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EXPERIMENTAL STUDY

In vitro vasoactive effects of dexmedetomidine on isolated human umbilical arteries

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ABSTRACT

OBJECTIVE: We aimed to investigate the vasoactive effects of dexmedetomidine on isolated human umbilical arteries and possible mechanisms involved.

METHODS: Human umbilical artery strips were suspended in Krebs–Henseleit solution and dose-response curves were obtained for cumulative dexmedetomidine before and after incubation with different agents; propranolol, atropine, yohimbine, prazosin, indomethacin, verapamil. Effects of calcium on cumulative dexmedetomidine-induced contractions were also studied.

RESULTS: Cumulative dexmedetomidine resulted in dose dependent contraction responses. Incubation with propranolol (Emax: 93.3 ± 3.26 %), atropine (Emax: 92.0 ± 6.54 %), or indomethacin (Emax: 94.25 ± 2.62 %), did not attenuate dexmedetomidine-elicited contractions ($p > 0.05$). There were significant decreases in the contraction responses of cumulative dexmedetomidine with yohimbine (Emax: 12.1 ± 11.9 %), prazosin (Emax: 28.8 ± 4.6 %) and verapamil (Emax: 11.2 ± 13.6 %) ($p < 0.05$). In Ca^{+2} free medium contraction responses to cumulative dexmedetomidine was insignificant (Emax: 5.20 ± 3.42 %). Addition of cumulative calcium to the Ca^{+2} free medium resulted in concentration dependent increase in contractions (Emax: 64.83 ± 37.7 %) ($p < 0.05$).

CONCLUSION: Dexmedetomidine induces vasoconstriction in endothelial-free umbilical arteries via both, α_1- and α_2-adrenergic receptors and also extracellular Ca^{+2} concentrations play a major role. β-adrenergic receptors, muscarinic cholinergic receptors, and inhibition of cyclooxygenase enzyme are not involved in this vasoconstriction *(Fig. 3, Ref. 36).* Text in PDF *www.elis.sk.*

KEY WORDS: alpha adrenergic receptors, dexmedetomidine, in vitro, umbilical cord, vascular smooth muscle.

Introduction

Dexmedetomidine, an α_2-adrenergic receptor agonist, has been used for sedation and analgesia and as an adjunct to anesthesia because of its sedative, analgesic and sympatholytic properties (1). The α_2:α_1 adrenoreceptor specificity ratio of dexmedetomidine is ten times than clonidine (1,600 : 1) (2). This α_2 specificity and a short half-life of six minutes make dexmedetomidine ideal for intravenous titration for sedation and anxiolysis. The Food and Drug Administration (FDA) has approved dexmedetomidine for limited use for sedation, mechanical ventilation and monitored anesthesia care in adults (3). There are current reports on the intraoperative use of dexmedetomidine for various indications including Cesarean sections (4–8). It is crucial to elucidate the possible effects of dexmedetomidine on the uterus and fetal circulation. Dexmedetomidine increases uterine contractility (9) and is transported into the fetal circulation in small amounts (10). Except for the segment that is closest to the fetus, the umbilical cord and the placenta do not contain nerve fibers and are not innervated. The umbilical blood flow mainly depends on local vasoconstrictors such as endothelin-1 and thromboxane and also vasodilators such as prostacyclin (PGI_2) and nitric oxide (NO) (11, 12). The direct effects of vasoactive agents on umbilical vessels are essential due to lack of autonomic innervations (13).

There is no information on the direct effects of dexmedetomidine on human umbilical vessels. This in vitro study was designed to investigate the vasoactive effects of dexmedetomidine on isolated human umbilical arteries and possible mechanisms involved.

Materials and methods

The Institutional Human Ethics Committee approved this study. The umbilical cords were remnant tissues which would have otherwise been discarded.

