Oxytocin and its role and effects – recent findings

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Abstract
Oxytocin is a cyclic nanopeptide synthetized in hypothalamus, best known for inducing contractions of smooth muscles during birth (in uterus) and milk ejection (in breast) during breast feeding. Recent studies have demonstrated various effects that oxytocin might have on different tissues and organs, such as lungs, kidneys, adipose tissue, liver and pancreas. Oxytocin has also been found to affect food intake and body weight as well as modulate reactivity to stress. Moreover oxytocin appears to have an association and influence on development and progress of various diseases including asthma, obesity and fatty liver, hence the pharmacological use of that hormone or its analogues should be possible. Variety and multiplicity of effects induced by oxytocin suggests that its role in physiology is not fully understood.

Key words: oxytocin, effect on tissues and organs

Introduction
Oxytocin is a cyclic nanopeptide synthetized in hypothalamus, best known for inducing contractions of smooth muscles during birth (in uterus) and milk ejection (in breast) during breast feeding [1]. Oxytocin consists of nine amino acids. Similarly to vasopressin, it contains a disulphide bond in its structure between cysteine sulphide groups in positions 1 and 6. Oxytocin and vasopressin belong to a group of peptides which have proven to be very persistent when evolutionary aspects are being considered [2].

Oxytocin receptors are present in various tissues, with the highest concentration found in breast and uterus in females. In males, the receptors are mostly accumulated in the main caval vein and penis. A moderate concentration of oxytocin receptors has been reported in variety of tissues in different organs including bladder, kidney, stomach, larynx, lung, testes and trachea [3]. Receptor for oxytocin belongs to a G-protein coupled receptors, group class I (rhodopsin like). It has seven transmembrane domains, and its activation is a consequence of changes occurring in orientation of domains 6 and 3. In addition, these receptors constitute of two or three glycosylation sites, depending on species. Even though glycosylation is involved in expression of the receptor, it does not in any way affect its function [2]. Moreover, a significant amount of cross-reactivity has been noted between oxytocin peptides and vasopressin receptors of V2 type [4], V1a subtype [5] and V1b subtype [6]. Oxytocin receptor changes inner cellular activity with a help of Gq/11α GTP binding protein which in turn stimulates (together with Gβγ) Cβ phospholipase activity. This process results in rise of inositol triphosphate concentration and furthermore, the 1,2-diacylglycerol causes release of Ca2+ ions from intracellular stores and activation of protein kinase C [2].

Recent studies have demonstrated various effects that oxytocin might have on different tissues and organs, such as lungs, kidneys, adipose tissue, liver and pancreas. Oxytocin has also been found to affect food intake and body weight as well as modulate reactivity to stress.

Our review will summarise recent discoveries associated with oxytocin. Then the following parts will provide an overview of its possible role in physiology and give some insight in mechanisms behind it.

Effects of oxytocin in human lungs and airways
Asthma is one of the most serious conditions affecting human lungs and airways and it may lead to serious maternal and foetal complications. These include low weight at birth, small for gestational age (SGA) infants, preterm delivery, and preeclampsia. In most cases, general practitioners are able to successfully treat asthma during pregnancy however, progressive asthma in pregnant women can have a profoundly detrimental impact on their health and might be difficult to treat [7, 8].

Amrani et al. have reported presence of functional oxytocin receptors in smooth muscle cells of airways.

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This discovery has brought aforementioned authors to the interesting conclusions. Namely, IL-13 and TNFα increase the number of oxytocin receptors in cultured cells. The quantity of oxytocin receptors mRNA also increases if monolayers of human cells which are treated with IL-13 and TNFα. Moreover, rise of oxytocin receptor expression correlated with the accumulation of mRNA. There is observed mobilisation of calcium rises in cells treated with IL-13, although calcium metabolism remains stable in cells treated with TNFα. Those observations are interesting especially despite the fact that IL-13 is ineffective in ex vivo tissues [3]. Oxytocin may induce contractions of murine tracheal rings with a 25% effect rate of carbachol with comparable molar concentration. Levels of oxytocin in broncho-alveolar fluid do not differ considerably between normal subjects and those suffering asthma. While relevance of those findings is yet to be determined, Amrani et al. [3] have come up with a hypothesis that density of oxytocin receptors might be more important in promoting airway hypersensitivity than oxytocin levels itself. Although the role of oxytocin as a contractile factor has been proven, its exact signalling pathways and epidemiologic character need to be addressed further.

