the amygdala do not respond to suckling or hemorrhage, but do respond to dehydration, which also stimulates both AVP and OXY magnocellular neurons. These observations provide a structural basis for understanding that the OXY pathways may insert specific influence on centrally regulated brain functions. It also provides evidence that OXY neurons are a heterogeneous population of neurons.

Peripheral acting OXY. Circulating OXY may originate in the brain or peripheral tissues. In this case, the brain OXY functioning as a typical hormone and it is a product of the above mentioned classical hypothalamic-neurohypophysial system (Morris et al., 1998; Mohr et al., 2002). PVN and SON represent a specialized class of peptidergic neurons called “neurosecretory” cells. Likewise vasopressin, OXY prohormone is packaged into neurosecretory granules of the magnocellular neurons. These neurons project via a well-defined axonal tract to the neural lobe where each axon is estimated to branch into hundreds of nerve terminals representing ~50% of the total tissue mass of the neural lobe. During axonal transport of the secretory granules from the hypothalamus to the posterior pituitary, enzymatic cleavage of the OXY prohormone generates the final products: OXY, neurophysin II and a carboxy-terminal glycoprotein. When afferent stimulation depolarizes the OXY-containing neurons, the three products are released into the general circulation either from terminals which end directly on capillary endothelial cells or on cells which adjoin the vessel wall. OXY, which is released directly into the bloodstream, acts on distant target organs including the mammary gland and kidney. Consequently, transcriptional rates and mRNA levels for this peptide is very high in the hypothalamo-neurohypophyseal system neurons, and peptide secretion from large dense core vesicles in the neural lobe is exceptionally massive. Thus, PVN and SON magnocellular cells are classical neuroendocrine cells, specialized in the synthesis and secretion of vast quantities of the OXY hormone.

On the other hand, a novel delivery mechanism of OXY mRNA has been observed in the hypothalamic–neurohypophysial system (Mohr et al. 1990). OXY mRNA, but also AVP mRNA (Trembleau et al. 1996), is actively transported towards the neurohypophysis in the axons of magnocellular neurons. Although the two OXY transcripts from posterior pituitary and hypothalamus show identical nucleotide sequences, the functional significance of OXY mRNA neurohypophyseal transport is unclear. It is also unclear, whether mRNA transport also occurs in axons of OXY neurons directed to central OXY-target areas, especially to the parasympathetic and sympathetic centers in the caudal brainstem and spinal cord areas, respectively. Beside PVN and SON, a smaller number of neurons that synthesize OXY and project to the neurohypophysis, has also been described to be located within the anterior commissural nucleus of the hypothalamus (Han et al. 1992), and others are clustered within the magnocellular accessory nuclei scattered between the PVN and SON (Riva et al. 1999).

Peripheral tissues also synthesize OXY, e.g., uterus, placenta, amnion, corpus luteum, testis, and heart. The multiple hormonal and neurotransmitter functions of OXY are mediated by the specific OXY receptors. There is only one OXY receptor gene and therefore, the same receptor protein is expressed in brain and peripheral organs. Thus, the OXY receptor can be considered as a “nonselective” receptor for neurohypophysial nonapeptides, since it binds both OXY and AVP with almost similar affinities. The OXY receptor is a typical class I G protein-coupled receptor that is primarily coupled via G(q) proteins to phospholipase C-beta. The high-
affinity receptor state requires both Mg(2+) and cholesterol, which probably function as allosteric modulators (Gimpl and Fahrendolz 2001). OXY receptors have also been demonstrated in many peripheral tissues, including the kidney, heart, thymus, pancreas, and adipocytes.

OXY is well known in female reproduction, where it is involved in the maintenance of parturition and the initiation of lactation (Blanks and Thornton 2003). Oxytocin secretion from the neurohypophysis is increased during parturition stimulated by the uterine contractions which vice versa induce further contractions of the uterus leading to the development of a positive feedback loop at the end of pregnancy. The neural pathway that drives oxytocin neurons via a brainstem involves A2 noradrenergic cells in the brainstem (Russell et al. 2003). OXY acts on the endometrium smooth muscle during labor to increase the intensity of the uterine contractions, and on the myoepithelial cells of mammillary glands to provoke milk ejection in response to suckling. During suckling dual mode of OXY secretion occurs. OXY neurons secrete large amount of neuropeptide from nerve terminals into the bloodstream to act in the mammary glands and parallelly, they also secrete OXY by paracrine way from their dendrites in the SON to synchronize the generate bursts of OXY release (Richard et al. 1997; Ludwig 1998). Ejaculation in males is also accompanied by circulating OXY elevations and OXY is involved in facilitating sperm transport within the male reproductive system and perhaps also in the female, due to its presence in seminal fluid (Ivell et al. 1997). Metabolic activity of OXY involves the triggering the insulin and glucagon secretions from the pancreas (Kolesnyk et al. 2000). It also acts on adipocytes, indicating for a role in metabolic regulation related to feeding (Egan et al. 1990). Vaginal and uterine distension receptors, somatic sensory receptors from the nipple and breast and nociceptive perception are all relayed firstly to the dorsal horn of the spinal cord, from where the axons are directed to the AI cell group and the caudal NTS (Komisaruk and Sansone 2003). Thereafter, appropriate stimuli to the hypothalamic OXY and AVP cells from the AI cell group and the NTS (A2 cells) may be mediated by enkephalin, somatostatin, inhibin B, and norepinephrine pathways (Day et al. 1984; Buller et al. 2001; Onaka et al. 2001).