Collection of samples

After written maternal consent, human umbilical cords were collected from full-term healthy normal vaginal deliveries. After delivery, the umbilical cord was clamped at both placental and fetal ends. An untouched 10–15 cm long segment of the cord from the

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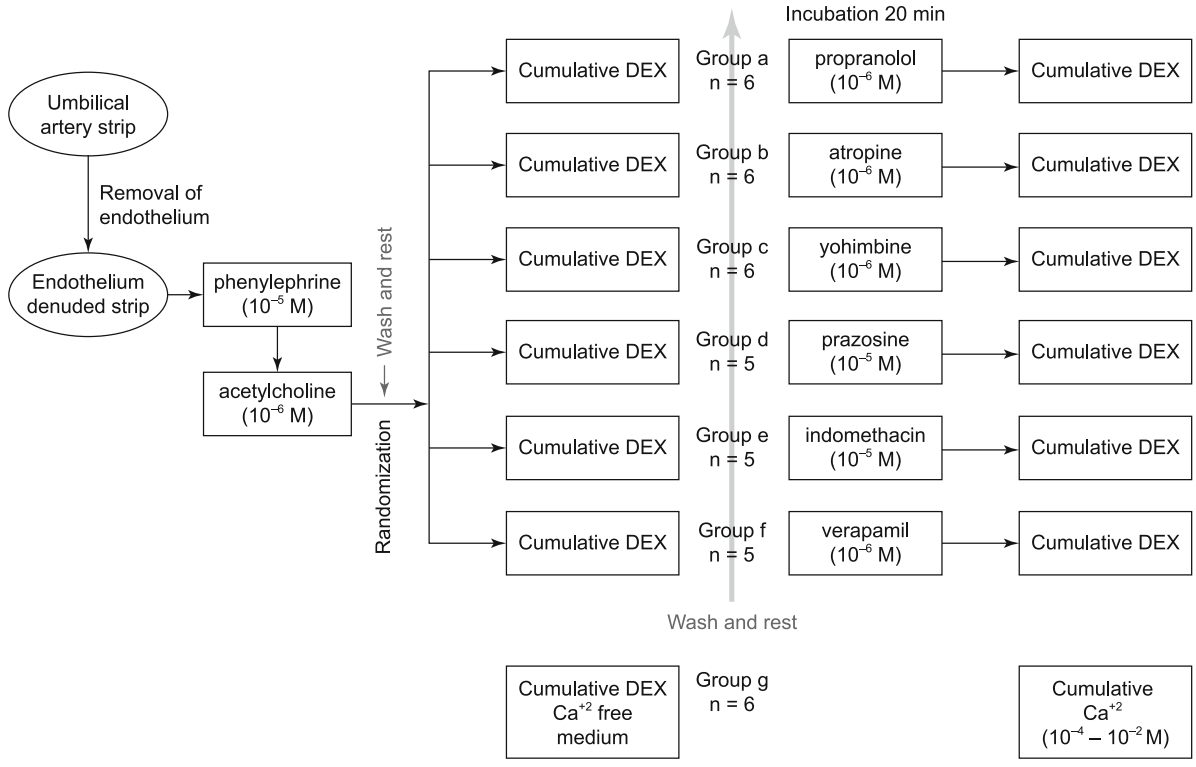

Fig. 1. Flow chart of experimental procedures. DEX: dexmedetomidine (10^{-9} – $2x10^{-5}$ M)

placental end was removed within 10 min of delivery and placed in cold Krebs-Henseleit (KH) solution for immediate transport to the laboratory.

Blood vessel preparation

Umbilical arteries were separated from the surrounding tissue in KH solution. The isolated artery was cut spirally to form 2–3 mm wide and 15–20 mm long strips. The strips were transferred to organ baths containing 20 ml of KH solution maintained at 37 °C. Then the strips were suspended between two hooks; one anchored onto the organ bath and the other connected to a transducer. Smooth muscle contractions were recorded with a force–displacement transducer and digitized data acquisition system (MP35, BIOPAC, Goleta, CA, USA). Strips were aerated with a gas mixture of 95 % O_2: 5 % CO_2 throughout the experiment. Strips were initially placed under a resting tension of 1 g and were allowed to equilibrate for one hour. During this period the bath solution was changed every 15 minutes, and the resting tension was readjusted to the 1 g level.

Experimental protocol

Experimental procedures are summarized in Figure 1. Human umbilical artery strips without endothelium were used during the experiment. Endothelium removal was done by gently denuding the endothelium with cotton swabs. Following the washout period endothelium removal of the strips was examined by contracting the strips with phenylephrine (10^{-5} M) and testing with acetylcholine (10^{-6}M). Strips free of endothelium did not relax with acetylcholine. The strips were rewashed with the buffer solution and allowed to rest. Strips were randomly allocated to study groups.

