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Oxytocin and Myometrial Contractility in Labor

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1. Introduction

Oxytocin (OT), a hormone exerting central and peripheral actions, plays an essential role in the mechanisms of parturition and lactation. It acts through its receptors, the number of which increases in the uterus towards labor, thus augmenting the uterotonic effect. Activated oxytocin receptors (OTR) by oxytocin, signal via a large number of intracellular pathways causing increased myometrial contractions by means of increased intracellular Ca^{+2} ion, increased myosin light chain phosphorylation and increased production of prostaglandins.

Molecules that antagonize the action of oxytocin have been developed for use as tocolytic agents in the treatment of preterm labor. One presently available tocolytic, the oxytocin receptor antagonist atosiban, acts on both myometrial and decidual OTRs. However, research is in progress aimed at the development and clinical application of new oxytocin receptor antagonists with an enhanced pharmacological profile translating as higher affinity for the receptor as well as better bioavailability and improved safety. In this chapter we describe the function of oxytocin in labor and review the use of atosiban for the treatment of preterm labor, while also evaluating the current development of other OTR antagonists that are potential candidates as tocolytic drugs in the future.

2. Oxytocin synthesis and function

Oxytocin (OT) is a nine amino acid neuropeptide synthesized by the magnocellular neurons of the supraoptic and paraventricular nuclei of the hypothalamus. It is released into the circulation by exocytosis from the posterior pituitary and nerve terminals in response to various stimuli. The amino acids sequence in the OT molecule is: Cysteine-Tyrosine-Isoleukine-Glutamine-Asparagine-Cysteine-Proline-Leukine-Glycinamide, and with a sulfur bridge between the two cysteines. The structure of OT is very similar to that of the nonapeptide vasopressin, which differs from oxytocin by two amino acids. Oxytocin is also

synthesized in such peripheral tissues as the uterus, corpus luteum, placenta, amnion, and testis (Gimpl and Fahrenholz, 2001).

Oxytocin, involved in numerous physiological and pathological processes, exerts a variety of actions, including the regulation of the hypothalamo-pituitary-adrenal axis in response to stress, cell proliferation, pregnancy, luteal function, maternal behavior, erectile function, and ejaculation (Viero et al., 2010).

3. The oxytocin receptor signaling

Oxytocin has only one receptor, which belongs to the rhodopsin-type class I G-protein coupled receptor (GPCR) superfamily. The gene of the oxytocin receptor is present in a single copy on chromosome 3p25 and contains 3 introns and 4 exons. Oxytocin and other molecules of similar structure, such as arginine vasopressin (AVP) and oxytocin agonists or antagonists, can bind to the receptor. The affinity for OT is about 10-fold higher than for AVP. The cell surface transmembrane OTR is activated after binding of OT molecule, and the receptor subsequently causes activation of the various intracellular signal pathways, this finally resulting in the numerous effects of the hormone, including contraction. OTR is coupled to the $G_{q/11}$ a- class guanosine triphosphate (GTP) binding proteins. Binding of OT activates, via $G\alpha_{q/11}$, phospholipase C (PLC) which hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP2) to inositol 1,4,5- triphosphate (InsP3) and diacylglycerol (DAG). InsP3 results in the release of Ca^{2+} ions from intracellular stores, while DAG activates protein kinases type C (PKC), which further phosphorylates other proteins, thus bringing about a trophic effect on myometrial cells via the eukaryotic translation elongation factor 2 (eEF2). Release of Ca^{2+} ions initiates smooth muscle contractions as Ca^{2+} binds to calmodulin and the Ca^{2+}-calmodulin system activates myosin light-chain kinase. This mechanism causes myometrial contractions, as well as contraction of mammary myoepithelial cells leading to milk ejection (Gimpl and Fahrenholz, 2001). The major pathway that mediates the signal of OTR after binding of OT is the Gq/PLC/InsP3 pathway. The OTR is, however, also coupled with other G proteins, Gs and Gi, which give rise to various other cellular effects, e.g. inhibition of cellular growth (Viero et al., 2010).