**Physiological events**

**Hyperosmolality.** Hyperosmotic stimuli such as dehydration or salt-loading result in an increase in the transcription of the OXY gene and the proportion of neurons expressing OXY (Meister et al. 1990). Magnocellular neurons in the SON increase cell size in response to hyperosmolar conditions and vice versa, decrease cell size in response to hypoposmolalar conditions (Zhang et al. 2001). These dramatic bidirectional changes in cell and nuclear size are parallel to changes in OXY and AVP gene expression in the magnocellular neurons of the SON (Zhang et al. 2001). Hyperosmolality is controlled by a complex of homeostatic mechanisms (Johnson and Thunhorst 1997). The median preoptic area (MnPO), anterior lateral hypothalamus, subfornical organ (SFO), anterior portion of the third ventricle (AV3V), SON, PVN, organum vasculosum laminae terminalis (OVLT), habenula, stria medullaris, and medial septal area form a neuroendocrine network which neural circuits are involved in the regulation of the body hydromineral balance (Bourque and Oliet 1997; Johnson and Thunhorst 1997). Finally, the OXY function in the regulation of the salt and water homeostasis is well documented eventuality. Beside vasopressin, OXY is secreted in response to hyperosmolality, whereas OXY is more potent natriuretic hormone than vasopressin. In this effect, estrogen-regulated OXY receptors in macula densa and proximal tubule cells are also involved.

Several lines of evidence indicate a possible physiological function of OXY in the mediation of atrial natriuretic peptide (ANP) release since i.p. or i.v. injection of OXY causes a dose-dependent increase in plasma ANP, urinary osmolality, natriuresis, kaliuresis, and a delayed antidiuretic effect. OXY is assumed to would act directly on the right atrium to stimulate ANP release (Favaretto et al. 1997). In addition, OXY presence in the right atrium homogenates was demonstrated, and OXY and oxytocin receptor synthesis have been demonstrated in the rat heart. Consequently, OXY released from the neural lobe may reach the heart by circulation to induce ANP release, but the intracardiac OXY might also play a paracrine role in stimulating ANP release. On the other hand, endogenous hypothalamic ANP seems necessary to stimulate OXY release in the hyperosmolality condition (Cirriquier et al. 2001). The mature magnocellular neurons respond to perturbations in water balance by releasing large amounts of stored AVP and OXY into the general circulation. This is accompanied by functional remodelling of the activity of the magnocellular neurosecretory neurons, the molecular basis of which is still far from understood.

**Hypovolemia.** Hypovolemia is a stimulus for cardiovascular and neuroendocrine reflexes, resulting in
sympathetic, adrenal, and hypothalamic activation. Experimentally, volume depletion is often induced by the polyethylene glycol (PEG) injection, which acts to draw iso-osmotic fluid from the tissues. Isosmotic hypovolaemia and isovolaemic, isosmotic hypotension have been shown to produce activation of very similar populations of oxytocin cells in the PVN and SON of the hypothalamus (Smith and Day 2003). Time-course and pharmacologic antagonist studies suggest that PEG-induced OXY release inhibits salt intake. Under conditions of hypovolemia, osmoreceptors controlling thirst located in systemic viscera and in central structures that lack the blood–brain barrier are stimulated. Angiotensin and aldosterone act on and through structures of the lamina terminalis and the amygdala to stimulate thirst and sodium appetite. Stimulatory effect of centrally applied ANG II and ANG III on dipsogenic compounds (Szczepanska-Sadowska 1996) and the role for systemic ANGII and systemic ANGII receptors in the control of blood pressure in hypovolaemia are well established (De Luca et al. 2000). AVP may also enhance the osmotic thirst and OXY and serotonin are additional candidate postulated in inhibitory central actions and with essential roles in the integration of sensory input devoted to maintaining hydromineral balance. The NTS and the lateral parabrachial nucleus (LPBN) receive neural signals from baroreceptors 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 OXY-specific response to increased osmolality, rather than sodium (Blackburn et al. 1993). A role for central ANG II in mediating the OXY responses has been suggested, because OXY antagonists potentiated the salt intake induced by ANG II. In addition, central administration of Ang II provoked systemic release of OXY and vasopressin in rats. There are also studies that have explored the synaptic mechanisms involved in ANG II–induced secretion of vasopressin, whereas there is less information on the OXY system.