To assess the possible mechanisms of dexmedetomidine's vascular effects, first, the reactivity of the human umbilical artery to dexmedetomidine was examined. The strips at resting tension in each study group (a to g) (n = 6 or n = 5) were subjected to cumulative concentrations of dexmedetomidine (10^{-9} – $2x10^{-5}$ M), and dose-response curves were recorded. After washing and allowing the strips to rest for one hour, response curves of cumulative dexmedetomidine (10^{-9} – $2x10^{-5}$ M) were obtained in these groups after the strips were incubated for 20 min with different agents; a) propranolol (10^{-6} M) (n = 6) a non-selective β-adrenergic antagonist, b) atropine (10^{-6} M) (n = 6) a competitive antagonist of muscarinic cholinergic receptors, c) yohimbine (10^{-6} M) (n = 6) an α_2-adrenergic antagonist, d) prazosin (10^{-5} M) (n = 5) an α_1-adrenergic antagonist, e) indomethacin (10^{-5} M) (n = 5) a cyclooxygenase enzyme inhibitor, f) verapamil (10^{-6} M) (n = 5) a L-type voltage-sensitive Ca^{2+} channel blocker, and g) in Ca^{+2} free modified KH solution (n = 6). The effect of Ca^{+2} was assessed by first recording $2x10^{-5}$ M dexmedetomidine-induced control contraction in KH solution. The strips were washed and allowed to rest in Ca^{+2} free KH solution for one hour. At the end of the resting period, dose-response curves of cumulative dexmedetomidine (10^{-9}–$2x10^{-5}$ M) in Ca^{+2} free medium were recorded.