OTR additionally acts on voltage-gated or receptor coupled channels; this activation, which leads to membrane depolarization and the entry of extracellular Ca^{2+} into the cells, eventually triggers various cellular responses and further promotes smooth muscle contractility.

OTR also activates the mitogen-activated protein kinase (MAPK) and the Rho kinase pathways. Rho associated protein kinases are involved in many cellular phenomena, among them cell migration, cell cycle control and cell contractility. Activation of OTR and MAPK results, in both cases, in elevated cytosolic phospholipase A2 (cPLA2) activity. cPLA2 hydrolyzes phospholipids while liberating arachidonic acid, that results in increased production of prostaglandins via cyclooxygenase-2 (COX-2), an enzyme up-regulated by MAPK (Molnar and Hertelendy, 1995; Soloff et al., 2000). RhoA kinase increases phoshporylated myosin light chains. The increase in intracellular Ca^{2+} ions, the activation of the Rho and MAP kinase pathways, and the increased production and secretion of prostaglandins all together result in the contractile effects of OT-OTR activation.

4. Changes in circulating oxytocin and oxytocin receptor levels in labor

In humans, circulating oxytocin is not necessary for the initiation and completion of parturition, since normal labor can be achieved in cases of pituitary dysfunction (Phelan et al., 1978). Additionally, oxytocin circulation levels do not increase significantly in pregnancy or at the beginning of labor but are increased at the expulsive stage, while oxytocin pulsatile changes occur in pregnant women at term. Apart from in the pituitary, OT is also produced locally, and, in fact, placental OT acting in a paracrine fashion may be more important than circulating OT for the mechanism of labor. OTR is also up-regulated at the end of gestation and sensitivity to oxytocin-induced contractions is greatly increased compared to the non-pregnant uterus. A significant increase in the number of oxytocin receptors in the myometrium and decidua is observed in women with both term and preterm labor (Petraglia et al., 1996). Although steroid hormones are also thought to influence the number of OTR, the mechanisms of regulation are complex and not yet fully elucidated (Mirando et al., 1990, Wathes et al., 1996; Zingg et al., 1995). After parturition the binding sites of OT in uterus decline rapidly, while OTR expression in mammary glands remains high during the period of lactation (Petraglia et al., 2010).

However, continuous exposure to high doses of oxytocin leads to desensitization and down-regulation of OTR (Plested and Bernal, 2001). Desensitization is a phenomenon that prevents overstimulation of cells after prolonged agonist stimulation. This phenomenon is observed in GPCR receptors and is brought about by means of different mechanisms at many levels, such as phosphorylation, internalization or changes at the receptor mRNA levels. Rapid desensitization of GPCR receptors, taking place within seconds or minutes, occurs in two steps: 1. phosphorylation of the receptor, causing inhibition of G-protein activation; 2. binding of proteins, called arrestins, preventing G-protein activation and promoting receptor internalization. Internalization of the receptor after continuous OT stimulation is yet another mechanism of desensitization. Though it has been suggested that once internalized, the receptor does not return to the cell surface, recent data suggest that intracellular trafficking and recycling of the OTR to the cell surface does indeed take place (Conti et al., 2009). OTR desensitization is a phenomenon that occurs after prolonged agonist stimulation, i.e. lasting for several hours (Terzidou, 2007). Continuous OT treatment reduces the mRNA of the OTR, this possibly due to suppression of OTR transcription or destabilization of the mRNA molecule. In cultured human myometrial cells, treatment with OT for up to 20 hours causes OTR desensitization which effects in a reduction of the OT binding sites from 210 x 10^3 sites/cell to only 20.1 x 10^3 sites/cell, without receptor internalization. However, while the total amount of OTR protein is not diminished, treatment reduces OTR mRNA levels (Phaneuf et al., 1998). In vivo, in women with oxytocin-induced or oxytocin-augmented labor there is also a reduction in myometrial oxytocin binding sites and in OTR mRNA levels. Compared to women not in labor, in cases of oxytocin-augmented or oxytocin-induced labor, the median number of binding sites was reduced from to 477 fmol/mg^{-1} protein to 140 fmol/mg^{-1} protein and 118 fmol/mg^{-1} protein, respectively, both differences being statistically significant. Compared to women not in labor, in cases of labor augmentation and induction OTR mRNA levels were reduced by 60- and 300-fold, respectively (Phaneuf et al., 2000). Oxytocin receptor down-regulation has great significance in clinical practice. Long-term oxytocin infusion may fail to augment labor or may lead to postpartum uterine atony which cannot be managed with additional