**Oxytocin in renal function**

Oxytocin shows a variety of effects on kidney function and may play significant role in water-electrolyte homeostasis. Oxytocin differs from vasopressin only by two positions of polypeptide and shows partial agonistic activity on V2 [4] and V1a [5] vasopressin receptors found in kidneys. Oxytocin has also been found to increase renin and atrial natriuretic peptide (ANP) levels by activating oxytocin receptors [9-11]. Although vasopressin has been long recognized as a major antidiuretic hormone, recently reported cases of oxytocin induced water intoxication suggest that oxytocin antidiuretic activity should not be neglected [12-13].

Furthermore, oxytocin mediates incorporation of aquaporin 2 water channels (AQP2) into luminal membrane of principal cells of renal inner medullary collecting ducts. Mechanisms behind this phenomenon are revealed in studies undertaken by Li et al. [4] on Sprague-Dawley rats and Brattleboro rats, which are unable to synthesize vasopressin. Brattleboro rats have shown no detectable vasopressin in their bloodstream and excreted large amounts of urine. Moreover oxytocin levels were higher compared with those found in Sprague-Dawley rats. In Brattleboro rats, administration of selected vasopressin receptor antagonist resulted in increase of urine flow rate and decrease in urine osmolality, accompanied by decreased quantity of AQP2 in cortex and medulla of rats’ kidneys. Administration of exogenous oxytocin resulted in decreased urine flow rate and increase of urine osmolality. Concentration of AQP2 in inner and outer medulla and cortex increased. These effects were alleviated in presence of V2 – vasopressin receptor antagonist but remained unaffected by oxytocin receptor antagonist.

Immunohistochemistry analysis has also found increased density of AQP2 and phosphorylated AQP2 in apical membrane of principal cells in inner medullary collecting ducts after oxytocin administration. Levels of AQP3 in basal membrane of those cells also increased. These effects were reversed by V2 receptor antagonist, however, oxytocin receptor antagonist did not have any impact on levels of AQP3. Li et al. [4] concluded that antidiuretic effect of oxytocin is a consequence of increased expression of AQP2 and AQP3 and trafficking of AQP3. Oxytocin evokes those effects primarily due to activation of V2 vasopressin receptors.

Loichot et al. [5] attempted to evaluate vasconstricting and vasodilatating properties of oxytocin on isolated kidneys from Sprague-Dawley and Brattleboro rats. In Sprague-Dawley rats, oxytocin caused constriction of arteries up to 44% maximal response of vasopressin noradrenaline measured in the same kidney. Level of constriction depended on concentration of oxytocin. Results were unaltered by addition of oxytocin receptor antagonist (d(CH2)5[Tyr(Me)2,Thr4,Orn8,Tyr-NH2]vasotocin), and blocked completely by administration of V1a vasopressin receptor antagonist. Following administration of prostaglandin F1α restored arteries to their previous state. Further administration of oxytocin in presence of V1a receptor antagonist showed no detectable vasorelaxation. Experiments conducted on kidneys extracted from Brattleboro rats also showed vasoconstriction occurring after oxytocin administration, which was reversed by administration of V1a vasopressin, but not oxytocin receptor antagonist. Total constriction levels were lower, compared to those measured in Sprague-Dawley rats. Vasopressin has also caused vasoconstriction in Brattleboro rats. Administration of vasopressin antagonists attenuated response to vasopressin, which proved to be more successful than oxytocin with similar concentration; EC50 ratio for vasopressin was around 200 times lower than EC50 for oxytocin.

