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ADVANCES IN THE ROLE OF OXYTOCIN RECEPTORS IN HUMAN PARTURITION

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ABSTRACT

Oxytocin (OT) is a neurohypophysial hormone which has been found to play a central role in the regulation of human parturition. The most established role of oxytocin/oxytocin receptor (OT/OTR) system in human parturition is the initiation of uterine contractions, however, recent evidence have demonstrated that it may have a more complex role including initiation of inflammation, regulation of miRNA expression, as well as mediation of other non-classical oxytocin actions via receptor crosstalk with other G protein-coupled receptors (GPCRs). In this review we highlight both established and newly emerging roles of OT/OTR system in human parturition and discuss the expanding potential for OTRs as pharmacological targets in the management of term and preterm labour.

HIGHLIGHTS:

- Role of OT/OTR system in parturition exceeds the initiation of uterine contractions
- OT can trigger inflammation and regulation of miRNAs
- Ligand-specific OTR/G-protein coupling can result in differential downstream signalling
- Dimerisation/Oligomerisation of OTR and subsequent receptor crosstalk introduces novel strategies for the development of combination tocolytics
- OTR could be used as a target for utero-specific tocolytic drug delivery

KEY WORDS:

Oxytocin receptor; Parturition; Uterine contractions; Inflammation; miRNA; GPCR dimerization

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1. Introduction

Oxytocin (OT) is a nonapeptide hormone, initially discovered by Sir Henry Dale in 1906 when it was noted that the extracts of human posterior pituitary gland had the ability to induce uterine contractions of a pregnant cat. It was named oxytocin from the Greek words *oxus* and *tokos* meaning sharp and childbirth, respectively [1]. Thus OT was soon introduced into clinical practice as a uterotonin to stimulate labour within 1940s [2]. In 1953, OT was sequenced and synthesised by Vincent du Vigneaud [3], and the gene was cloned 30 years later [4]. In mammals, it has been established that OT is synthesized in the magnocellular neurons of the paraventricular (PVN) and supraoptic (SON) nuclei of the hypothalamus [5]. The produced peptide is then transported down the axons of the posterior pituitary gland where it is released to modulate its function. Moreover, OT has been found to be synthesised locally in humans to contribute to the processes of labour [6].

There is only one type of oxytocin receptor (OTR) identified to date, which belongs to the rhodopsin-type (class I) G protein-coupled receptor (GPCR) family. Similar to other GPCRs, activation of OTR drives conformational changes in the relative orientation of the transmembrane domains to enable G protein binding. On the basis of the amino acid sequence, the molecular mass of OTR can be calculated to be ~40-45 kDa. However, previous studies in guinea pig myometrial membranes identified OTR as a 68- to 80-kDa protein [7], and photoaffinity labelling experiments in rat mammary gland and rabbit amnion cells found OTR to be 65 kDa [8, 9]. Such discrepancy in the molecular mass of OTR in various tissues may be due to their differential glycosylation patterns, with each glycosylation core accounting for approximately 10 kDa. OTR has been found to have two or three putative N-glycosylation sites depending on the species. Despite the differential glycosylation patterns, OTR expression, ligand binding affinity, and its function are not affected as recombinant deglycosylation mutants of OTR showed unaltered functional properties [10].

Oxytocin/Oxytocin receptor (OT/OTR) system can drive central as well as peripheral actions with a plethora of roles in both physiological and pathological processes, including reproduction/parturition, maternal behaviour, social behaviour, lactation, erectile dysfunction and ejaculation. Traditionally, OT/OTR has been considered to play a significant role in the myometrium during pregnancy and in labour. The most established effect of OT/OTR is the initiation of uterine contractions but it has been found to influence prostaglandin (PG) synthesis in other gestational tissues such as the decidua, amnion, and chorion.

Knowledge of G protein-coupled receptors (GPCRs) continues to evolve, and the diversity of their actions and the complexity of their signalling mechanisms are becoming increasingly evident. OT/OTR biology appears to be no exception. This review summarizes the knowledge surrounding the role of OT/OTR in parturition, with special emphasis on the recent advances, and highlights specific issues that warrant further investigation.