oxytocin infusion. However, oxytocin is normally secreted in pulses, this pulsatile secretion likely being a mechanism that prevents desensitization from occurring. This might explain why in women in labor, induction of labor requires significantly lower doses of oxytocin when oxytocin is administered in pulses, compared with continuous oxytocin infusion (Dawood, 1995).

5. Experimental or clinical use of oxytocin agonists

The widespread distribution of OTR has led to the development of OTR agonist molecules that could be used as pharmacological tools (agents used experimentally to study the functions of oxytocin and its receptor) or as potential drugs for the management of obstetric disorders and neuropsychiatric diseases, including anxiety-related disorders, autism and schizophrenia. OTR agonists may be peptide (such as [Thr^4]OT, [HO^1][Thr^4]OT, [Thr^4,Gly^7]OT and [HO^1][Thr^4,Gly^7]OT) or non-peptide molecules (such as WAY-267464 and other compounds) (Borthwick, 2006; Manning et al., 2008). WAY-267464 exerts oxytocinergic actions, such as anxiolytic effects, in mice (Ring et al., 2010).

Clinically, synthetic oxytocin is used for labor induction and augmentation and the treatment of postpartum hemorrhage. Carbetocin, a synthetic oxytocin analog, is also indicated for prevention of uterine atony after delivery by cesarean section in spinal or epidural anesthesia. It also has the advantage of longer half life than oxytocin (4-10 times) and it is administered in a single dose, intramuscularly or intravenously, compared to oxytocin continuous infusion (Rath, 2009).

6. Tocolytic action of oxytocin antagonists

Since the most recognized signs of preterm labor are uterine contractions, the main method for postponement of preterm labor is currently the pharmacological inhibition of uterine contractions. The inhibition of myometrial contractions is called tocolysis, and a drug administered to that end is referred to as a tocolytic agent. The aim of tocolytic agents is to maintain pregnancy for 24-48 hours, to allow the beneficial effects of corticosteroids administration to take place (reduced risk of perinatal death, neonatal respiratory distress syndrome, etc), usually after 18 hours, and also to permit safe transfer of the mother to a center with neonatal intensive care facilities. There are several tocolytics agents, such as ritodrine (a beta-receptor agonist), calcium-channel blockers, nitric oxide donors (as glyceryl trinitrate), and COX-2 inhibitors such as indomethacin (Simhan and Caritis, 2007).

Selective human oxytocin receptor antagonists, such as atosiban and barusiban have also been synthesized as tocolytic agents for the management of preterm labor. Atosiban, an oxytocin analog (1-Deamino-2-D-Tyr-(O-ethyl)-4-Thr-8-ornoxytocin), is based on modification of amino acids in the structure of oxytocin at positions 1, 2, 4 and 8, thus being a competitive inhibitor of the OTR that blocks OT binding. It is also a mixed vasopressin V1a/OT antagonist that results in the incidence of related unwanted effects. Vasopressin V1a receptors (V1aR) expression are also present in myometrium.

The onset of uterine relaxation after atosiban administration is fast. Atosiban is given intravenously as shown in Table 1 and the total dose should preferably not exceed 330 mg.