Findings of Loichot et al. [5] show that oxytocin can induce vasoconstriction on isolated kidneys with no observable vasodilatation effects, and this is a consequence of partial agonist activity of oxytocin on V1a receptors.
Studies by Huang et al. [9], in tests performed on rats, provide experimental data to confirm the connection which oxytocin has with the renin-angiotensin-aldosterone system. Oxytocin was administered at doses corresponding to physiological secretion in 24 h water deprivation (25 ng/kg/h) or hypotension (125 ng/kg/h) and this first dose did not alter plasma renin concentration significantly. Application of a much higher dose of oxytocin at 125 ng/kg/h caused two-fold increase in plasma renin activity (PRA). This effect was blocked by introducing oxytocin receptor antagonist, unable to regulate its PRA. Injection of nadolol (β-adrenergic receptor) reduced PRA and prevented any effects which the oxytocin might have had on renin secretion.

Experiments conducted by Huang et al. [9] confirm that concentration and activity of plasma renin is increased by introducing oxytocin in physiological levels of conscious rats. Renin secretion induced by oxytocin, has led Huang et al. to believe that effects of oxytocin on PRC were mainly due to secretion of cathcholamines and not direct interaction between oxytocin and cells found in macula densa itself.

Moreover oxytocin also affects kidney function through ANP. Gutkowska et al. [11] and Haanwinckel et al. [10] provide data which confirms this phenomenon. Studies undertaken by Haanwinckel et al. were performed on water-loaded Wistar rats exhibiting dose-dependent increase in sodium and potassium excretion, as well as increase in urine osmolality and decrease in urine output after oxytocin injection. Haanwinckel et al. have concluded that oxytocin could cause an increase in natriuresis, kaliuresis and urine osmolality, through inducing release of ANP. Whereas Gutkowska et al. have identified oxytocin receptors in both atria and ventricles of the heart. Experiments conducted on isolated perfused hearts confirm that oxytocin administration can cause increase in ANP excretion. This effect can be stopped by administration of oxytocin receptor antagonist. Interestingly, oxytocin has also been found to synthesize in the heart itself [11]. Gutkowska et al. have provided data confirming the hypothesis by Haanwinckel et al. stating that secretion of Na and K is possibly a consequence of ANP activity.

Effects of oxytocin on food intake and body weight

Obesity is a significant and complicated medical problem [14], with not yet fully understood psychobiological and hormonal background. Leptin, ghrelin and insulin have been identified to significantly affect energy metabolism and body weight [15]. Moreover, oxytocin has also been proven to affect food consumption [16]. Maejima et al. [16] studied effects of acute and chronic exposure of oxytocin on mice. Single intraperitoneal injection of oxytocin in doses 200 μg/kg and 400 μg/kg caused suppression of food intake lasting from 0.5 to 6 hours afterwards. Moreover, the higher the doses had been given, the more they affected various parts of the brain and its activity (measured by c-Fos expression). Such phenomenon was observed in the areas such as paraventricular nucleus, arcuate nucleus, locus coeruleus, nucleus tractus solitaries, dorsal motor nucleus of vagus nerve and area postrema. However, subcutaneous injection of oxytocin at 1600 μg/kg caused a significant decrease in amount of food being ingested by mice fed standard diet, as well as those fed high fat diet. Daily injections of the same dose of oxytocin for 17 days caused decrease in amount of food ingested by mice being fed high fat diet. This effect lasted for up to 6 subsequent days. From the 7th day no significant differences were observed in volume of consumed food between high fat diet mice and the control group. One of the most noticeable consequences of oxytocin injections was a considerable weight loss in mice within the first 9 days. Thereafter, their weight stabilised at lower than previous levels, with a decrease of 3.6% on average. Weight of mice had not changed significantly until day 17, when the oxytocin injections were switched to vehicle injections. From day 17 to 26 a significant increase in mice’s body weight could be observed. On the other hand, chronic application of oxytocin by osmotic minipumps in doses of 1600 μg/kg/day caused a 13% decrease in mice’s body weight with decreased amount of food being consumed for the first 6 days. Based on observed changes in brain activity, Maejima et al. [16] have proposed two pathways which could enable oxytocin to exert its anorectic capabilities, the first being a direct interaction between oxytocin and arcuate nucleus, and the latter including vagal efferent pathway terminating in nucleus tractus solitarius. While both pathways and their characteristics are theoretically possible, the exact mechanisms in which oxytocin may induce anorexia are not yet clear.

