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ARE α-ADRENERGIC ANTAGONISTS POTENT TOCOLYTICS? *IN VIVO* EXPERIMENTS ON POSTPARTUM RATS

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ABSTRACT The aim of this study was to investigate the effects of α-adrenergic antagonists on the motor activity of the postpartum uterus of the rat *in vivo*. Intrauterine pressure was assessed by means of a Millar catheter fitted with a latex microballoon. Some of the tested compounds (urapidil, yohimbine, phentolamine, benoxathian and prazosin) decreased the uterine activity to a significant extent (57.4–67.4%). However, none of the investigated α-receptor blockers exerted the same effect as β-adrenergic agonists. Our results suggest that α-adrenergic antagonists could possibly be used as an alternative to β-adrenergic agonists in clinical tocolysis after an appropriate clinical evaluation.

Key Words: tocolysis, α-adrenergic antagonists, spontaneous uterine activity

Introduction

Premature labor is one of the main causes of perinatal death in the developed countries (1). The authorized choice for the treatment of premature labor includes β-adrenergic agonists and magnesium sulfate. The latter is not so frequently used in Europe at present. The other disadvantage to the use of magnesium sulfate for tocolysis is the lack of an effective oral dosage form for maintenance use. As regards the β-adrenergic agonists, there are numerous clinical situations (e.g. tachycardia, diabetes mellitus and arrhythmias) where these drugs are contraindicated. Such data indicate that tocolysis is not a solved clinical problem. Many examples can be cited of the opposite effect, i.e. of physiological processes mediated by α- and β-adrenergic receptors. Since Garrett demonstrated this relation for the case of the human myometrium (2), it has been concluded that the α-adrenergic receptor antagonists may have a similarly beneficial effect to that of β-agonists on the uterine activity. However, the published data in support of this theory are at present very limited. Lechner et al. investigated the effect

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of doxazosin on human isolated myometrial strips and suggested that α-blockade could be a logical substitution for β-stimulation (3). A bolus dose of prazosin administered at midday on day 22 completely blocks the normal process of the parturition of the rat throughout the next 6 h. Administration of phentolamine at term induced a significant decrease of the uterine activity of the rat *in vivo* (4). Palop et al. demonstrated that prazosin abolished the methoxamine-induced increase of the uterine motility of the rat (5). Ko et al. found that xylazine, a selective α_2-adrenergic agonist, was able to enhance the porcine myometrial contractility *in vitro* and this effect was antagonized by yohimbine in a dose-dependent manner (6).

The objective of the present study was a comparative investigation of the inhibitory effects of α-adrenergic receptor antagonists, including α_1 and α_2 subtype-selective compounds, on the uterine motor activity. A reliable method was elaborated which is suitable for testing drugs acting on the uterine activity *in vivo*. The effects of eight α-antagonists were investigated on the spontaneous uterine activity of the postpartum rat.

Methods

Female Sprague-Dawley rats were anaesthetized with urethane (1 g/kg, i.p.) 8–12 h after spontaneous delivery. After cannulation of the jugular vein, the abdominal cavity was opened and a Millar catheter fitted with a latex microballoon was inserted into the uterus through a small section above the cervical part. The intrauterine pressure was recorded (Hewlett-Packard 7702B) and the effects of the drugs were assessed by expressing the integrated tension in the 1–6 min. period after administration of each compound as a percentage of the average for three 5-min. periods before administration. The maximal inhibition and ED_{50} value were calculated by means of Grafit 3.01.

The following drugs were diluted with physiological saline: phentolamine (Ciba-Geigy AG, Switzerland), urapidil (Byk Gulden, Germany), fenoterol (Boehringer Ingelheim, Germany), terbutalin (Egis-Astra, Hungary), CH-38083 (Chinoin, Hungary), BRL-41992 and BRL-44408 (SmithKline Beecham, U.K.), benoxathian (a gift from Prof. C. Melchiorre, Dept. of Chemical Sciences, University of Camerino, Italy), prazosin and yohimbine (Sigma-Aldrich Ltd., Hungary). The final dilutions of the BRL compounds contained 0.01% hydrochloric acid.

Results

All of the tested compounds decreased the spontaneous uterine activity in a dose-dependent manner **(Table 1)**. In spite of the fact that no significant difference was found between the effectivities of phentolamine, prazosin, yohimbine, urapidil and benoxathian, on the basis of the calculated values the most effective and most potent α-receptor blocking agent was prazosin. The non-selective α-antagonist phentolamine, the α_1-blocker urapidil, the α_2-blocker yohimbine and the α_{1A}-selective antagonist benoxathian were similarly effective, but slightly less potent. The α_{2A} and α_{2B}-selective antagonists (BRL-44408 and BRL-41992, respectively) and the non-selective α_2-blocker CH-38083 had only limited effects (7, 8). To compare the inhibitory effects of α-blocking agents with those of traditionally used tocolytics, we examined fenoterol and terbutalin in the same *in vivo* system. Both had a higher efficacy and a much lower ED_{50} value **(Fig. 1)**.