Dose and administration		
Step 1	6.75 mg	i.v. bolus, in one minute
Step 2	18 mg/h i.v.	i.v. infusion for 3 hours
Step 3	6 mg/h i.v.	i.v. infusion for up to 45 hours

Side effects: Nausea, vomiting, hyperglycemia, headaches, dizziness, tachycardia, hot flushes, hypotension, injection site reactions, pruritis, rush, pyrexia, insomnia

Table 1. Dose, method of administration, and side effects of atosiban.

Clinically, atosiban, which requires continuous intravenous administration, is as effective as β2-adrenergic agonists, but without producing their adverse effects. Subcutaneously administered after a period of preterm labor, atosiban given as maintenance therapy was not shown to be associated with a reduction of the incidence of preterm birth nor with any improvement of neonatal outcome. In a study in which a total of 513 women were randomized to receive either atosiban or placebo administered with a subcutaneous infusion pump in order to prevent recurrence of preterm birth, atosiban compared to placebo did not reduce the incidence of preterm birth before 37 weeks (RR 0.89; 95% CI 0.71 to 1.12), 32 weeks (RR 0.85; 95% CI 0.47 to 1.55), or 28 weeks (RR 0.75; 95% CI 0.28 to 2.01). Outcomes were also similar for both groups with respect to birth weight, respiratory distress syndrome, patent ductus arteriosus, necrotizing enterocolitis, and intraventricular hemorrhage (Papatsonis et al., 2009).

In Europe and other countries atosiban is the only oxytocin/vasopressin antagonist used today for preterm delivery. However, this does not apply to the USA where the Food and Drug Administration has not granted approval of the drug as a tocolytic because of sufficient lack of evidence as to its efficacy and improvement of neonatal outcomes.

Clinical studies have determined that atosiban is safer than beta-receptor agonists. A large study (Worldwide Atosiban versus Beta-agonists Study Group, 2001) demonstrated that atosiban was comparable in clinical effectiveness to conventional beta-agonist therapy (ritodrine, salbutamol or terbutaline), but was better tolerated and was associated with fewer maternal cardiovascular side effects (ClinicalTrials.gov, 2001). Atosiban is also safer than calcium channel blockers. Meanwhile, clinical studies have shown nifedipine to be equally effective as atosiban, although the maternal side effects were significantly more common among women allocated to nifedipine rather than atosiban (Al-Omari et al., 2006). Cyclooxygenase inhibitors act as tocolytics by inhibiting prostaglandins production but also present significant side effects (King et al., 2005). Conversely, evidence is as yet not strong enough for recommendation of the use of nitric oxide donors as inhibitors of preterm delivery (Duckitt and Thornton, 2002). Nevertheless, atosiban has not been proven to be superior in terms of neonatal outcome, concerns having been expressed in other studies (Papatsonis et al., 2005).

Atosiban's limited bioavailability—which necessitates parenteral administration and hospitalization—together with its low affinity for OTR and the binding to V1a receptors that causes side effects, have led to endeavors for the identification of new peptide and non-peptide oxytocin antagonists for the management of preterm labor. While many such substances have been discovered, these drugs are still being evaluated at the experimental level and clinical studies in most cases have ceased or have been completed unsuccessfully (Manning et al., 2008). These compounds are either peptide or non-peptide molecules.

The OT antagonists shown in Table 2 bind for both oxytocin and AVP receptors. However, limitations exist, these being: a) there are major differences among them with regard to their selectivity for a specific OT receptor; b) selectivity also varies according to the AVP receptor (V1a, V1b, V2); c) there are striking differences among species as to both receptors' affinity for a given antagonist; and d) specification as to receptors' affinity varies in the literature according to the experimental method used.