Oxytocin and adipose tissue interaction

Excessive volume of visceral fat is associated with hyperinsulinemia, hyperlipidemia and lowered HDL cholesterol fraction – all of which promote development of atherosclerosis [14]. Moreover, size of adipocytes has been associated with insulin resistance and elevated risk of type 2 diabetes mellitus. Oxytocin turns out to be significant factor when it comes to both volume of adipose tissue and size of adipocytes [16-17].
In Maejima et al. studies [16], reduction of food intake was associated with a decrease of abdominal fat mass after prolonged administration of oxytocin. After 14 days of oxytocin application in 1600 μg/kg/day dose, animals were dissected and examined. Wet weigh of fatty tissue, epidymal fat and visceral fat in cross section areas were all found to be lower in a group treated with oxytocin. Furthermore, adipocytes were found to be smaller in size, both in visceral and epidymal fat.

Research undertaken by Eckertova et al. [17] provides detailed information on oxytocin influence on adipocytes. Adult male Wistar rats were subjected to 14 day oxytocin treatment in dose of 3600 μg/100 g/day via osmotic minipump. Relative and absolute mass of fat was not affected significantly by oxytocin treatment. Epididymal adipose tissue showed increased protein content as well as decreased diameter of adipocytes. There was a significant increase of adipogenesis markers in group treated with oxytocin, those markers included: adipocyte fatty acid binding protein (FABP4), peroxisome proliferator activated receptor γ (PPARγ), insulin sensitive glucose transporter 4 (GLUT4) and leptin. An increase in expression of platlet endothelial cell adhesion molecule (CD31) and eucaryota elongation factor (eEF2) was also observed. Oxytocin exerts positive effect on remodelling and growth of white fatty tissue metabolism. Adipocites show increased protein synthesis due to dephosphorylation of eEF2 after oxytocin administration. There is an apparent negative correlation between measured concentration of oxytocin and size of adipocytes. Increased number of small adipocytes is mainly a consequence of PPARγ expression instigated by oxytocin. A rise in CD31 expression suggests increased angiogenesis caused by oxytocin. Consequently, retroperitoneal fatty tissue is less sensitive to oxytocin than epididymal tissue.

Effects of oxytocin on liver metabolism

Oxytocin turns out to be an effective agent in regulating glycogen levels in hepatocytes, as it was proved by Ariño et al. [18]. In hepatocytes isolated from rats, oxytocin caused a dose dependent decrease in glycogen synthase activity, with maximal effectiveness at 1 μM concentration and half maximal at 0.1 μM. Meanwhile, when the time scale was being considered, there was a noticeable drop in synthase activity commencing 2 minutes after application, with the most significant effect achieved 8 minutes after administration. Subsequently, a slight increase in synthase was observed within 25 minutes of oxytocin application. This was then followed by inactivation of glycogen synthase which was correlated with about three-fold increase in phosphorylated form of the enzyme. These effects were abolished by absence of Ca²⁺ ions and partly alleviated by adding insulin. Glycogen phosphorylase activity was greater when oxytocin was added to the medium and the highest activity was observed 2 minutes after administration of 1 μM oxytocin.

Ariño et al. [18] proved that oxytocin does inhibit glycogen synthase activity, however they also noted that oxytocin was 100-times less potent in doing so than either vasopressin or angiotensin II.