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2. Previously established roles of OT/OTR system

There is conflicting evidence for the role OT in the initiation of parturition [11]. The key prolabour responses induced by OT are indistinguishable to that of normal spontaneous labour and OT is one of the strongest uterotonins available to stimulate uterine contractions for labour induction or augmentation. Moreover, there is significant increase in uterine sensitivity to OT via upregulation of OTR in both rats and humans during the onset of labour [12-14]. Additionally studies in rats [15-17], non-human primates [18-20] and in humans [21, 22] reported that OT antagonists can inhibit late gestational uterine contractions and the process of parturition. The role of OT varies between different animal species. Although in rodents, OT is believed to play a significant role in the initiation and maintenance of parturition [13, 23], in humans, circulating OT does not seem to be essential for the initiation and maintenance of labour [24]. Normal parturition has been observed in the absence of OT in mice [24] as well as in cases of clinical pituitary gland dysfunction [25] and the concentrations of maternal or fetal OT does not increase with the onset of or during labour [26].

A hypothesis proposed to explain the absence of OT increase in humans during labour was that it is not the peripheral OT but a local OT synthesis that initiates labour. In 1993, mRNA of OT was isolated in human uterine tissues in late gestation [27]. A semi-quantification analysis revealed that OT mRNA is principally localised/or identified in decidua but also found in the chorion and amnion. Interestingly, significantly greater concentrations of OT mRNA were detected in the chorio-decidua after spontaneous onset of labour (at the expulsive stage of parturition) compared to before the onset of labour at term [27-29]. Post labour chorio-decidua samples showed similar levels of OT mRNA to that of spontaneous labour, indicating the maximal level of gene expression. These findings demonstrate that localised synthesis of OT increases around the time of labour onset, and play a role in the physiology of human labour.

Moreover, the uterine sensitivity to OT markedly increases at the onset of labour. This is associated with an upregulation of OTR mRNA levels and a strong increase in the density of myometrial OTRs reaching a peak during early labour [30]. This was first described in rats [13], and subsequently demonstrated in rabbits and humans [12, 31]. In both species, OTRs are present in the endometrium as well as the myometrium, chorio-decidua and amnion [12, 32]. This increase in OTR is one of the most consistent findings in the study of parturition in several species, which introduces the possibility that changes in the expression or the function of the OTRs are important for the onset of labour. In addition, a more recent gene association study showed that maternal genetic variation such as single nucleotide polymorphisms (SNPs) in OTR coding region may be associated with gestational age-dependent susceptibility to preterm birth [33]. This finding is in line with the hypothesis that OTR has a significant role in the process of labour onset.

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The most established, and the longest known role of OT/OTR system in parturition is stimulation of uterine contractions. The uterus must contract and relax rhythmically to enable the propelling of the fetus into the vagina and delivery. Human myometrium comprises of smooth muscle cells arranged into bundles delineated by connective tissue and interspersed with microvasculature. Activation of OTR in the uterus triggers coupling of $G\alpha_{q/11}$ to phospholipase Cβ (PLCβ), which mediates the hydrolysis of phosphatidylinositol-4, 5-bisphosphate (PIP_2) to inositol-1, 4, 5-trisphosphate (IP_3) and diacylglycerol (DAG). Subsequently, these control the mobilisation of Ca^{2+} from the sarcoplasmic reticulum into the cytoplasm and the activation of protein kinase type C (PKC), respectively [34] (Figure 1). The increase in intracellular Ca^{2+} can lead to smooth muscle contractions via activation of Ca^{2+}-dependent calmodulin which triggers myosin light chain kinase (MLCK) activity. MLCK phosphorylates the regulatory myosin light chains and drives acto-myosin cross-bridge cycling and myometrial contractions [35] (Figure 1).

In addition to regulating smooth muscle contractility by electromechanical coupling, membrane potential independent, pharmacomechanical coupling can also be accounted for the physiological mechanisms that regulate contractions [36]. Activation of OTR in human myometrium can convert inactive RhoA-GDP to its active form, RhoA-GTP through guanine nucleotide exchange factors (GEFs) [37]. RhoA-GTP acts via Rho kinase (ROCK) to phosphorylate the regulatory subunit of MLC, leading to contractions. There have been records of RhoA and ROCK upregulation in human myometrium during pregnancy [38] and ROCK has been shown to mediate OT-induced myometrial contractions [39] (Figure 1). Another alternative (and parallel) pathway to induce myometrial contraction may be through activation of the enzyme CPI-17 by protein kinase C [40] (Figure 1).

