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## BETA-ADRENOCEPTORS IN OBSTETRICS AND GYNECOLOGY

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### Abstract

*One hundred and twenty years after the description of extracts from the adrenal medulla, the use of beta-blockers and beta-agonists evolved from antianginal drugs and tocolytics to ligand-directed signaling. Beta-blockers in the fields of obstetrics and gynecology have so far been limited to the consideration of continuing treatment of disorders of the cardiovascular system and other dysfunctions that started before pregnancy. Studies in recent years have shown that beta-adrenoceptor signaling might be crucial in carcinogenesis and metastasis, apoptosis and anoikis. On the other hand, the use of beta-adrenoceptor agonists in tocolysis is, as yet, the primary method for inhibiting premature uterine contractions. Unfortunately, the efficacy of current pharmacological treatment for the management of preterm labor is regularly questioned. Moreover, studies related to non-pregnant myometrium performed to date indicate that the rhythmic contractions of the uterus are required for menstruation and have an important role in human reproduction. In turn, abnormal uterine contractility has been linked to dysmenorrhea, a condition associated with painful uterine cramping. The benefits of the use of beta2-adrenoceptor agonists in dysmenorrhea are still unclear and should be balanced against a wide range of adverse effects recognized with this class of medication. The ideal tocolytic agent is one which is effective for the pregnant or non-pregnant woman but has no side effects on either the woman or the baby. Looking to the future with both caution and hope, the potential metamorphosis of beta3-adrenoceptor agonists from experimental tools into therapeutic drugs for tocolysis warrants attention.*

**Key words:** beta2-adrenoceptor agonists, beta3-adrenoceptor agonists, adrenoceptor signaling, cancer treatment, propranolol

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### INTRODUCTION

Over one hundred and twenty years ago, two men: George Oliver, a physician, and Edward Schäfer, a professor of physiology, described the way in which the crude extracts from the adrenal medulla produced pressor effects. Thus, the year 1895 marked the birth of adrenaline (A) for biomedical research. The presence of more than one adrenergic receptor was first suggested in 1948 by Raymond Ahlquist, a professor of pharmacology. In the late 1950s, Sir James Black, a physician, developed propranolol, which is still considered the prototypical beta-adrenoceptor (ADRB) antagonist. At present, almost 70 years after Ahlquist first postulated the heterogeneity of adrenergic receptors [1], the number of receptor subtypes is still unclear. Moreover, the use of beta-blockers and beta-agonists evolved from antianginal drugs and tocolytics to ligand-directed signaling.

The aim of this Commentary is to briefly review the current state of knowledge on beta-blockers and beta-agonists in the fields of obstetrics and gynecology.

### BETA-BLOCKERS

Beta-blockers, also known as beta antagonists, beta-adrenergic blocking agents, or beta-adrenergic antagonists, block the actions of beta-adrenergic substances, such as A (or, epinephrine) and noradrenaline (or, norepinephrine, NA) in the sympathetic nervous system (Tab. I). The sympathetic nervous system activates the “fight or flee” response and is a component of the autonomic (involuntary) nervous system [2].

Beta-blockers are drugs that are approved to treat several different types of conditions, including hypertension (high blood pressure), angina, some abnormal heart

rhythms, heart attack (myocardial infarction), anxiety, migraine, glaucoma, and overactive thyroid symptoms. Even though this list is long, it can continue to grow as other therapeutic applications are found.

The use of beta-blockers in the fields of obstetrics and gynecology has so far been limited to the consideration of continuing treatment of disorders of the cardiovascular system and other dysfunctions that started before pregnancy, provided that the influence of ADRB-antagonists on pregnancy and the fetus are taken into account. On the other hand, some of them are used for pregnancy complications, such as pregnancy-induced hypertension [3].

Women with medical complaints should receive advice before pregnancy to ensure their treatment is relevant and to make them aware of any consequences for pregnancy and childbirth [4]. Hypertensive disorders remain common medical complications of pregnancy related to considerably increased risks of developing preeclampsia, characterized by proteinuria and multi-organ involvement [5]. While there is general agreement on the need to regulate blood pressure with antihypertensive treatment in non-pregnant patients, whether and how to control blood pressure for hypertensive disorders of pregnancy has not been clearly defined [6]. Chronic hypertension, with or without treatment during pregnancy, is an independent and significant risk factor for adverse

perinatal outcomes, such as intrauterine growth restriction, small fetus for gestational age, placental ablation, and preterm delivery [7].