Maejima et al. [16] were the first to distinguish that oxytocin significantly improves fatty liver in high fat diet being fed to obese mice. Although oxytocin does affect liver metabolism, the exact cause of this improvement is unknown.

Oxytocin in pancreatic hormone secretion

Diabetes is a growing medical concern and its importance is rising globally. Impaired control of blood glucose levels puts individuals at risk of succumbing to a wide range of diseases. Although there are many complex factors underlying type 2 diabetes, a general consensus is that it is mainly connected to obesity, metabolic syndrome and impaired glucose tolerance [19]. While oxytocin is rarely taken into consideration when discussing diabetes, it has been proven to interact with insulin [20] and glucagon [6] secretion.

Fujiiwara et al. [6] have studied effects of oxytocin and vasopressin on isolated pancreas islets from wild type mice and knockout mice unable to synthetize V1b vasopressin receptor. In wild type mice, arginine vasopressin caused a five-fold increase of glucagon secretion from isolated islets at concentration of 10⁻⁶ M. Exposing islets to oxytocin caused a six-fold increase at 10⁻⁷ M concentration. Antagonists were then added alongside oxytocin and vasopressin to determine which receptors had been involved. V1b vasopressin receptor antagonist at 10⁻⁶ M dose caused a 30% drop in glucagon secretion. Another of oxytocin receptor antagonist at 10⁻⁶ M resulted in a 45% drop of glucagon secretion induced by oxytocin. When both inhibitors had been added simultaneously the ratios of glucagon secretion fell to lower levels resulting in 57% fall for vasopressin and 69% fall for oxytocin.

Results from V1b receptor knockout were similar when oxytocin or vasopressin had been used without receptor blockers. 10⁻³ M of any of the hormones resulted in six-fold increase in glucagon secretion. Addition of
V1b vasopressin receptor antagonist did not change glucagon secretion in any way while oxytocin receptor antagonist might have decreased significantly if both hormones were added separately. Administration of both hormones at the same time caused a cumulative effect on glucagon secretion, reaching 10-12 times of baseline secretion rate for the wild type mice. No cumulative effects were observed for V1b knockout mice.

Fujiwara et al. [6] confirmed in their experiments that oxytocin and vasopressin could induce glucagon secretion through oxytocin and V1b vasopressin receptors with both hormones working on both receptor types.

In certain conditions oxytocin can induce insulin secretion as well, as experiments of Gao et al. prove [21].

Arginine vasopressin and oxytocin both caused a 10-fold increase of insulin secretion. However this could only be observed when isolated islets were perfused in medium containing glucose in 15 nM concentration. No change was observed in presence of glucose at a lower concentration (6, 9 and 10 nM). Both hormones used separately did not cause any change in 0.1 nM. Half maximal rise was observed at 2 nM and maximal reaction at 100 nM. When one of the hormones had been used at 100 nM, the other did not increase insulin secretion any further. However, in this scenario the release of insulin could still be greater if acetylcholine was added. Synthetic selective agonists of V1 vasopressin receptor ([Phe2,Orn5]-VT) and oxytocin receptor ([Thr4,Gly7]-OT) caused changes similar to their natural counterparts. Interference of the following receptor antagonists was then examined: [d(CH2)5,Tyr(Me)2]-AVP (regular V1 blocker), phenylacetyl-D-Tyr(Me)-Phe-Gln-Asn-Arg-Pro-Arg-Tyr-NH2 (highly selective V1 blocker), [d(CH2)5,Tyr(Me)5], Th4,TyrNH26-OVT (oxytocin receptor blocker). Response to Vasopressin was not affected by regular V1 blocker and oxytocin receptor blocker, and was reduced by highly selective V1 blocker. Synthetic selective agonist of V1 receptor action was blocked by selective V1 blocker and not affected by the other two. The action of Oxytocin and its synthetic analogue was blocked by highly selective V1 blocker and oxytocin receptor blocker and partiality inhibited by regular V1 blocker.