	Oxytocin antagonists	OT and AVP receptor binding
I. Peptide	Atosiban	Yes
	FE 200 400 (Barusiban)	Yes
II. Non-peptide	GSK221149A (Retosiban)	Yes
	SSR-126768A	Yes
	L-368,899	Yes

Table 2. OT antagonists with tocolytic action and AVP receptor binding

The V2 and V1a peptide antagonist $d(CH_2)_5$[Tyr(Me)^2]AVP (known as Manning compound) is a potent OT antagonist in vitro and in vivo (Chan et al., 1996). $d(CH_2)_5$[Tyr(Me)^2]AVP is also a mixed V1a/OT antagonist for human VP and OT receptors.

Several others highly selective OT peptidic antagonists have been designed and synthesized. These include $d(CH_2)_5$[Tyr(Me)^2]OVT, desGly–NH_2,$d(CH_2)_5$[Tyr(Me)^2,Thr^4]OVT (which is about 18 times more potent as an OT antagonist in the rat than as a V1a antagonist) and desGly–NH2,$d(CH_2)_5$[D-Tyr^2,Thr^4]OVT (which is 95 times more potent as an OT antagonist in the rat than as a V1a antagonist). Moreover, the peptide $d(CH_2)^5$,[D-Thi^2,Thr^4,Tyr–NH_2^9]OVT is a very selective oxytocin antagonist while being a very weak V1a antagonist, as is also desGly–NH_2,$d(CH_2)_5$ [D-Trp^2, Thr^4, Dap^5]OVT in the rat. On the other hand, there are between species striking differences in the affinity of most antagonists for OT and AVP receptors. The first peptide above, $d(CH_2)_5$[Tyr(Me)^2]OVT, is 5 times more potent as an V1a antagonist than as a OT antagonist in the rat, whereas in humans it is about 9 times more potent as an OT antagonist than as a V1a antagonist.

Some of the new peptide OT/VP antagonists have higher affinity for human receptor than the peptide atosiban, which, as noted, is the only antagonist used today in Europe. These new peptides are desGly–NH_2,$d(CH_2)_5$[D-2-Nal^2,Thr^4]OVT, desGly–NH_2,$d(CH_2)_5$[2-Nal^2,Thr^4]OVT, $d(CH_2)_5$[D-2-Nal^2,Thr^4,Tyr–NH_2^9]OVT, and $d(CH_2)_5$[2-Nal^2, Thr^4, Tyr–NH_2^9]OVT. These four peptides may be candidates as potential tocolytic agents for the prevention of preterm labor (Manning et al., 2008).

Barusiban is a selective peptide oxytocin antagonist that exerts a high affinity for the human oxytocin receptor On the contrary, it displays low affinity for the vasopressin (V1a) receptor. It possesses greater potency and a longer duration of action than atosiban. Contractility studies with isolated human myometrium have revealed that barusiban inhibits oxytocin-induced myometrial contractions of both preterm and term myometrium, this action being at least as potent as that of atosiban (Pierzynski et al., 2004). In a study with eight pregnant monkeys, following induction of stable contractions by OT, barusiban or atosiban were administered. Barusiban's duration of action was generally longer than 13–15 hours, while

atosiban's effect ceased within 1.5–3 hours. For long-term treatment, continuous high-dose infusions of barusiban (150 µg/kg/h) or the beta-2 agonist fenoterol (3 µg/kg/h) were administered. Barusiban reduced uterine activity in response to daily OT challenge and prolonged pregnancy more effectively than fenoterol (Reinheimer, 2007).

Although barusiban suppresses oxytocin-induced preterm labor in non-human primates, in a recent study it was no more effective than placebo in terminating preterm labor in pregnant women at between 34^{+0}-35^{+6} weeks of gestation. This study was conducted at 21 participating centers with subjects from six different European countries. Participants were randomly assigned to receive a single intravenous bolus dose of 0.3, 1, 3, or 10 mg barusiban or placebo (acetate buffer). The percentage of women who did not deliver within 48 hours was not significantly different between the placebo group and any of the barusiban groups (P = 0.21-0.84). No significant decreases in the number of uterine contractions compared with placebo were registered. All doses of barusiban were well tolerated and there were no adverse events that would lead to withdrawal from the study. Finally, there was no statistically significant difference in maternal or neonatal adverse effect between the placebo and barusiban groups (Thornton et al., 2009).

