Effects of dexmedetomidine on porcine pulmonary artery vascular smooth muscle

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Abstract

Background Dexmedetomidine is added to local anesthetics to increase their potency and extend their duration of action, thus providing postoperative analgesia with a single administration. However, the effects and mechanism of action of dexmedetomidine on pulmonary arteries have not been determined. The aim of this study was to investigate the effect of dexmedetomidine on pulmonary artery vascular smooth muscle, evaluating changes in contraction tension. Methods Endothelium-denuded porcine pulmonary arteries were sliced into 2- to 3-mm rings. Changes in isometric contraction tension were measured with the addition of various substances at various concentrations, under different conditions of baseline stimulation (with KCl, Adrenaline, caffeine, or histamine) and different conditions of Ca2+ depletion with intracellular reservoirs or extracellular stores depleted. Results Dexmedetomidine increased the contraction tension induced by high-KCl depolarization in a concentration-dependent manner. Dexmedetomidine inhibited receptor-activated Ca2+ channels (RACCs) and phosphatidylinositol-1,4,5-triphosphate-induced Ca2+ release (IICR), but not Ca2+-induced Ca2+ release (CICR). Conclusions Dex increased the contraction tension resulting from depolarization stimulation by high KCl in a concentration-dependent manner in porcine pulmonary artery vascular smooth muscle. The enhancement of high KCl-induced contraction with Dex addition was mediated by α2 receptors. Dex suppressed increases in contraction tension induced by receptor stimulation with adrenaline, also in a concentration-dependent manner. Dex inhibited RACC and IICR, but not CICR. Elucidating the effects and mechanisms of action of Dex in the central arteries is likely to be useful as basic data for creating Dex-containing local anesthetics.

Background

Alpha$_2$-receptor agonists have been shown to produce sedative and analgesic effects not only with systemic administration but also when administered in the extradural space and around peripheral nerves [1-3]. Among these, dexmedetomidine hydrochloride (Dex) is added to local anesthetics to increase their potency and extend their duration of action, thus providing postoperative analgesia with a single administration. Narcotics, autonomic nerve agonists, and steroids have recently been studied extensively for this purpose. In dentistry, the current use of local anesthetics containing adrenaline may cause abnormal blood pressure increases, leading to adverse effects such as cerebrovascular disease. To prevent these complications, the adrenaline in local anesthetics should be replaced with an additive that causes smaller fluctuations in circulation during local anesthesia. Dex has recently attracted attention for this purpose. Studies in guinea pigs have shown that percutaneously injected Dex-containing lidocaine hydrochloride resulted in concentration-dependent increases in the anesthetic effect [4], decreases in local blood flow without fluctuations in blood pressure or pulse rate [5], and suppression of inflammation at the injection site [6]. The use of Dex-containing lidocaine as a local anesthetic may offer simultaneous prolongation and potentiation of anesthetic effects and may be useful for dental treatment in patients with cardiovascular disease. Dex has thus attracted attention and is being tested in clinical studies as a new additive agent for dental local anesthetics. However, the effects and mechanism of action of Dex on

cardiopulmonary vascular system have not been studied. To elucidate the effects and mechanism of action of Dex in the vascular smooth muscle of the pulmonary artery, we simultaneously measured isometric contraction tension in the pulmonary artery. We then attempted to determine the effects of Dex on depolarization stimulation and receptor stimulation.

Materials And Methods

This study was approved by the Institutional Review Committee on the Ethics of Animal Experiments of Iwate Medical University. All experiments were conducted in accordance with the Institutional Animal Care and Use Committee guidelines (Ethical number is 26-010).

Experimental materials

The pigs are slaughtered as part of routine procedure in a slaughter house. We obtained the lung of the pig from this slaughter house. The third of pulmonary arteries, which were 2 to 3 mm in diameter, were excised from the lung of a slaughtered pig (6 months of age) and cut into rings 2 to 3 mm in length. The endothelium, which was rubbed gently against the thin arm of stainless steel tweezers, was then denuded and the rings inverted to prepare specimens of pulmonary artery vascular smooth muscle, with the inner surface presented outward. It was confirmed that 3μM acetylcholine-induced relaxation of the artery rings disappeared after this procedure. N means number of rings.

