Vasopressin and oxytocin in normal reproduction and in the patophysiology of preterm labour and primary dysmenorrhoea. Development of receptor antagonists for therapeutic use in these conditions

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Abstract

Vasopressin and oxytocin are synthesised in the hypothalamus and released to the blood stream via the posterior lobe of the hypophysis. Research during later years has shown that these peptides are also produced in other parts of the brain. The secretion to plasma is stimulated by oestrogen, an effect which is counteracted by progestagen. During delivery the fetus can also produce substantial amounts of vasopressin and oxytocin. Additionally, the uterus itself may be a source of these hormones and we have recently found oxytocin mRNA in the endometrium of non-pregnant women with the highest levels around the time of ovulation.

In the onset of labour preterm and at term pregnancy vasopressin and oxytocin are centrally involved and in primary dysmenorrhoea the former hormone seems to play a key role in the mechanisms of increased contractions and reduced blood flow in the uterus of the condition. In women with the latter condition the plasma concentration of vasopressin is several-fold higher than that in healthy control persons. Both in pregnant and non-pregnant women the myometrium is activated via specific vasopressin V_{1a} and oxytocin receptors. This vasopressin receptor is different from the vasopressin V_{1b} receptor of the anterior lobe of the hypophysis, which is important in mood changes and V_2 receptor of the kidneys mediating fluid reabsorption. At the onset of labour preterm and at term the vasopressin V_{1a} and oxytocin receptors are elevated to a moderate degree. In non-pregnant women the receptor density varies over the menstrual cycle and increase markedly at the onset of menstruation. Substances, which block the uterine vasopressin V_{1a} and oxytocin receptors inhibit preterm labour and primary dysmenorrhoea.

Key words: vasopressin, oxytocin, receptors, antagonists.

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Introduction

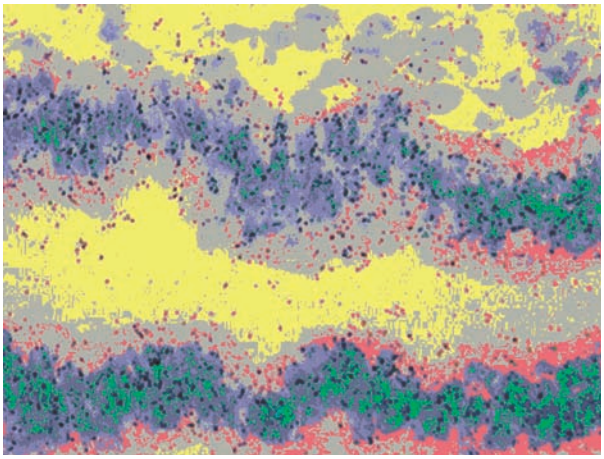
The importance of vasopressin and oxytocin as uterine stimulants has been studied extensively during recent years. Several important discoveries have been made and programs have started to develop antagonists to the uterine effect of these hormones. One of these antagonists, atosiban (Tractocile®, Ferring Pharmaceuticals, Denmark) has been registered for the treatment of preterm labour. This overview will briefly summarise this research.

Synthesis and secretion of vasopressin and oxytocin

Vasopressin and oxytocin are synthesised in the hypothalamus and released to the blood via the posterior lobe of the pituitary. Neurones containing these peptides have also been demonstrated in other parts of the brain than the hypothalamus [1]. The secretion to the blood stream of vasopressin and oxytocin in non-pregnant women is stimulated by oestrogen, an effect which is counteracted by progesterone [2-4]. The level of ovarian hormones also influences osmotically-induced release of vasopressin and oxytocin [5].

During the stress of labour the fetus produces vasopressin and oxytocin in substantial amounts [6]. Other fetal sources than the brain also probably exist, since circulating vasopressin and oxytocin have been demonstrated in anencephalic foetuses [7].

