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REVIEW

Oxytocin and vasopressin V_{1A} receptors as new therapeutic targets in assisted reproduction

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Abstract Embryo transfer, the final stage of IVF/embryo transfer (IVF/ET) treatment, independently influences treatment outcome. Successful embryo implantation following embryo transfer, among other factors, is also dependant on uterine receptivity. Uterine contractile activity may adversely affect the implantation. Although increased contractions have been found in approximately 30% of patients undergoing embryo transfer, to date it has not been a subject to any diagnosis or therapy. Pharmacological tocolytics may be expected to improve pregnancy rates; however, targeting uterine adrenergic receptors, calcium channels or prostaglandin synthesis has since proven ineffective. The novel class of drugs which could be the most useful in this indication is oxytocin antagonists. In animal models, oxytocin significantly reduced embryo implantation rates, and this was reversed by an oxytocin antagonist. In humans, peptidyl oxytocin and mixed vasopressin V_{1A}/oxytocin antagonists have been found to significantly reduce uterine contractions in egg donors undergoing mock embryo transfer. It has further been demonstrated that the vasopressin V_{1A}/oxytocin receptor antagonist atosiban can improve pregnancy success in patients with recurrent IVF failures. This article reviews the uterine oxytocin/vasopressin V_{1A} receptor systems and their potential influence on embryo implantation. It is suggested that the clinical application of oxytocin antagonists might improve results of IVF/ET treatment.

KEYWORDS: embryo implantation, embryo transfer, oxytocin antagonist, vasopressin V_{1A} antagonist

Introduction

In spite of spectacular progress in assisted reproduction technology over the past 20 years, the overall effectiveness of even the most advanced treatments such as IVF/embryo transfer (IVF/ET) is relatively low, averaging at about 30% live births per treatment cycle (Nyboe-Andersen et al., 2009). Embryo transfer is an independent factor affecting the outcome of the treatment (Tomas et al., 2002). The determinants of success of embryo transfer involve the quality of embryo(s) and uterine receptivity, the quality of the intrauterine environment (Cavagna and Mantese, 2003).

Uterine contractions constitute one of and the most fundamental components of uterine receptivity. Contractile

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activity of the uterus plays an important role in embryo implantation (Fanchin, 2009). Excessive uterine contractions may decrease implantation rates in IVF cycles as contractile activity might expel embryos from the uterus (Fanchin et al., 1998). Up to date, treatment strategies to reduce uterine contractions before embryo transfer such as the use of beta agonists or non-steroid anti-inflammatory drugs have not been shown to provide sufficient benefit (Bernabeu et al., 2006; Moon et al., 2004; Tsirigotis et al., 2000).

Oxytocin and vasopressin V_{1A} antagonists represent a novel class of drugs developed for patients experiencing threatened premature birth. Their effectiveness and favourable safety profile make them an attractive alternative in this indication. A reduction of uterine contractions occur with a decrease in intrauterine production of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and improvement of uterine blood supply, both of which could be potentially beneficial for embryo implantation. This paper presents a review of what is known about the application of oxytocin/vasopressin V_{1A} antagonists for implantation support in assisted reproduction.

Oxytocin, vasopressin and their receptors

Oxytocin and vasopressin are closely related nonapeptides synthesized in the neurohypophysis and in the periphery, both having receptors in the uterus. Oxytocin receptors (OTR) have been found in ovary, testis, blood vessels, heart myocytes, pancreas and kidney as well as on several types of cancer cells (Cassoni et al., 2006; Gimpl and Fahrenholz, 2001; Zingg, 2000). Oxytocin itself is an important mediator in the central nervous system, with significant roles in maternal, sexual and social behaviour (Pedersen and Boccia, 2006). Vasopressin mediates its effects via several subtypes of receptors, of which the V_{1A} subtype is found in the uterus, being responsible for contractile responses. V_{1A} receptors are also found in vascular smooth muscle cells, platelets and hepatocytes where they mediate contraction, proliferation, hypertrophy of cells and platelet aggregation (Thibonnier et al., 1994; Tsukada et al., 2005).