TABLE I

Calculated ED_{50} and maximal inhibition values of the tested compounds

Compound	ED_{50} (mg/kg)	Maximal inhibition (%)
Phentolamine	0.569	57.6
Prazosin	0.073	67.4
Yohimbine	0.084	57.5
Urapidil	0.093	57.4
CH-38083	0.630	31.3
BRL-41992	0.120	47.6
BRL-44408	0.010	42.1
Benoxathian	0.091	63.8
Fenoterol	0.0010	93.4
Terbutalin	0.0076	93.6

ED_{50}: dose causing 50% of the maximal inhibitory effect

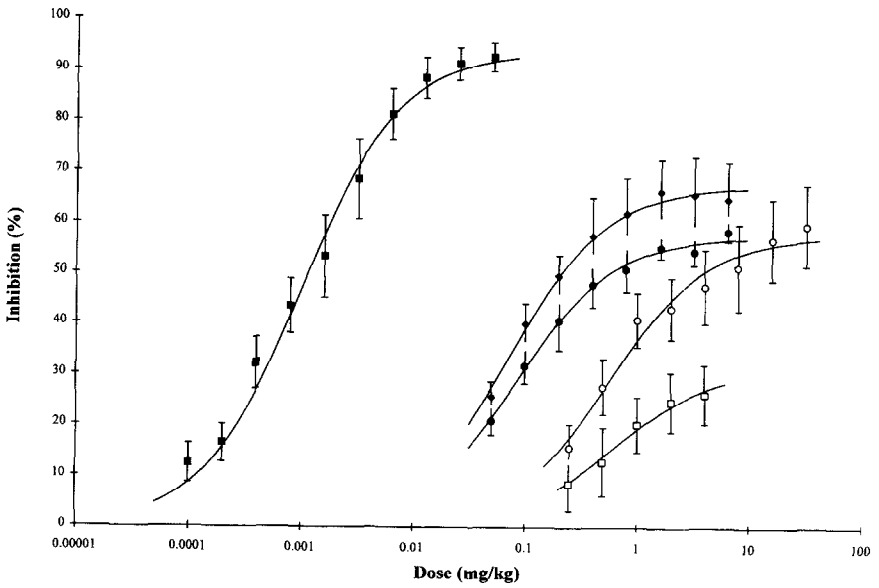

Fig. 1

Inhibition of spontaneous uterine activity of the rat by fenoterol (■), prazosin (◆), yohimbine (●), phentolamine (○) and CH-38083 (□). The data are the averages of the results from six experiments ± S.E.M.

Discussion

In spite of the obvious hormonal differences between the postpartum rat and the human situation, this preparation can be regarded as an animal model of pregnancy (9). Agents affecting the human pregnant uterus exert a similar effect on this object. The novelty in our method is the application of a Millar catheter fitted with a latex microballoon, which makes the measuring more precise. Our results clearly demonstrate that α-adrenergic antagonists have a potential tocolytic effect. Five of the eight tested α-blockers decreased the uterine activity to a significant extent. The question arises of whether the relaxant effect of the tested α-receptor blockers is a consequence of the decreased blood pressure, or whether they have a direct effect on the uterus. We carried out experiments on isolated uterus from the rat (unpublished data), and found similar results. Moreover, the α_2-blocker yohimbine increases the blood pressure, but decreases the motor activity of the uterus of the rat. These data support the theory that α-blockers have a direct relaxing effect on the myometrium. Since the effects of both α_1 and α_2-adrenergic receptors are at least partly mediated by a calcium current, it is possible that these agents exert their tocolytic effect not only on the α-adrenergic receptor, but also on the calcium channel (10, 11). On the other hand, some of the calcium channel blockers (e.g. nifedipine) are under clinical investigation as tocolytics (1). From these facts we conclude that an α-antagonist which has a definite calcium channel blocking activity (e.g. monatepil) may have a higher tocolytic potency and/or efficacy than those of prazosin. None of the tested drugs were as potent and effective as fenoterol and terbutalin. However, there are special groups of patients (e.g. with pregnancy-induced hypertension, tachycardia, diabetes and arrhythmia) where these α-receptor blockers, and in particular prazosin and its congeners, might be preferred to traditionally used β_2-sympathomimetics. Our results may encourage further scientific input into the development of highly subtype-selective (myometrium-specific) α-blockers as clinically usable tocolytics. As concerns the rank order of efficacy of the tested α-blockers, it is suggested that α_1 subtype-selective antagonists might be the most reliable agents. On the basis of these animal experiments, a well-controlled clinical trial could be recommended for an evaluation of the uterus-relaxing effect of the currently used α-blockers.

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