Figure 1. **Illustration of oxytocin mRNA detection (dots) by in situ hybridisation in endometrial gland of a non-pregnant woman at the time of ovulation**



Vasopressin and oxytocin are possibly also synthesised in the uterus itself. Immunoreactive vasopressin and oxytocin have been demonstrated in the non-pregnant human uterus, in particularly in cervical part of the isthmus [8]. These peptides have also been demonstrated in human follicular fluid, a finding indicating that the hormone is of importance for ovulation [9]. During human pregnancy immunoreactive vasopressin and oxytocin have been demonstrated in the myometrium [10]. There are also signs of formation of oxytocin in the placenta, fotal membranes and decidua in the human and the rat [11-13]. Recently, our group has demonstrated oxytocin mRNA in the endometrium of non-pregnant women by in situ hybridisation (*Fig. 1*) and real time PCR [14]. The amount of oxytocin in the endometrium seems to vary during the menstrual cycle, reaching the highest level around time of ovulation [14]. It is, however, unclear if oxytocin is released from uterine and foetal sites in amounts sufficiently high to have physiological and/or patophysiological effects.

Importance of vasopressin and oxytocin in activation of the uterus – effect of receptor-blocking substances

Pregnant uterus

Circulating vasopressin could play a role in the onset and regulation of human labour, but data regarding this is limited [15]. Oxytocin has since long been ascribed a major involvement in mechanisms of labour, both preterm and at term pregnancy. It is not established that the onset of labour is caused by increased plasma concentrations of oxytocin [16,17]. An importance of increased plasma concentration is supported by the finding that oxytocin is released in a pulsatile manner and that the frequency of pulses is increased as labour progresses [18]. A nocturnal peak in plasma concentration of oxytocin paralleling increased uterine activity has also been demonstrated [19]. However, women with diabetes insidipus usually have normal labour, even those who almost lack oxytocin [20].

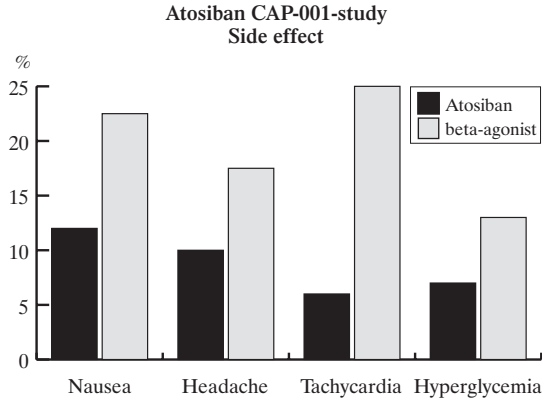
The pregnant uterus contains receptors for vasopressin and oxytocin [21,22]. Three different types of vasopressin receptors have been demonstrated, V_{1a} V_{1b} and V_2 receptors, whereas oxytocin only has one type of receptor. The vasopressin V_{1a} receptor is distinctly different from the receptor of V_2 type, which regulates kidney function and the V_{1b} receptor of the anterior pituitary. Results from studies of receptor binding indicate that vasopressin in the myometrium acts both over its own receptor, V_{1a}, and to some extent of the oxytocin receptor [23]. Oxytocin on the other hand acts mainly over the oxytocin receptor, but activates the myometrium also to some extent via the vasopressin V_{1a} receptor [23]. The effect of vasopressin in the pregnant uterus is somewhat more pronounced than that of oxytocin and the same relation exists also regarding the number of binding sites for the two peptides [22].

A markedly increased number of oxytocin receptors in the uterus was previously believed to be the mechanism initiating labour preterm and at term pregnancy [24]. More recent studies have only shown a tendency to an increase in protein and mRNA for the oxytocin receptor in connection with the onset of labour [21,22,25]. Neither are there any firm proofs for a substantial upregulation of the vasopressin V_{1a} receptor at the onset of labour [22,26]. However, individual myometrial cells can show great heterogenocity and rapid changes in their expression of oxytocin receptor at the onset of labour [27]. Spontaneous contractions in vitro of human myometrium anyhow seem to be dependent on the oxytocin receptor [28]. The difficulty to confirm an importance of increased plasma levels of vasopressin and oxytocin or elevated receptor density in the myometrium at the onset of labour suggests that also other mechanisms may be involved. A local synthesis in the uterus with paracrine effect could be such a mechanism.

The importance of vasopressin and oxytocin for the initiation of labour preterm is confirmed by the therapeutic effect in this condition of an antagonist to the oxytocin and vasopressin V_{1a} receptor, atosiban [29,30]. This substance was discovered and developed by author of this survey together with scientists at Ferring AB in Malmö, Sweden. Atosiban has been shown to be at least as effective in postponing delivery as the previously used treatment, β_2-adrenoceptor stimulating substances, but having far less side effects [31] (*Fig. 2*). The time when the uterus is relaxed can be used for treating the underlying cause of labour, which in many cases, e.g. urinary infection, can be eliminated [32].