Among commonly used beta-blockers in the treatment of hypertension in pregnancy are: propranolol, labetalol, mepindolol, pindolol and oxprenolol, nonselective beta blockers; and acebutolol, atenolol, metoprolol, selective beta1 adrenergic inhibitors with a negative chronotropic and inotropic effect on the myocardium [5] (Tab. I). Over the last two decades, labetalol, a mixed alpha/beta adrenergic antagonist, has become the drug of choice in the treatment of hypertension in pregnancy at many centers [5]. Several studies, however, have found an association between exposure to beta-blockers in pregnancy and the low birth weight of infants [8, 9]. Compared with methyldopa (a selective alpha2 adrenergic receptor agonist), the use of labetalol for chronic hypertension of pregnancy may be related to the increased rate of hospitalization during infancy [10]. Pooling the results of labetalol versus other antihypertensive therapy with the results from studies comparing beta-blockers with other antihypertensive therapy did not show any statistically significant results, either [5, 7, 11].

Significant changes in drug metabolism during pregnancy result in increased clearance and decreased pharmacological effect. The dosage of drugs, such as atenolol, of which the primary disposition is dependent

Table I. Characteristics of beta adrenergic receptors, or ADRBs. A – adrenaline, NA – noradrenaline, ISO – isoproterenol.

Subtype	Gene Coding	Natural Agonists	Synthetic Agonists	Non-Specific Beta-Blocker Examples	Specific Beta-Blocker Examples
Beta 1	protein coding for 477 amino acids located on chromosome 10, 10q24-q26	A, NA	ISO, Denopamine, Dobutamine, Xamoterol	Propranolol, Timolol, Nadolol	Acebutolol, Atenolol, Betaxolol, Bisoprolol, Esmolol, Metoprolol, Nebivolol, Vortioxetine
Beta 2	protein coding for 413 amino acids located on chromosome 5, 5q31-q32	A, NA	ISO, Salbutamol (Albuterol in USA), Terbutaline, Bitolterol mesylate, Levosalbutamol (Levalbuteral in USA), Ritodrine, Orciprenaline Sulfate	Propranolol, Timolol, Nadolol	Butoxamine, ICI-118,551
Beta 3	protein coding for 408 amino acids located on chromosome 8, 8p12	A, NA	ISO, Amibegron (SR-58611A), CL-316,243, L-742,791, L-796,568, LY-368,842, Mirabegron (YM-178), Ro40-2148, Solabegron (GW-427,353)	Propranolol, Timolol, Nadolol	L-748,328[8], L-748,337[8], SR 59230A

on renal filtration, should be increased in line with the increased glomerular filtration rate associated with pregnancy [12]. Studies have also shown that women with chronic hypertension treated with atenolol had higher rates of intrauterine growth restriction and preterm delivery. Metoprolol and propranolol are substrates for the cytochrome CYP2D6, which is also upregulated in pregnancy [13]. Labetalol is metabolized through conjugation to glucuronide metabolites, which also appear to be upregulated in pregnancy [14].

Beta-blockers are often administered in order to specifically decrease cardiac output and thus reduce the burden of pregnancy on the mother's circulatory system. The therapeutic effect of drugs, such as beta-adrenoceptor blockers, can be directly observed by measuring changes in the heart rate. In this regard, it might be argued that some impairment in fetal growth must be accepted to safeguard the mother's health. However, the final clinical decision as to the choice and duration of beta-blockade in pregnancy should be made on an individual basis. Careful attention must be paid to fetal growth, which is a factor which needs to be taken into consideration.

Studies in recent years have shown that ADRB signaling might be crucial in carcinogenesis and metastasis, apoptosis and anoikis [15, 16]. Epidemiological studies have revealed a relationship between the use of ADRB-antagonists and reduced cancer risk [17, 18]. Experimental *in vitro* studies have shown that NA, A, isoproterenol (a nonspecific ADRB-agonist), and cortisol can all enhance the production of the vascular endothelial growth factor by ovarian cell lines [19]. Moreover, these effects were most likely mediated by the stimulation of metalloproteinases [20]. In a model of human ovarian cancer, cells exposed to either A or NA, exhibit lower levels of anoikis, the process by which cells enter apoptosis when separated from the extracellular matrix and neighboring cells [21]. Treatment of the human ovarian cells with catecholamine reduced anoikis and promoted their growth by activating focal adhesion kinase. These effects were blocked by propranolol or butoxamine but not atenolol [21]. The findings presented may point to potential new therapeutic targets for cancer management. A recent multicenter review of 1425 women with anatomopathologically confirmed epithelial ovarian cancer (EOC) has revealed that the use of nonselective beta-blockers was associated with longer overall survival. However, the appropriate dosage for EOC could not be proposed, because in the studies which examined the effects of beta-blockers on survival, patients were taking beta-blockers for cardiac or other clinical indications and not specifically for cancer therapy [22]. These findings may have implications for new therapeutic approaches. There are currently two clinical trials evaluating the combination of chemotherapy and variable doses of propranolol on cancer biology, as well as the effect of nonselective beta-blockers on stress modulators in patients newly diagnosed with EOC [23, 24]. Dr. Anil Sood's team expected that the preliminary data from these practicability trials would help design adequately-powered, prospective, randomized clinical trials to determine whether nonselective beta-blockers can improve outcomes for patients with EOC. These findings

could be relevant for other cancer types as well. There are data showing that chronic stress and persistent adrenergic activation can affect cancer growth and spread, and these kinds of stress pathways are suspected to stimulate the growth of certain forms of breast, colon, as well as head and neck cancer [15, 16].