The lack of peptide antagonists characterized by oral bioavailability have led researchers to seek an effective non-peptide oxytocin antagonist. The non-peptide oxytocin antagonist 2′-methyl-1′,3′-oxazol-4′-yl morpholine amide derivative 74 (GSK221149A or retosiban) when administered orally or intravenously produced a dose-dependent decrease in oxytocin-induced uterine contractions in rats, after either single or multiple dosing for 4 days. In addition, spontaneous uterine contractions in late-term pregnant rats (at 19–21 days gestation) were significantly reduced by intravenous administration of GSK221149A at a dose of 0.3 mg/kg. In vitro experiments using Chinese hamster ovary (CHO) cell membranes expressing human OT receptors or human V1a, V1b, or V2 receptors, and human endothelial kidney (HEK) cells expressing rat oxytocin receptors showed that GSK221149A also has a higher affinity for human and rat oxytocin receptors than for V1a and V2 receptors (McCafferty et al., 2007). GSK221149A is over 15-fold more potent compared to atosiban for the OTR (Borthwick and Liddle, 2011). GSK221149A is on a Phase ll Clinical trial described as "A randomized, double-blind, placebo-controlled, dose ranging study to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of GSK221149A administered intravenously and to investigate the pharmacokinetics of GSK221149A administered orally to healthy, pregnant females with uncomplicated pre-term labor between 30^{+0} and 35^{6} weeks' gestation" . The estimated date for study completion was June 2011 and no results have so far been published.

Another non-peptide molecule, 1-((7,7-Dimethyl-2(S)-(2(S)-amino-4-(methylsulfonyl) butyramido) bicyclo[2.2.1]-heptan-1(S)-yl)methyl)sulfonyl)-4(2methylphenyl) piperazine, known as L-368,899, was shown to be a potent OT antagonist that inhibits spontaneous nocturnal uterine contractions in pregnant rhesus monkeys. L-368,899 also blocked OT-stimulated uterine activity in postpartum women with a potency similar to that in the pregnant rhesus monkey (Pettibone et al., 1995). The pharmacokinetics and oral bioavailability, however, were suboptimal, and further clinical evaluation was not undertaken (Freidinger and Pettibone, 1997). L-368,899 is moreover brain penetrant. In a study, the non-peptide OT antagonist L-368,899 was accumulated when injected intravenously in four male monkeys in limbic brain areas. This antagonist when injected iv in one adult female monkey altered maternal and sexual behavior (Boccia et al., 2007).

WAY-162720 is another high-affinity, potent, and selective non-peptide antagonist of the OTR. WAY-162720 also penetrates the brain and is a tool for studies of OT on the CNS effects. In one study, the effects of OT on both the behavioral and autonomic parameters of the anxiety response in male mice were examined. Oxytocin showed an anxiolytic-like effect comparable to those observed with the reference anxiolytic alprazolam. The administration of WAY-162720 fully reversed the effects of centrally administered OT (Ring et al., 2006).

The non-peptide SSR-126768A (4-Chloro-3-[(3R)-(+)-5-chloro-1-(2,4-dimethoxybenzyl) -3-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-N-ethyl-N-(3-pyridylmethyl)-benzamide, hydrochloride) produced a competitive antagonistic effect against OT in rat myometrial strips, while after oral administration in conscious pregnant rats in labor it significantly delayed parturition, in a manner similar to ritodrine. The onset of its action was rapid and the duration was still observed 24h after treatment. In experiments performed in human uterine sections in term pregnancies, SSR-126768A inhibited the response to OT and this effect was observed in a concentration-dependent manner (Serradeil-Le et al., 2004).