3. Novel roles of OT/OTR system

3.1. Inflammation

Clinically, labour is defined by uterine contractions, however, there is growing evidence that this is preceded by carefully regulated biochemical changes in the gestational tissues including the fetal membranes (composed of amnion and chorion) [41]. Such changes involve NF-κB activation and inflammatory stimulation which triggers a cascade of pro-inflammatory signalling in both the myometrium and the amnion [42, 43], and lead to elevation of inflammatory cytokines/chemokines as well as PGs, particularly $PGF_{2\alpha}$ and PGE_2 [44]. Previous studies have shown that OT/OTR activation stimulate cytoplasmic phospholipase A_2 ($cPLA_2$) activity and induce COX-2 expression, the two major enzymes in PG synthetic pathway [45]. PG synthesis is one of the key steps involved in the onset of human labour [46]. Increased PG synthesis occurs first in the region overlying the cervix where it is thought to mediate cervical ripening and dilation. Mechanical stretch of human amnion epithelial cells has been shown to lead to the activation of AP-1 and NF-κB systems and in turn, increase COX-2 and PG expression [47]. PGs have been shown to play a role in placental separation

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[48], fetal membrane rupture by inducing matrix metalloproteinase (MMP) activity [49], and promoting myometrial contractility. $PGF_{2\alpha}$ induces contractions via electromechanical coupling and pharmacomechanical coupling, resembling that of OT-induced contractions [50]. Activation of decidua and OTRs induce PGF_{2a} release, which results in enhanced uterine contractions whilst driving cervical ripening and luteolysis. Inhibition of PG synthesis decreases the upregulation of OT binding sites as well as the effect of OT on promoting myometrial contractions [41].

In addition to stimulating PG synthesis, recent study has shown a novel inflammatory role of OT/OTR, where it acts as an endogenous inflammatory mediator in human gestational tissues by inducing cytokine/chemokine release via tissue-specific activation of NF-κB and mitogen-activated protein kinases (MAPKs) [51]. In myometrium, OT/OTR activates the established canonical pathway involving p65/p50 heterodimers with no crosstalk between NF-κB and MAPKs whereas in amnion, NF-κB activation involves only p65 homodimer nuclear translocation and this is dependent on crosstalk with MAPKs.

The OTR-G protein coupling in human myometrium is well described and OTR has been shown to couple with both $G_{\alpha q/11}$ and $G_{\alpha i}$ to collectively regulate diverse cellular functions through complex signalling pathways [52]. In human amnion, OTR was found to initiate its pro-inflammatory signal transduction via $G_{\alpha i}$ -dependent signalling [53], whilst mainly $G_{\alpha q/11}$ coupling has been found to be involved in OT-induced myometrial contractions [52]. Recent findings show ligand-dependent discrimination of G protein family subtypes [54]. It has been suggested that binding of OTR-antagonist, Atosiban, to myometrial OTR drive anti-labour signalling in the myometrium through inhibition of $G_{\alpha q/11}$ -dependent OT-mediated contractions but initiate pro-labour signalling in the amnion via $G_{\alpha i}$, resulting in activation of inflammation [53] (Figure 2). Collectively, these findings highlight the importance in considering the dual role of OT/OTR in stimulation of inflammation and onset of uterine contractions and the effects of differential G protein coupling of OTR in the management of preterm labour.

3.2. miRNA regulation

MicroRNAs (miRNAs) are small, single-stranded, non-coding RNAs of 19-25 nucleotides in length. They function in a manner similar to small-interfering RNAs to down-regulate gene expression by regulating mRNA stability and transcription. There has been increasing evidence highlighting the role for miRNAs in vascular smooth muscle as well as in female reproductive tissues, where they have been shown to be associated with differentiation, proliferation and embryo implantation [55-57]. More recently, miRNAs have been implicated in hormone responsiveness and the regulation of key gene expression pathways involved in parturition [58]. Enquobahrie *et al.* reported a distinct group of miRNAs, such as hsa-miR-199a-3p, -202-5p, and -214-3p, differentially expressed in human fetal membranes in term labouring samples [59].

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A recent study in human myometrium has identified a miRNA 'fingerprint' in term labouring samples that is different to those following exogenous oxytocin administration [60]. This illustrated a unique profile different to that observed in samples from spontaneous labour. Activation of OTR via exogenous OT administration contributes to the onset of labour by regulating the expression of miRNAs, hsa-miR-146a-5p, -196a-3p, -876-5p, and -146b-3p [60]. While further work is required to define the exact biological significance of these changes, *in silico* miRTarBase platform analysis indicates that hsa-miR-146a-5p and hsa-miR-146b-3p regulate NF-κB activity and could reduce expression of NF-κB-regulated genes including the key labour-associated genes IL-8, IL-6 and MMP9 [61-63]. Consistent with this, hsa-miR-146a-5p was found to attenuate the expression of α-smooth muscle actin, the major protein constituent of uterine smooth muscle and essential component of the contractile machinery in human dermal fibroblasts [64].