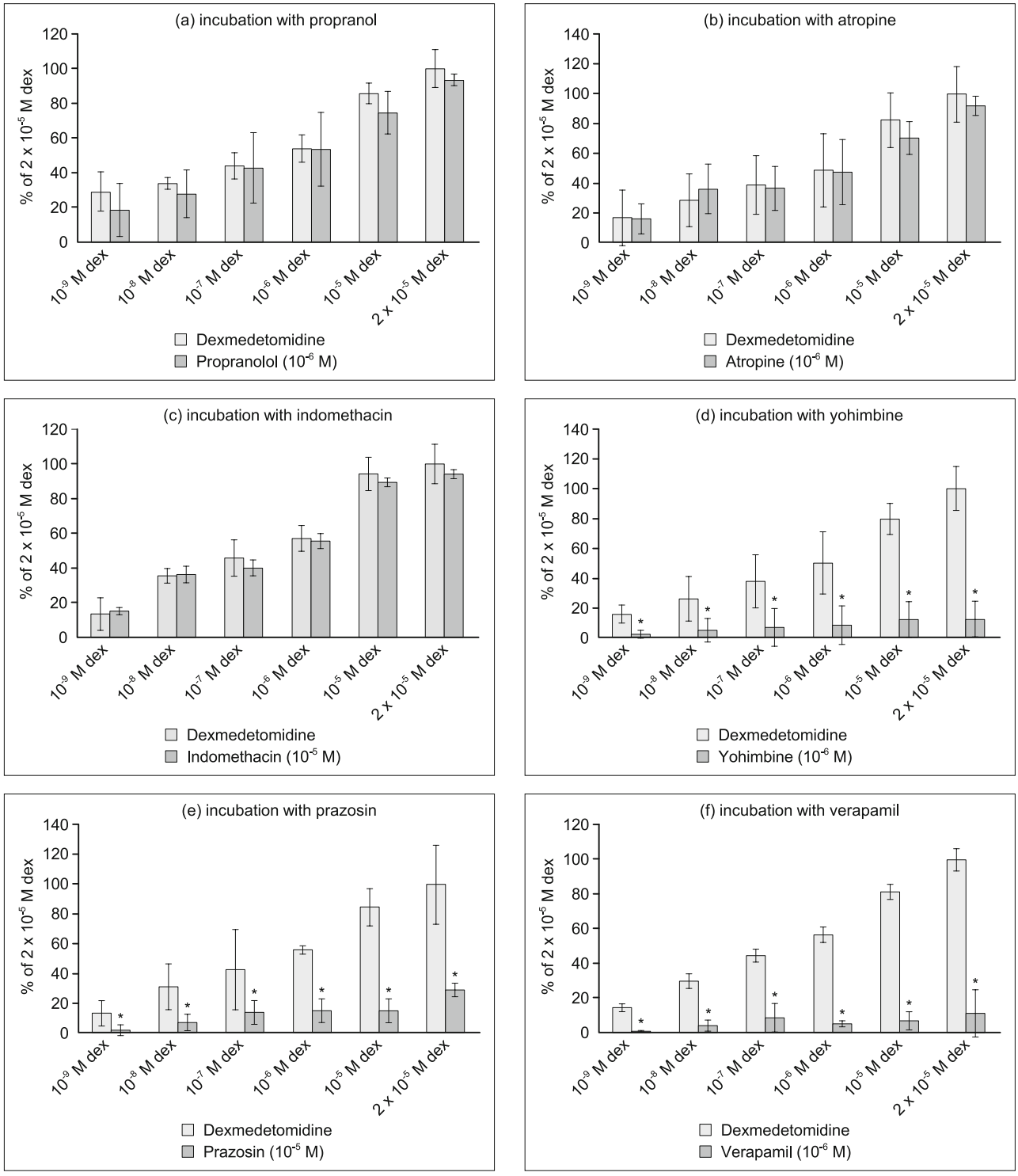

Fig. 2. Effects of incubation with different agents on cumulative dexmedetomidine induced contractions in human umbilical arteries. Groups: propranolol (a), atropine (b), yohimbine (c), prazosin (d), indomethacin (e) or verapamil (f). Results are % of 2 x 10^{-5} M dexmedetomidine induced maximum contraction (mean ± SD), dex: dexmedetomidine, * p < 0.05 compared to same concentration of dexmedetomidine.

After recording the contraction to the maximum concentration of dexmedetomidine (2x10^{-5} M) in Ca^{+2} free medium, contraction responses were obtained by adding cumulative Ca^{+2} (10^{-4}–10^{-2} M) into the media.

Each strip was used for only one experiment. Results are given as % of maximum contraction induced by 2x10^{-5} M dexmedetomidine in each group. Wilcoxon rank test was used for analysis, a p-value less than 0.05 was considered as significant.