## BETA-MIMETICS

ADRB-agonist ligands mimic the action of A and NA signaling in the heart, lungs and smooth muscle tissue, with A being of the highest affinity. Binding of the agonist to ADRB2s activates adenylate cyclase. This enzyme leads to the activation of the second messenger 3',5'-cyclic adenosine monophosphate, or cAMP, which in turn decreases calcium concentrations within cells and activates protein kinase A. Both of these changes inactivate myosin light chain kinase and activate myosin light chain phosphatase. In addition, ADRB2-agonists open large conductance calcium-activated potassium channels and thereby hyperpolarize smooth muscle cells. The combination of decreased intracellular calcium, increased membrane potassium conductance, and decreased myosin light chain kinase activity leads to smooth muscle relaxation [25] (Fig. 1).

The use of tocolysis is, as yet, the primary method for inhibiting the premature uterine contractions. All available ADRB2 tocolytics (salbutamol, terbutaline, ritodrine, fenoterol) are substantially equally effective for prolonging pregnancy for at least 48 hours. Unfortunately, the efficacy of current pharmacological treatment for the management of preterm labor is regularly questioned. ADRB2-agonists are becoming less used worldwide as tocolytic agents, because of possible important maternal and fetal side effects [26-28]. For these reasons, much research in the last decade has focused on the development of novel agents, such as next-generation calcium channel blockers and oxytocin antagonists [9-12].

Beta-mimetics stimulate beta-adrenergic receptors and may cause trembling, tremors, nausea, vomiting, anxiety, headaches, chest pain, shortness of breath, together with a variety of biochemical disturbances, such as hyperglycemia and hypokalemia. Furthermore, pulmonary edema may occur [29] and has even been associated with maternal death. The appearance of side effects may require some women to cease treatment. ADRB2-agonists cross the placenta and may cause fetal tachycardia and neonatal hypoglycemia and hyperinsulinism [30]. When considering the use of tocolytic agents in preterm labor, the risks and benefits for both mother and infant should be carefully considered.

While there is voluminous information in the literature devoted to the subject of uterine contractility during pregnancy, the characterization and significance of contractions of the non-pregnant uterus have been investigated far less. Studies performed to date indicate that constant, rhythmic contractions are required for menstruation and have an important role in human reproduction, particularly during fertilization and embryo implantation [31]. In contrast, abnormal uterine contractility has been linked to dysmenorrhea, a condition associated with painful uterine cramping [32]. Randomized