MiRNAs have not only been implicated in the OT/OTR-induced labouring phenotype, but also to increase the myometrial sensitivity to OT. Renthal *et al.* found that the miR-200 family of miRNAs is upregulated in the labouring murine and human myometrium at term. The family of miR-200 was found to be associated with labour by modulating the expression of the two critical contraction-associated proteins including connexin-43 (CX-43) and OTR via ZEB1 and ZEB2 [65], thus preparing the myometrium for contractions and enhancing the myometrial sensitivity to OT. There is also an increasing interest in the miR-200 family in relation to cancer prognosis and treatment. Changes in miR-200 expression have been reported in multiple types of cancers including pancreatic [66], prostate [67], breast [68] and ovarian cancer [69]. Down-regulation of miR-200 as a result of DNA methylation at miR-200 promoter region and transcription factors such as ZEB1 and ZEB2 have been shown to be involved in cancer development and progression [70]. Therefore, induction of miR-200 expression has become a strategy for potential cancer therapy. Recently, a miR-based drug, tetraindole SK228, which induces miR-200c, has been shown to reduce breast cancer growth *in vivo* [71], further supporting the development of miR-based drugs for therapeutic purposes.

3.3. Receptor crosstalk

Functional GPCR crosstalk can occur in multiple different ways (Figure 3). GPCRs can have integrated cellular signals with or without physical interaction at the receptor level [72]. There have been increasing number of reports on GPCR dimerization over the past decade and OTR is not an exception. In membrane fractions of mammary glands from lactating rats, OTR was found to form homodimers and even oligomers [73], however, the relevance of homodimerization is still under debate as both would drive the same intracellular signalling pathways [74]. It has been suggested that binding of one OT peptide to its receptor would reduce the affinity of another ligand binding to the second receptor (negative cooperative binding) [73] (Figure 3). Differences in the downstream G protein coupling and signalling pathways between the monomers and dimers have not yet been

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described. Several heterodimer combinations have been reported to occur including $V_{1a}R$/OTR, V_2R/OTR, β-adrenergic receptor/OTR, and PG receptor/OTR [75, 76]. The functional significance of GPCR heterodimerization varies; some GPCRs require dimerization with a specific partner to achieve functional activity, some do not require dimerization but may still exert crosstalk and mutual regulation between specific receptor subtypes, and others may completely alter their pharmacological properties of the associated receptors via dimerization [77] (Figure 3). As GPCRs are highly desirable targets for therapeutic pharmaceuticals, it is important to investigate any GPCR dimerizations that may have clinical significance.

3.3.1. OTR/AVPR

Arginine vasopressin (AVP) is a cyclic neurohypophysial petide which is structurally very similar to OT with only two amino acid differences (in positions 3 and 8). Similar to OT, AVP also signals through GPCRs, $V_{1a}R$, $V_{1b}R$ and V_2R, which have high homology to OTR. Due to the structural similarity of the ligands and the high sequence homology of the receptors, there are some cross-reactivity between them. Both *in vitro* and *in vivo* studies have demonstrated that OTR can form heterodimers with $V_{1a}R$ and V_2R [75]. AVP has been suggested to have a physiological role in the myometrium as it can induce uterine contractions [78], and similar with OTR regulation, there are some studies that suggest increase in the density of V1aR during the later weeks of gestation and in preterm labour tissues [79, 80]. Therefore it may be hypothesized that OTR/$V_{1a}R$ or OTR/V_2R dimers have a functional role in the onset of labour. However, the precise physiological relevance of the OTR associations with both $V_{1a}R$ and V_2R remains to be determined.

3.3.2. OTR/β_2-Adrenergic receptor

Human myometrium expresses both GPCRs, OTR and β_2-adrenergic receptor (β_2-AR), which play opposing roles in the regulation of uterine contractions. OTR antagonists and β_2-AR agonists are currently used in clinical practice for the management of preterm labour. There have been previous studies that have shown a possible crosstalk between these two receptors where β_2-AR signalling altered OTR signalling in the myometrium [81, 82]. However, the details of such crosstalk have not been investigated. Despite the fact that the two receptors relay physiologically antagonistic effects, they have been found to activate a common intracellular signalling molecule, ERK1/2. ERK1/2 consists of p42 and p44 MAPKs. Upon activation via phosphorylation, MAPKs are able to mediate various different cellular processes including cell proliferation, differentiation and apoptosis. Specifically, ERK1/2 has been reported to play a role in the regulation of myometrial contractility, downstream prolabour expression as well as PG synthesis via activation and upregulation of PG synthetic enzymes, cytoplasmic phospholipase A_2 ($cPLA_2$) and COX-2 [83, 84]. The mechanism through which these receptors individually activate ERK1/2 is different. OTR can lead to ERK1/2 activation via multiple mechanisms; OTR couples mainly with $G_{\alpha q/11}$ to activate PLC and trigger a