Relcovaptan, a vasopressin (V1a) receptor antagonist, was reported to inhibit uterine contractions in women with preterm labor, thus indicating a role for V1a receptors (Steinwall et al., 2005). In a study including 18 women with preterm labor between 32–36 weeks, 12 patients received at random a single oral dose of 400 mg relcovaptan and 6 patients received placebo; uterine contractions were monitored up to 6h after administration. Relcovaptan inhibited uterine contractions and the decrease in the frequency of contractions was significantly higher than the frequency in the placebo-treated group. It has also shown positive initial results when used against Raynaud's disease and dysmenorrhea, although it has not yet been approved for clinical use (Decaux et al., 2008). When relcovaptan was given orally once a day for 7 days in patients with Raynaud's disease, it showed favorable effects compared with placebo on finger systolic pressure and temperature recovery after cold immersion, without inducing side effects (Hayoz et al., 2000). Relcovaptan is administered orally 100 mg or 300 mg daily in women suffering from primary dysmenorrhoea, from 4 hours up to a maximum of 3 days before the onset of bleeding and/or menstrual pain. After the start of dysmenorrhea (defined as the onset of vaginal bleeding or the onset of pain, whichever occurred first), treatment was prolonged for up to 3 days. Relcovaptan showed a therapeutic effect in the prevention of dysmenorrhea (Brouard et al., 2000). Relcovaptan also produced significant neuroprotective actions and reduced ischemic brain edema in an embolic model of stroke in rats when given immediately or 1 hour after middle cerebral artery occlusion, but not when administered at 3 hours after middle cerebral artery occlusion (Shuaib et al., 2002).

As our knowledge on OT/OTR system expands, the development and use of different OTR antagonists becomes an increasingly promising field in the management of preterm labor.

7. Conclusion

OT exerts its myometrial and other actions through a transmembrane receptor that belongs to the G- protein coupled receptor superfamily. Various peptide and non-peptide antagonists have been developed in order to be used as potential tocolytic agents or as research tools in assessing different OT functions. Atosiban is at present the only available OTR antagonist used as a tocolytic agent. Barusiban, L-368,899, SSR-126768A, and

GSK221149A (retosiban) are some other OTR antagonists demonstrating tocolytic properties when tested, but have not so far been approved for clinical use.

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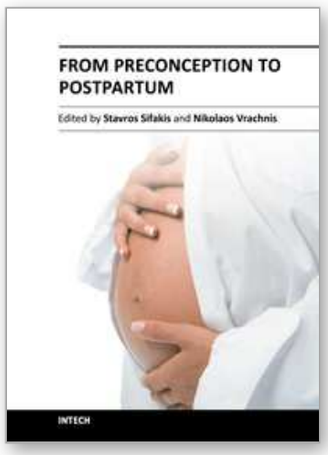
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From Preconception to Postpartum

Edited by Dr. Stavros Sifakis

ISBN 978-953-51-0353-0
Hard cover, 314 pages
Publisher InTech
Published online 23, March, 2012
Published in print edition March, 2012

Obstetrics is evolving rapidly and finds itself today at the forefront of numerous developments. Providing selected updates on contemporary issues of basic research and clinical practice, as well as dealing with preconception, pregnancy, labor and postpartum, the present book guides the reader through the tough and complex decisions in the clinical management. Furthermore, it deepens the scientific understanding in the pathogenetic mechanisms implicated in pregnancy and motivates further research by providing evidence of the current knowledge and future perspectives in this field. Written by an international panel of distinguished authors who have produced stimulating articles, the multidisciplinary readers will find this book a valuable tool in the understanding of the maternal, placental and fetal interactions which are crucial for a successful pregnancy outcome.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

N. Vrachnis, F.M. Malamas, S. Sifakis, A. Parashaki, Z. Iliodromiti, D. Botsis and G. Creatsas (2012). Oxytocin and Myometrial Contractility in Labor, From Preconception to Postpartum, Dr. Stavros Sifakis (Ed.), ISBN: 978-953-51-0353-0, InTech, Available from: http://www.intechopen.com/books/from-preconception-to-postpartum/oxytocin-and-myometrial-contractility-in-labor

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