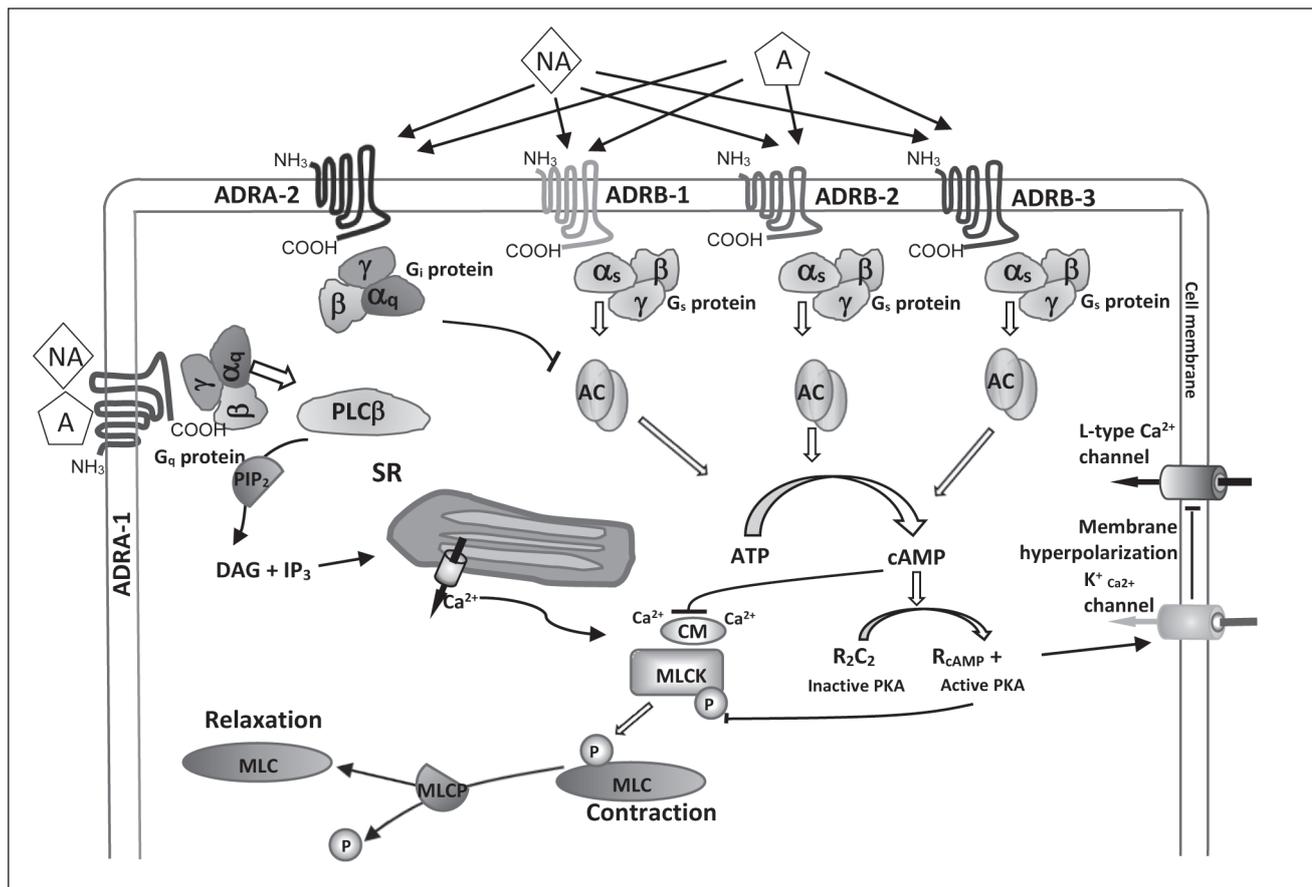


Fig. 1. Adrenergic receptor-mediated control of smooth muscle contraction and relaxation. Binding of agonists to alpha1 adrenergic receptors (ADRA1s) and ADRA2s leads to smooth muscle cell contraction whereas activating beta adrenergic receptors (ADRBs) results in the relaxation of these cells. AC, adenylate cyclase; cAMP, 3',5'-cyclic adenosine monophosphate; CM, calmodulin; DAG, diacylglycerol; MLC, myosin light-chain; MLCK, myosin light-chain kinase; MLCP, myosin light-chain phosphatase; PIP<sub>2</sub>, phosphatidylinositol-4,5-bisphosphate; PKA, protein kinase A; PLCβ, phospholipase C β isoform; SR, a sarcoplasmic reticulum. Adapted from <http://themedicalbiochemistrypage.org/muscle.php>

controlled trials compared ADRB2-agonists with placebo or no treatment, as well as with any other conventional treatment in women of reproductive age with primary dysmenorrhea, but their effects were found unclear. Again, benefits, as reported in one study, should be balanced against a wide range of adverse effects recognized with this class of medication [33].

### EMERGING ADRB3s

The ideal tocolytic agent is one which is effective for the pregnant or non-pregnant woman but has no side effects either on her or her baby. ADRB3s have been identified in a variety of tissues of humans and animals: white and brown adipose tissues, skeletal muscles, heart, gastrointestinal smooth muscles, the respiratory tract or urogenital system [34]. ADRB3s have also been described in the uterus, where similarly to ADRB2s, they play an important functional role in mediating relaxation of the myometrium. The presence of functional ADRB3s has recently been demonstrated in the human near-term [35, 36] and non-pregnant myometrium [37, 38].

They are the predominant over the ADRB2 subtype in human myometrium and over-expressed in the pregnant uterus [35]. Furthermore, ADRB3s are resistant to the long-term agonist-induced desensitization of the human myometrium at the end of pregnancy [35]. It was reported that using ADRB3-agonists for the treatment of obesity or diabetes might have cardiac side effects, especially in patients with congestive heart failure [39, 40]. On the other hand, some researchers observed the possibility of having less or no cardiovascular side effects after beta3-agonist administration [41]. Before ADRB3-agonists metamorphose from experimental tools into therapeutic drugs with a potential target for tocolysis, it is vital to obtain more comprehensive studies on functions mediated by this receptor subtype in humans.

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**Conflicts of interest/Konflikt interesu**

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