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calcium response which in turn activates ERK1/2, whereas coupling with $G_{\alpha i}$ can result in ERK1/2 phosphorylation via PKC and $G_{\alpha i}$ - $G_{\beta\gamma}$ pathways, and OTR interaction with the scaffolding protein β-arrestin can initiate ERK1/2 activation [85, 86]. Unlike OTR, β_2-AR-mediated ERK1/2 activation has been shown to involve $G_{\beta\gamma}$ subunits, via a Ras-dependent or $G_{\alpha s}$ -PKA-dependent pathways [87]. Other studies have reported Src activation and β-arrestins to play a role in the stimulation of ERK1/2 [88, 89]. Wrzal *et al.* have recently demonstrated that OTR and β_2-AR interact physiologically and that β_2-AR requires interaction with OTR to activate ERK1/2 via PTX-sensitive, PKC-dependent pathway [90]. The fact that the ligands of OTR and β_2-AR modulate the downstream signalling of either partner receptor in human myometrial cells provided further evidence for OTR- β_2-AR crosstalk [76]. The significance of these receptor crosstalk on myometrial contractions is still unclear but further investigation can impact the development of future therapeutics.

3.3.3. OTR/FP receptor

The role of both OT and $PGF_{2\alpha}$ in inducing myometrial contractions has been well established and both their receptors have been popular targets for the development of new tocolytics for the management of preterm labour. The first indication of OTR/FP receptor crosstalk was observed when administration of low dose $PGF_{2\alpha}$ improved uterine response to OT in 1980 [91]. Further *in vitro* research by Fukai *et al.* identified a possible mechanism to explain this phenomenon as incubation of term non-labouring myometrial tissue in $PGF_{2\alpha}$ resulted in an increase in OTR binding affinity, although the reverse was not observed. This change in OTR binding affinity was also observed in amnion and decidua at term before labour, however, the significance or the extent of this effect is yet to be understood [92]. Interestingly, studies in pregnant rats reported that long-term exposure to Atosiban, an OTR antagonist, increases myometrial sensitivity to $PGF_{2\alpha}$ stimulation. This effect of OTR blockade appears to work partially at genetic level as Atosiban exposure augmented the expression of FP receptors [93]. Further evidence of OTR/FP receptor cross talk was provided by a more recent study in human uterine contractility. Use of an allosteric FP receptor antagonist, THG113.31, resulted in suppression of OT-induced myometrial contractions in a dose-dependent manner [94]. Although further investigations are required to establish the potential of these receptor crosstalk, the increasing reports of OTR/FP receptor crosstalk opens up a new target for the development of novel tocolytics.

3.4. OTR as a target for cell/tissue/organ-specific drug delivery

One of the major concerns of using tocolytics to prolong gestation is the potential side effects. Although OTR-As are developed specifically to treat PTL, other tocolytics such as nitric oxide donors, magnesium sulphate, PG synthase inhibitors, and β_2-agonists were originally developed for other reasons. These agents were found to have tocolytic effects but due to their lack of utero-specificity, most of them have multi-organ side effects. It has been reported that PG synthase

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inhibitors have minimal maternal side effects, but have serious fetal and neonatal side effects. Conversely, β_2-agonists are safe for the fetus, but have adverse maternal effects [95]. Development of a new approach to minimise systemic toxicity of tocolytic agents through increase in their utero-specificity would improve the therapeutic efficacy. A recent study has utilised a ligand-targeted liposomes as a platform to deliver drugs to target cells, tissues or organs. Liposomes were conjugated to antibodies specific for the extracellular domain of OTR and these OTR-targeted liposomes were used to deliver other tocolytic agents. These OTR-targeted liposomes were found to inhibit human uterine contractions in vitro and in vivo studies demonstrated that these liposomes localise to the uterine tissues of pregnant mice [96]. This raises the significance of OTR as a target for tissue-specific tocolytic drug delivery system to reduce maternal/fetal multi-organ side effects.

4. Conclusion

There is growing emphasis on the role of OT/OTR system in human parturition and with increasing understanding of the complex GPCR signalling, the OT/OTR system has proven to be an important target for future development of a safer, more effective therapeutics. The OT/OTR system not only appears to exceed the stimulation of uterine contractions and involves modulation of miRNAs and activation of inflammatory responses to mediate fetal membrane remodelling and cervical ripening, but also to affect a more diverse range of downstream signalling involved in the onset of labour through receptor crosstalk. Further studies are necessary to determine the full extent of the OT/OTR effects in human parturition and whether receptor crosstalk between GPCRs can shed some light to a potential combinational therapeutic target for the management of term and preterm labour.