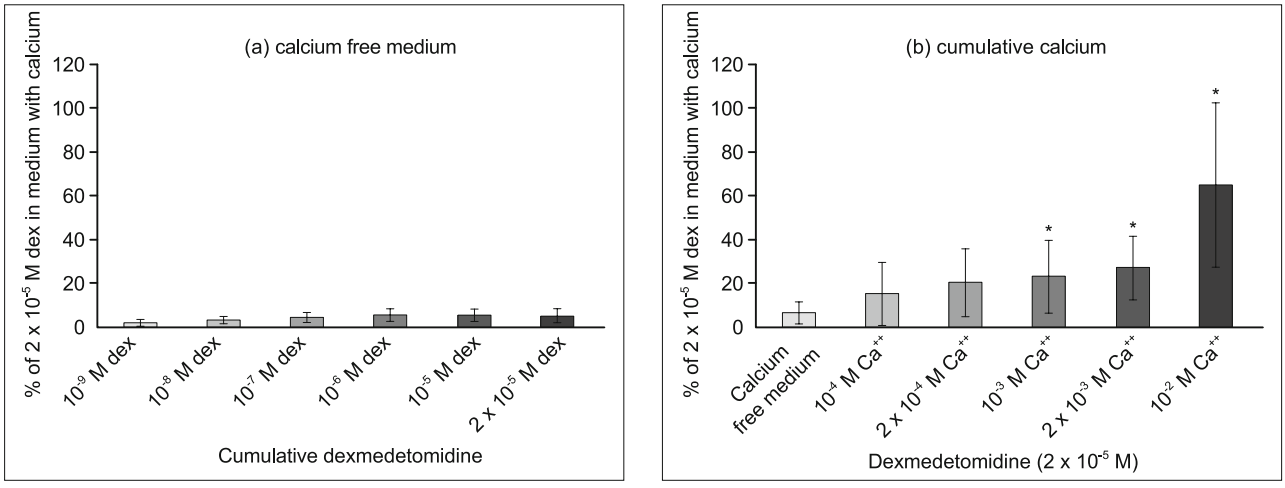

Fig. 3. Effects of calcium on dexmedetomidine induced contractions in human umbilical arteries. a) cumulative dexmedetomidine in calcium free medium, b) cumulative calcium on maximum dexmedetomidine contraction. Results are % of 2 x 10^{-5} M dexmedetomidine induced control contraction (mean ± SD), dex: dexmedetomidine, * $p < 0.05$ compared to calcium free medium.

Materials

Modified Krebs-Henseleit solution and modified Krebs-Henseleit without Ca^{+2} were prepared in the laboratory with compositions of (in mM) NaCl 119; KCl 4.7; $MgSO_4$ 1.5; KH_2PO_4 1.2; $CaCl_2$ 2.5; $NaHCO_3$ 25; glucose 11, and NaCl 119; KCl 4.7; $MgSO_4$ 1.5; KH_2PO_4 1.2; $NaHCO_3$ 25; glucose 11, EGTA 1 respectively. Dexmedetomidine was obtained from Koçak Farma (Istanbul, Turkey). All other drugs (atropine, acetylcholine, phenylephrine, indomethacin, prazosin, propranolol, verapamil, and yohimbine), were obtained from Sigma-Aldrich (St. Louis, MO, USA). The drugs were prepared and subsequently diluted in distilled water. All concentrations are expressed as final molar concentrations (M).

Results

Cumulative dexmedetomidine resulted in dose dependent contraction responses in umbilical artery strips. Incubation with propranolol (Emax: 93.3 ± 3.26 %), atropine (Emax: 92.0 ± 6.54 %), or indomethacin (Emax: 94.25 ± 2.62 %), did not significantly attenuate dexmedetomidine-elicited contractions (Figs 2a, b, c) ($p > 0.05$). There were statistically significant decreases in the contraction responses of cumulative dexmedetomidine in the presence of yohimbine (Emax: 12.1 ± 11.9 %) (Fig. 2d), prazosin (Emax: 28.8 ± 4.6 %) (Fig. 2e) and verapamil (Emax: 11.2 ± 13.6 %) (Fig. 2f) ($p < 0.05$).

In Ca^{+2} free medium the contraction responses to cumulative dexmedetomidine were insignificant (Emax: 5.20 ± 3.42 %) (Fig. 3a). Addition of cumulative calcium to the Ca^{+2} free medium resulted in concentration dependent increase in the dexmedetomidine induced contractions (Emax: 64.83 ± 37.7 %) (Fig. 3b) ($p < 0.05$).

Discussion

The present in vitro study shows that in endothelium free umbilical arteries, dexmedetomidine causes dose-dependent vasoconstriction. Our results also demonstrate that dexmedetomidine leads to vasoconstriction in endothelium-denuded umbilical artery strips via both the $\alpha_1$and α_2-adrenergic receptors at both low and high concentrations. These results are in part different from previous research which reported that through postsynaptic α_2-receptor activation, dexmedetomidine causes vasoconstriction in various human and animal vessels, including coronary arteries, peripheral arterioles, cerebral arteries, gastroepiploic and brachial arteries (14–17). According to some of these studies, α1-adrenergic receptors contribute to vasoconstriction at high concentrations of dexmedetomidine (15, 17). In a study showing the vasoconstrictor effect of dexmedetomidine on human internal mammary artery (IMA), yohimbine attenuated the contraction resulting from lower doses of dexmedetomidine, whereas prazosin attenuated contraction resulting at higher doses of dexmedetomidine. Their data suggest that dexmedetomidine causes contraction by activating α_2-adrenergic receptors at lower concentrations, but it may also activate α_1-adrenergic receptors at higher concentrations in IMA (15). It is suggested that the contractile adrenergic receptors in the human umbilical artery consist of both α_1 and α_2 subtypes (18). In the present study α_1- adrenergic receptor antagonist prazosin significantly inhibited the constriction at both low and high concentrations of dexmedetomidine; suggesting that both α_1-receptors, as well as α_2-receptors, are involved in the vasoconstrictor effect of dexmedetomidine on the umbilical artery.