Gao et al. proposed two possible explanations of these findings. The first is a possible existence of a new type of receptor with binding properties similar to those in regular oxytocin receptor. The other is a possibility of coexistence of oxytocin receptors and V1a vasopressin receptors subtype in the pancreas [21]. Moreover in studies by Oshikawa et al. [22] RNA for oxytocin receptor was detected in mouse pancreatic islets.

**Oxytocin and Stress**

Chronic stress is a generally negative phenomenon. In animals and humans being exposed to stress over prolonged time it could contribute to development of various diseases, such as coronary heart disease [23] (cardiovascular disease [24]) and atherosclerosis [25]. Stress also negatively affects the hypothalamic-pituitary-adrenal axis causing its deregulation and thus reduction of the pro-inflammatory cytokine response to infectious agents. Although cortisol plays a significant role in stress response, there has been a number of recently conducted studies, which emphasise the importance of oxytocin in managing stress levels as well [24]. As Ondrejakova et al. research shows the main function of oxytocin as a cardioprotective hormone is its influence on the release of other hormones when experiencing stress. Chronic stressors increase oxytocin levels in the circulation, which in turn causes an activation of the hypothalamus-pituitary-adrenocortical axis. This effect manifests itself by elevated levels of plasma ACTH, corticosterone and enlarged adrenal glands [26]. Consequently, different stress stimuli can cause diverse increase in plasma oxytocin concentration [27].

Elevation of oxytocin levels does not result in proliferation of cardiac muscle cells and higher heart/body weight ratio is probably caused by myocardial cell hypertrophy (studies in rats). Rats pre-treated with oxytocin showed less reactivity to phenylephrine (α1-adrenergic agonist) and the rise of their blood pressure was significantly less pronounced [26].

Grewen et al. research shows direct interaction between oxytocin and magnitude of stress reaction. High levels of plasma oxytocin during stress decrease norepinephrine levels and reduce vasoconstriction and heart rate (this was observed in a woman who had just given birth, and continued for about six months after that) [27]. The relationship between oxytocin and its impact on the sympathetic nervous system can manifest itself in reduced levels of norepinephrine, as observed in women experiencing the support of their partners [5]. Stress responses can vary quite significantly, depending on the gender, for example the oxytocin levels are higher in women’s plasma after exposure to uncontrollable noise, but in men they do not change [27]. Furthermore, chronically elevated levels of oxytocin have no effect on the secretion of vasopressin, which as a similar peptide, may have similar physiological functions [26].

**Summary**

Variety and multiplicity of effects induced by oxytocin suggests that its role in physiology is not fully under-
stood (tab. 1). Further research is needed to fully determine its role in human body, as most of the experiments described above were conducted on rats and mice and until now, there is prove that comparable effects will have occurred in humans. G protein coupled receptors show a lot of differences in their structure and pathways when different species are being considered [1]. Oxytocin appears to have an association and influence on development and progress of various diseases, including: asthma [3]; obesity and fatty liver [16], hence the pharmacological use of that hormone or its analogues should be possible. So far, oxytocin has been used since 1980 to induce labour and to treat post-partum haemorrhage. Further pharmaceutical applications might be possible but will require further studies, as development of peptide drugs proves to be difficult in practice due to problems associated with bioavailability and production costs, as well as many other factors [1].

Nevertheless, the plethora of effects generated by oxytocin provides an array of research possibilities which should provide a broader understanding of its role.

### Table 1. Oxytocin effects in summary

<table>
<thead>
<tr>
<th>Tissue/organ/process</th>
<th>Receptor</th>
<th>Effect</th>
<th>Studies on</th>
<th>Ref.</th>
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<tr>
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<td>Tracheal rings, smooth muscle culture</td>
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<td>Increased AQP2 expression</td>
<td>Sprague Dewley rats</td>
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<td>Sprague Dewley rats isolated kidneys</td>
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<td>Increased renin secretion</td>
<td>Sprague Dewley rats</td>
<td>[9]</td>
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<td>Rats</td>
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