The usefulness of blocking vasopressin V_{1a} and oxytocin receptors in preterm labour is confirmed by results from a newly completed study with the orally active antagonist SR 49059 [33]. A marked inhibition of labour was observed in patients receiving the compound, whereas contractions were more or less unchanged in a control group of women treated by placebo [33]. Comparative studies of the peptide substance atosiban and the non-peptide, steroid-shaped SR 49059 showed a similar receptor binding and inhibiting effect on isolated myometrium from pregnant women delivered preterm and at term pregnancy [23]. In non-pregnant volunteers a similar inhibitory effect on

Figure 2. **Side effects of atosiban and betamimetrics in a worldwide comparison involving 742 patients [31]. Three cases of pulmonary oedema also occurred at treatment by betamimetrics, but no such complication after atosiban**



vasopressin- and oxytocin-induced contractile activity was also observed [34,35].

Atosiban has a more pronounced antagonistic effect on the vasopressin V_{1a} than on the oxytocin receptor [36,37]. A new analogue has now been discovered, barusiban, which has an equal potency to that of atosiban in inhibiting oxytocin effects on myometrium from preterm and term pregnant women, but lacks effects on the vasopressin V_{1a} receptor [38,39]. This substance could be a valuable tool in elucidating the relative importance of vasopressin V_{1a} and oxytocin receptors for activating the human uterus preterm and at term pregnancy. Our group is also involved in testings in vitro and in vivo on healthy volunteers of new vasopressin V_{1a} and oxytocin antagonists, studies which could lead to important advances in the understanding of mechanisms activating the human uterus.

Non-pregnant uterus

Vasopressin is an important pathophysiological factor in the increased myometrial activity and reduced uterine blood flow of primary dysmenorrhoea [40]. Women with primary dysmenorrhoea have an increased plasma concentration of vasopressin [41-43]. Vasopressin activates the smooth muscle activity of myometrium and uterine arteries in non-pregnant women via vasopressin V_{1a} receptors and to some extent via oxytocin receptors [44]. The vasopressin V_{1a} receptor can possibly have two subfractions, one for activating in the myometrium and one for stimulating the smooth muscle of vessel walls [45]. Oxytocin is probably less important than vasopressin in non-pregnant condition, since the amount of oxytocin receptors in the myometrium and the effects of the peptide are both about five times lower than those of vasopressin [23,44]. A role of oxytocin also in non-pregnant condition is however supported by the finding of a high amount of oxytocin mRNA in endometrial glandular cells of non-pregnant women, particularly around the time of ovulation [14].

In studies of uterine arteries from non-pregnant women undergoing hysterectomy we found that the smallest arteries, the so called resistant vessels are the most sensitive ones [46,47]. Vasopressin is highly active on the vessels followed in order by endothelin, oxytocin and noradrenaline [46,47].

The etiological importance of vasopressin and oxytocin in primary dysmenorrhoea is confirmed by the therapeutic effect in this condition of substances, which block vasopressin V_{1a} and oxytocin receptors [48,49]. Both spontaneous and vasopressin-induced myometrial activity in dysmenorrheic women are inhibited by atosiban, in parallel to a decrease in experienced pain. We have also shown that an endoperoxin-2 agonist inhibits both spontaneous and vasopressin-induced contractile activity in women, an observation which could be of therapeutical importance [50].

Conclusions

Preterm labour is the most therapeutic importance of preneonatal mortality and morbidity. Vasopressin and oxytocin seem to play key roles in this condition, the hormones being synthesised in the hypothalamus, by the fetus and, at least regarding oxytocin, in the uterus itself. The hormones stimulate contractions via vasopressin V_{1a} and oxytocin receptors, which may be upregulated to some extent in connection with onset of contractions. Receptor blocking substances may stop preterm labour contractions and the invention of atosiban has been a milestone in the treatment. However, preterm labour has several aetiologies and specific therapies have to be designed.

Menstrual pain is a problem in up to 50% of all non-pregnant women who have not had any children and in 10% they have to be absent from school or work because of pronounced symptoms. Vasopressin secretion is markedly elevated in primary dysmenorrhoea and the uterus is extremely sensitive to this hormone, much more than to oxytocin. Vasopressin V_{1a} and oxytocin receptor blocking agents may have a therapeutic potential also in this condition.

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