Experimental methods

Method for isometric contraction tension

Specimens were placed in the incubator (1.0 mL) and a resting tension of 4 mN was applied. After perfusion with the Hank's balanced salt solution (HBSS) for 30 min, various stimulants were administered; the resulting contraction tension was simultaneously measured. To measure contraction tension, one end of the specimen in the incubator was fixed to a manipulator (M-152; NARISHIGE, Tokyo, Japan) and the other end was fixed via a tungsten wire to a tension transducer (UL-2GR; Minebea, Tokyo, Japan). Data were recorded on PowerLab® (ADInstruments, Bella Vista, Australia) via a pressure amplification unit (N4438; NEC San-ei, Tokyo, Japan). The composition of HBSS was as follows: 0.34 mM $Na_2HPO_4{\cdot}7H_2O$, 0.44 mM KH_2PO_4, 0.8 mM $MgSO_4$, 1.26 mM $CaCl_2$, 4.2 mM $NaHCO_3$, 5.55 mM glucose, 5.36 mM KCl, and 137 mM NaCl at pH 7.37.

Effects of various α receptors on the vascular smooth muscle of pulmonary arteries

Direct effects of various concentrations of Dex and imidazoline on vascular smooth muscle

After an approximate 2-min perfusion with 60 mM KCl solution, contraction tension was measured, recorded, and used as control values. Next, HBSS containing 10^{-10}, 10^{-9}, 10^{-8}, 10^{-7}, 10^{-6}, 5×10^{-6}, and 10^{-5} M Dex (Wako; molecular weight, 266.55, Tokyo, Japan) or imidazoline (Wako; molecular weight,

236.74, Tokyo, Japan) were administered for 2 min each, in that order. Changes in the resulting isometric contraction tension at each concentration were measured and recorded (Fig. 1).

Effects of various concentrations of Dex and imidazoline on high KCl-induced contraction tension

After an approximate 2-min perfusion with 60 mM KCl solution, contraction tension was measured, recorded, and used as control value. Next, 60 mM KCl containing 10^{-10}, 10^{-9}, 10^{-8}, 10^{-7}, 10^{-6}, 5×10^{-6}, and 10^{-5} M Dex or imidazoline were administered for 2 min each, in that order. Change in isometric contraction tension at each concentration was measured and recorded and dose dependence curve was constructed (Fig. 2).

Effects of yohimbine, rauwolscine, and prazosin on high KCl-induced contraction tension

After an approximate 2-min perfusion with 60 mM KCl solution, contraction tension was measured, recorded, and used as control value. Next, 60 mM KCl solution containing 5×10^{-6} M Dex was administered, and changes in contraction tension was measured and recorded. Then 60 mM KCl solutions containing 5×10^{-6} M yohimbine, rauwolscine, or prazosin were administered for 2 min each, and change in contraction tension was measured and recorded (Fig. 3).

Effects of various concentrations of Dex, imidazoline, yohimbine, and rauwolscine on adrenaline-induced contraction tension

After an approximate 2-min perfusion with HBSS containing 5×10^{-6} M adrenaline (Wako; molecular weight, 333.6, Tokyo, Japan), contraction tension was measured, recorded, and used as control value. Next, 5×10^{-6} M adrenaline solutions containing 10^{-10}, 10^{-9}, 10^{-8}, 10^{-7}, 10^{-6}, 5×10^{-6}, and 10^{-5} M Dex , imidazoline, yohimbine, and rauwolscine were administered for 2 min each, in that order. Change in contraction tension at each concentration was measured and recorded (Fig. 4).