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CONFLICT OF INTEREST:

VT has worked as a consultant to GlaxoSmithKline. PB has worked as a consultant to Boehringer Ingelheim, GlaxoSmithKline, Merck Serono, ObsEva SA and Tokyo Tanabe Pharmaceuticals, drug companies with an interest in the pharmacological effects of oxytocin and oxytocin antagonists. PB holds shares of ObsEva SA.

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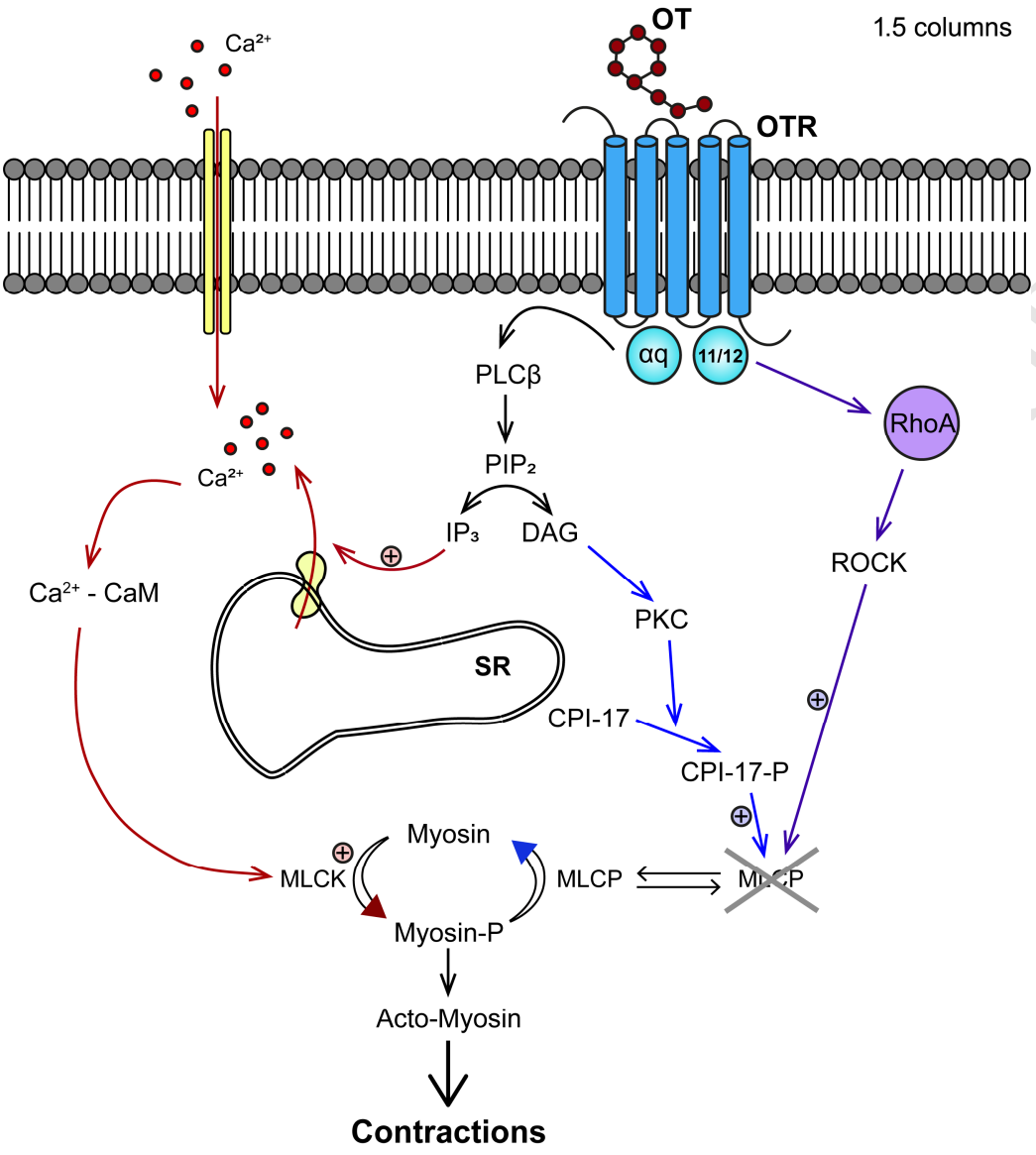
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FIGURE LEGENDS:

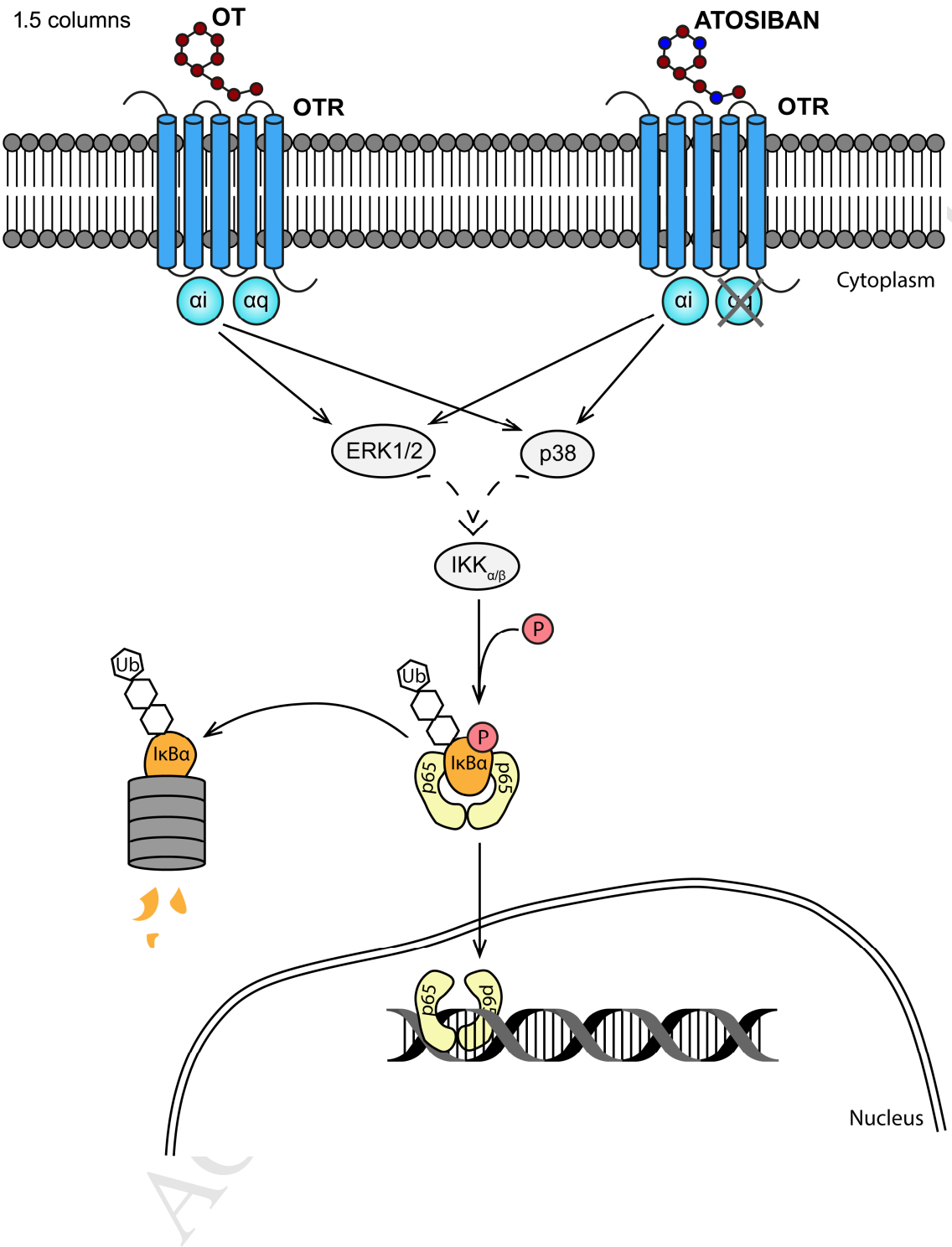
Figure 1. Oxytocin receptor signalling in the induction of myometrial contractions. Upon OT-OTR binding the $G\alpha_q$ subunit, coupled to the receptor, gets activated. This then activates phospholipase C-β, which is responsible for inositol-tris-phosphate (IP_3) and diacylglycerol (DAG) synthesis via the hydrolysis of phosphoinositide-bis-phosphate (PIP_2). IP_3 stimulates the release of Ca^{2+} from the sarcoplasmic reticulum (SR) and DAG activates protein kinase C (PKC). $G\alpha_q$ activation is thought to result in the opening of voltage-operated Ca^{2+} channels in the cell membrane and therefore induce Ca^{2+} entry. The overall increase in Ca^{2+} levels leads to activation of the Ca^{2+}-calmodulin (Ca^{2+}-CaM) complex, which in turn activates myosin light-chain kinase (MLCK). This promotes myosin activity and therefore stimulates myometrial contractions. Activation of $G_{11/12}$ subunit leads to activation of RhoA and Rho kinase (ROCK) to regulate phosphatase (MLCP).