The hypothalamic–hypophyseal–adrenal system (HHA). The HHA axis is a key player in an animal’s response to stressful stimuli. While the role of the CRH in the stress response is well described (Fisher and Brown 1991; Aguilera et al. 2004) the role of OXY in the “hypothalamic–hypophyseal–adrenal system” is rather controversial and its effect seems to be limited to controlling adrenocorticotropic (ACTH) release only under certain circumstances. For example, OXY elicited by immobilization stress might contribute to the ACTH secretion during short-term adrenalectomy (Laguna-Abreu et al. 2005). Although OXY-positive fibers are rare in the external zone of the ME, large amounts of OXY are present in the hypophysial portal blood of the rat and rhesus monkey, and high-affinity receptors for OXY have been found in the anterior pituitary of the rat. The presence of OXY along with a few AVP but a large AVP amount of immunoreactive fibers in the internal palissade zone of the ME support the view that not only CRH but also AVP and OXY are released into the hypophysial portal blood and involved in the control of pituitary endocrine function in ruminant species (Kikusui et al. 1997). However, OXY appears to be less potent actor than AVP in enhancing ACTH release, but passive immunoneutralization of OXY blunts the ACTH response to some types of stress in rats. OXY appears to inhibit rather than to stimulate ACTH release in primates and humans (Swaab et al. 2005). Oxytocin is released from the pituitary gland in response to a variety of stressful stimuli which stimulate the HHA, 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). OXY, but not AVP, for instance, has been found to be released into the PVN and peripheral blood in response to shaker stress indicating that local release of OXY into the PVN may play a role in the neuroendocrine stress cascade events (Nishoka et al. 1998).

Cardiovascular control. In the cardiovascular control, the SON, but particularly the PVN neurons play an important role (Coope 2005). Both PVN regions, i.e., the magnocellular region containing neurons synthesizing vasopressin and oxytocin which are released into the blood via the neurohypophysis and the parvicellular region containing neurons also synthesizing vasopressin and oxytocin which are, by the help of the long-descending monosynaptic projections, delivered to the brainstem areas (NTS, DMV, RVLM, IML), are involved in the autonomic control of heart and vessels. The NTS appears to act also as an important relay for pathways ascending to OXY magnocellular neurons. Whereas electrical stimulation of the NTS leads to indirect activation of AVP neurons via the A1 cell group of the ventrolateral medulla, there is a direct excitatory input to OXY neurons that is mediated, at least in part, by the A2 noradrenergic cell group lying within the NTS. OXY 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
Cardiovascular centers in the hindbrain and the spinal cord activated by OXY of the PVN origin mediate the increases in blood pressure and heart rate induced by stimulation of substance P receptors in the forebrain. These neurons may also transmit signals, which are generated by substance P in the hypothalamus and are responsible for the sympathoadrenal activation in response to stress (Maier et al. 1998). 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. OXY and OXY receptors are present in the vasculature, heart, and kidney, and OXY has effects on blood pressure, renal function, and salt intake. The oxytocinergic system has also been shown to be involved in the exercise stress-induced tachycardia and to interact with the central vasopressinergic system in cardiovascular control. The neural pathways that inhibit vasopressin release in response to an increase in blood pressure and an increase in blood volume may overlap at the perinuclear zone of the supraoptic nucleus. Inhibition of supraoptic vasopressin neurons during volume expansion is mediated by cardiac afferents, the activation of supraoptic oxytocin is independent of cardiac afferents and may be mediated by other visceral afferents or humoral factors (Cunningham et al. 2002).

Sexual control. Paraventricular oxytocinergic neurons projecting to the extrahypothalamic brain areas and to the spinal cord play an important role in the control of the erectile function and the male sexual behaviour in mammals (Argiolas and Melis 2004). In rats, stimulation of the PVN induces penile erection, but the link between the nucleus and penile innervation remains unknown. However, the hypothesis that oxytocin, transporting by a long descending paraventriculo-spinal pathways, activates proerectile spinal neurons has been established (Veronneau-Longueville et al. 1999).

Ingestive behavior. Ingestive behavioral challenges induce both peripheral and central OXY release. Variety of treatments including plasma hyperosmolality or hypotension, gastric distension, and systemic administration of cholecystokinin that inhibit ingestion of food and NaCl, provoke secretion of OXY from the posterior pituitary. However, each of these treatments also activates the mediocellular population of OXY neurons in the PVN resulting in the OXY elevation in OXY-targeted extrahypothalamic brain areas. The PVN modulates vagal digestive motor functions via oxytocinergic projections to the NTS and dorsal motor nucleus of the vagus (DMV) in adult rats (Blevins et al. 2003). Retrograde transport of cholera toxin neural tracer from the NTS-DMV in newborn rats confirmed that PVN neurons are the sole source of these brainstem oxytocinergic fibers (Rinaman 1998). Oxytocin axons within the descending pathway from the PVN to the NTS are anatomically positioned to interact with NTS neurons that respond to vagally mediated peripheral CCK signals such as those that occur following ingestion of a meal. These findings support the hypothesis that oxytocin exerts a tonic stimulatory effect on the response of key neurons within the NTS to CCK and further reduce meal size (Blevins et al. 2003). The inhibition of food and NaCl intake produced by treatments that activate central and systemic secretion of OXY may represent a coordinated way how to reduce solute concentrations in the body, since circulating OXY of neurohypophysial origin increases urinary sodium excretion in rats.

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