Effects of Dex on adrenaline-induced contraction tension with $[Ca^{2+}]_i$ reservoir depletion

After an approximate 2-min perfusion with 60 mM KCl solution, contraction tension was measured, recorded, and used as control value. Next, under perfusion with a Ca^{2+}-free HBSS containing 1×10^{-3} M EDTA, the following drugs were administered: 2.5×10^{-2} M caffeine (Wako: molecular weight, 212.21, Tokyo, Japan) was administered for 2 min, 3×10^{-5} M ryanodine (Wako: molecular weight, 493.55, Tokyo, Japan) was administered for 5 min, and then 2.5×10^{-2} M caffeine was administered twice for 2 min each. Subsequently, a Ca^{2+}-containing HBSS containing 5×10^{-6} M adrenaline or Ca^{2+}-containing HBSS containing 5×10^{-6} M adrenaline supplemented with 5×10^{-6} M Dex was administered for approximately 30 min . Change in contraction tension was measured and recorded (Fig. 5).

Effects of Dex on adrenaline-, caffeine- and histamine-induced contraction tension in the absence of extracellular Ca^{2+}

After an approximate 2-min perfusion with 60 mM KCl solution, contraction tension was measured, recorded, and used as control value. Next, after 15 min of perfusion with a Ca^{2+}-free HBSS containing 1×10^{-3} M EDTA, 5×10^{-6} M adrenaline and histamine, and 25 mM caffeine were administered for 2 min, and contraction tension was measured and recorded. Next, reference values were measured in the same manner as control values, 5×10^{-6} M adrenaline and histamine, and 25 mM caffeine supplemented with 5×10^{-6} M Dex were administered for 2 min after 30 min of perfusion with a Ca^{2+}-free HBSS containing 1×10^{-3} M EDTA, and then contraction tension was measured and recorded (Fig. 6).

Statistical Analysis

Values are presented as mean ± SEM. Statistical analysis was performed with SPSS, version 11.0 (SPSS, Chicago, IL, USA). Differences between the means of two groups were evaluated with Student's *t* test. Differences among multiple groups, whose homogeneity of variance was assessed with Levene's test, were evaluated with repeat measure analysis of variance (ANOVA) followed by Scheffe's multiple comparison procedure. Differences were considered significant at p-values of <0.05.

Results

Direct effects of various concentrations of Dex and imidazoline on pulmonary artery vascular smooth muscle

No significant changes in contraction tension was observed with the addition of Dex or imidazoline to the untreated samples. However, slight increases in contraction tension were observed with high concentrations of Dex and imidazoline (Fig. 1).

Effects of various concentrations of Dex and imidazoline on high KCl-induced contraction tension

Dex increased the 60 mM KCl-induced contraction tension in the pulmonary artery vascular smooth muscle in a concentration-dependent manner. The observed increases reached significance at concentrations of Dex $\geq 10^{-7}$ M in the pulmonary artery vascular smooth muscle. Imidazoline increased 60 mM KCl-induced contraction tension in the pulmonary artery vascular smooth muscle in a concentration-dependent manner. The increases reached significance at $\geq 10^{-5}$ M in the pulmonary artery vascular smooth muscle (Fig. 2).

Effects of yohimbine, rauwolscine, and prazosin on high KCl-induced contraction tension

Yohimbine, rauwolscine, and prazosin showed no significant effect on 60 mM KCl-induced contraction tension in the pulmonary artery vascular smooth muscle. Increases in contraction tension by stimulation with 60 mM KCl containing Dex were significantly suppressed by yohimbine and rauwolscine, which are α_2-receptor antagonists. However, no significant difference was observed with the α_1-receptor antagonist prazosin (Fig. 3).

Effects of various concentrations of Dex, imidazoline, yohimbine, and rauwolscine on adrenaline-induced contraction tension

Dex, Imidazoline, yohimbine, and rauwolscine decreased adrenaline-induced increases in contraction tension in a concentration-dependent manner in the pulmonary artery vascular smooth muscle (Fig. 4).