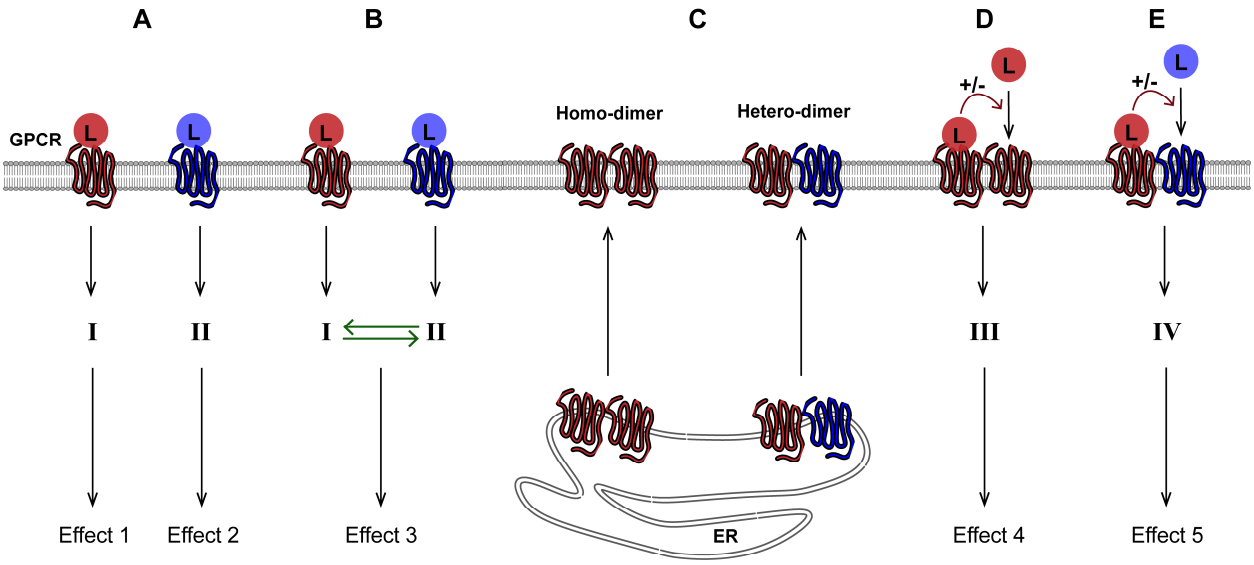
Figure 2. Oxytocin receptor signalling activated by oxytocin and atosiban in human amnion epithelial cells. Activation of OTR by OT in amnion cells lead to the activation of NF-κB pathway via mitogen activated protein kinases (MAPKs), ERK1/2 and p38 kinase. Atosiban, an OTR-antagonist mimics the effect of OT, subsequently resulting in the expression of pro-labour genes.

Figure 3. Potential functional and physical interactions of G protein coupled receptors. GPCRs can activate two independent signalling pathways I and II, resulting in two different downstream effects 1 and 2, respectively (A). A purely functional GPCR interaction occurs in the absence of physical interaction, where signalling pathways I and II integrate to result in effect 3 (B). GPCR dimerization can occur from the endoplasmic reticulum (ER) during the process of receptor maturation, or at cellular membrane level (C). Both homo- and hetero-dimerization can lead to positive (+)/negative (-) ligand cooperative binding, which can lead to activation of signalling pathways III and IV, producing effects 4 and 5.



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1.5 columns
OT
ATOSIBAN
OTR
OTR
αi
αq
αi
αq
Cytoplasm
ERK1/2
p38
IKKα/β
P
Ub
Ub
IκBα
P
IκBα
p65
p65
p65
p65
Nucleus



2 columns

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HIGHLIGHTS:

- Role of OT/OTR system in parturition exceeds the initiation of uterine contractions
- OT can trigger inflammation and regulation of miRNAs
- Ligand-specific OTR/G-protein coupling can result in differential downstream signalling
- Dimerisation/Oligomerisation of OTR and subsequent receptor crosstalk introduces novel strategies for the development of combination tocolytics
- OTR could be used as a target for utero-specific tocolytic drug delivery

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