Oxytocin and V_{1A} vasopressin receptors share similar structures as they both belong to the class I family of G-coupled receptors (Zingg, 2000). Binding stimulates phospholipase C activity, which releases triphosphoinositol and diacyloglycerol, inducing mobilization of intracellular calcium. Calcium triggers phosphorylation of light myosin chains, which in turn promotes contractile activity (Mackenzie et al., 1990). In myometrial cells, activation of OTR also leads to phosphorylation and activation of mitogen-activated protein kinase (Nohara et al., 1996; Ohmichi et al., 1995), which mediates an increase in cyclooxygenase-2 production (Molnar et al., 1999), which further enhances uterine contractions.

Oxytocin evokes the calcium influx through receptor-coupled calcium channels which are independent from nifedipine (Sanborn et al., 1998). Braileanu et al. (2001) have demonstrated that vasopressin acting through V_{1A} receptors also increases phospholipase C activity, although an associated increase in intracellular calcium has not been demonstrated.

In the uterus, oxytocin remains closely associated with another strong uterotonin, $PGF_{2\alpha}$ (Duras et al., 2005; Silvia et al., 1994). In endometrial stromal and glandular cells, oxytocin enhances the secretion of $PGF_{2\alpha}$ (Braileanu et al., 2001; Stormshak, 2003; Uzumcu et al., 1998, 2000). It was shown that oxytocin also increases the expression of $PGF_{2\alpha}$ receptor (Liang et al., 2008). However, there is no consensus regarding the influence of vasopressin on the $PGF_{2\alpha}$ system and published data is conflicting (Braileanu et al., 2001; Ludwig et al., 1998; Whiteaker et al., 1994).

Oxytocin is locally synthesized in the endometrium and in fetal membranes where it stimulates uterine contractions (Chibbar et al., 1993, European Atosiban Study Group, 2001; Lefebvre et al., 1992). This occurs through action on its own receptors and by increasing $PGF_{2\alpha}$ synthesis (Flint et al., 1986; Smith and Kelly, 1988; Steinwall et al., 2004b). In the animal model, the administration of oxytocin stimulates uterine $PGF_{2\alpha}$ expression and leads to a reduction in endometrial blood supply as well as a reduced embryonic survival rate (Lemaster et al., 1999; Seals et al., 1998). In non-pregnant conditions it seems likely that endometrium-derived oxytocin acts on the most adjacent, subendometrial zone of uterine muscle (Bossmar et al., 1995; Lesny et al., 1999b; Steinwall et al., 2004b).

Synthesis of oxytocin is strongly influenced by oestradiol (Chibbar et al., 1995). Oxytocin and vasopressin plasma concentrations increase during the follicular phase, reaching the maximum around the time of ovulation while they decrease during the luteal phase (Amico et al., 1981; Salonia et al., 2005; Shukovski et al., 1989). Oxytocin mRNA in the endometrium follows a similar pattern and also reaches its maximum in the mid-cycle phase (Steinwall et al., 2004b). A relative increase in oestradiol concentrations stimulates the synthesis of oxytocin receptors in the myometrium before labour (Giussani et al., 1996; Mecenas et al., 1996). As demonstrated by Kimura et al. (1996), there is a 300-fold increase in the production of OTR mRNA in pregnant myometrium near term. Expression of vasopressin V_{1A} receptors and concentrations of vasopressin do not seem to be affected by steroids and are not altered in pregnancy (Bossmar et al., 2007; Maggi et al., 1991, 1992; Wing et al., 2006).

Both oxytocin and vasopressin are involved in induction and maintenance of uterine contractions during labour (Akerlund, 2002). Vasopressin may also be involved in the pathogenesis of dysmenorrhoea (Akerlund, 2002; Liedman et al., 2008). Similarities between oxytocin, vasopressin and their receptors may explain cross reactivity of oxytocin to V_{1A} receptors. It has been shown that oxytocin may still exert its actions even when OTR are blocked, through action upon the V_{1A} receptors (Akerlund et al., 1999).

To some extent, the endocrine situation, oxytocin receptor status and resulting increased excitability of the uterus during the very last days of ovarian stimulation in IVF treatment might resemble those seen before the onset of labour. Treatment cycles induce an abundant increase in oestradiol concentrations which are about 10—20 nmol/l at the end of ovarian stimulation as compared with less then 2 nmol/l before the ovulation in the natural cycle (Ayoubi et al., 2003). Supraphysiological concentrations of oestradiol are expected to induce local (endometrial) production of oxytocin, formation of oxytocin receptors, and — indirectly — formation/release of $PGF_{2\alpha}$ (Liedman et al., 2008; Richter et al., 2004), which is in fact similar to the prelabour status.