The present study was conducted on endothelium denuded vascular rings, which provides us to study the direct effects of drugs on vascular smooth muscle by removing endothelial factors. In vivo, α_2-adrenergic agonists can have different results. They may diminish norepinephrine release by prejunctional α_2-adrenergic receptor stimulation, thereby decreasing local and circulating catecholamines (19, 20) or may activate α_2-adrenergic receptors on endothelial cells, resulting in the release of endothelium-derived NO (14).

Vasoconstriction is controlled by calcium-dependent and calcium sensitization mechanisms (21). Calcium influx from the ex-

tracellular space and release from the sarcoplasmic reticulum are associated with intracellular free Ca^{2+}concentrations. Dexmedetomidine-induced vasoconstriction involves calcium sensitization mediated by Rho kinase, protein kinase C, and phosphoinositide 3-kinase (22). In the present study, verapamil and Ca^{2+} free medium resulted in minor contractions. Incubation with verapamil and Ca^{2+} free medium significantly decreased but did not block these contractions suggesting; significant involvement of extracellular Ca^{2+} rather than release from intracellular Ca^{2+} stores. Some of the effects of postsynaptic α_2-adrenergic receptors on vascular smooth muscle cells are mediated by molecular mechanisms that are common to α_2 and α_1 adrenergic receptors (23). Different G protein signal transduction pathways mediate the primary coupling mechanisms of α1 and α2 adrenergic receptors. α_1 adrenergic receptors signal through Gq-proteins (24), activate smooth muscle contraction through the phospholipase C- inositol trisphosphate (IP_3) signal transduction pathway (25). In addition to mobilizing intracellular calcium, depending on the receptor subtype of the vessel, the α_1-adrenergic receptors have also been shown to activate calcium influx via L-type voltage-sensitive Ca^{2+} channels (26, 27, 28), whereas α_2 adrenergic receptors signal via Gi proteins that inhibit adenylyl cyclase activity and decrease intracellular cAMP in smooth muscle cells but may also mediate stimulation extracellular Ca^{2+} influx through voltage-sensitive Ca^{2+} channels (23, 29, 30).

Potentially useful features of dexmedetomidine have expanded the off-label use of the drug outside of the ICU, including adjunctive for spinal and epidural anesthesia for Cesarean section (5–7), sedation for eclampsia (31), anxiolysis during laboring or Cesarean section (32, 33). Potential advantages of α_2-agonists during obstetric practice bring the need to further assess the pharmacological effects and safety of dexmedetomidine on the uterus, placenta and the umbilical circulation. Dexmedetomidine enhances spontaneous contractions in-vitro in rat and human myometrium (8, 34). Due to its high lipophilicity dexmedetomidine crosses the placenta less readily than clonidine but still should be used during pregnancy only if the benefits justify the risk to the fetus (10, 35).

This study has several limitations. It is an in vitro study. The clinical effects of dexmedetomidine on umbilical vessels may be different from our in-vitro results. It was conducted on endothelium denuded vasculature aiming to study the direct effects of drugs on vascular smooth muscle. Our results were not affected by the vasoactive substances of the endothelium such as NO. Dexmedetomidine possesses an imidazoline ring in its structure, and vascular K_{ATP}-channel inhibition may be an underlying mechanism of the vasoconstriction (36). The present study did not assess the K^+ channel activity.

Conclusion

Different from other vasculature, dexmedetomidine has a concentration-dependent vasoconstrictive effect on the endothelial-free umbilical artery via both α_1- and α_2-adrenergic receptors. Dexmedetomidine-induced vasoconstriction is dependent on extracellular Ca^{2+} concentrations and calcium influx via L-type voltage-sensitive Ca^{2+} channels. Also β-adrenergic receptors, muscarinic cholinergic receptors and inhibition of cyclooxygenase enzyme are not involved in direct mechanisms regulating the effects of dexmedetomidine on smooth muscle vascular tone of the umbilical artery.

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