Effects of Dex on adrenaline-induced contraction tension with Ca^{2+} reservoir depletion

The first administration of caffeine, which caused the intracellular reservoir to release Ca^{2+} during perfusion with a Ca^{2+}-free HBSS, induced transient increases in contraction tension. The second and third caffeine doses, which were administered after fixing the Ca^{2+}-induced Ca^{2+} release (CICR) channels in the open state with ryanodine, induced no appreciable changes in contraction tension. When Ca^{2+}-containing adrenaline was administered in this state, the contraction tension slowly increased and then remained in a steady state (control). The Ca^{2+}-containing adrenaline solution containing Dex administered under the same conditions as the control induced similar changes in contraction tension as in the control. However, the maximum value was significantly lower (Fig. 5).

Effects of Dex on adrenaline-, caffeine- and histamine-induced contraction tension in the absence of extracellular Ca^{2+}

When Ca^{2+} was present in the intracellular reservoir but absent in the extracellular fluid, contraction tension transiently increased with administration of adrenaline, caffeine and histamine, and then rapidly decreased (control). Dex-containing adrenaline, caffeine and histamine administered under the same conditions as the control induced similar change in contraction tension as the control. In Dex containing adrenaline and histamine, the maximum values were significantly lower, and Dex-containing caffeine had no effects on contraction tension (Fig. 6).

Discussion

This study had two major findings. First, in porcine pulmonary artery vascular smooth muscle, Dex increased contraction tension induced by depolarization stimulation with high KCl and reduced increases in contraction tension induced by adrenaline receptor stimulation. These effects were concentration-

dependent in both cases. Second, Dex suppressed receptor-activated Ca^{2+} channels (RACCs), which allow extracellular Ca^{2+} into the cells, and phosphatidylinositol-1,4,5-triphosphate (IP_3)-induced Ca^{2+} release (IICR), which releases intracellular Ca^{2+} within cells. However, Dex did not suppress CICR.

The concentration-dependent increases in contraction tension induced by depolarization stimulation with high KCl and the suppression of increases in contraction tension induced by adrenaline-receptor stimulation seen with Dex administration. In this study, Dex did not induce significant contraction in resting smooth muscle (Fig. 1). However, Dex enhanced the contraction induced by high KCl stimulation in a concentration-dependent manner (Fig. 2). Dex-induced enhancement of contraction induced by high KCl was completely suppressed by yohimbine and rauwolscine, which are α_2-receptor antagonists, but not by the α_1-receptor antagonist prazosin (Fig. 3). This result suggests that the enhancing effect of Dex on vascular smooth muscle contraction induced by high KCl depolarization is mediated by an α_2-receptor mechanism. A study of endothelium-denuded human gastroepiploic arteries showed that the enhancement of high KCl-induced vascular smooth muscle contraction observed with Dex addition was completely antagonized by the α_2-receptor antagonists yohimbine and rauwolscine; the authors concluded that the enhancing effect of Dex was mediated by α_2 receptors [7]. A study on the human forearm showed that the vasoconstriction effect of Dex after administration of a β- or α_2-receptor antagonist was completely antagonized by the α_2-receptor antagonist yohimbine [8]. In general, high KCl-induced contraction of vascular smooth muscle is mediated by increased Ca^{2+} through influx of extracellular Ca^{2+} via voltage-dependent Ca^{2+} channels (VDCC) . These channels open in response to cell membrane depolarization and the resulting intracellular CICR occurs via ryanodine receptors on the endoplasmic reticulum (ER) [9]. Dex-induced increases in high KCl-induced contraction tension (Fig. 2) may promote VDCC-mediated influx of extracellular Ca^{2+} and/or CICR. Stimulation with caffeine activates ryanodine receptors on the ER and promotes CICR to increase Ca^{2+} resulting in contraction. In the present experiment, Dex was found to produce no effects on caffeine-induced increases in contraction tension in the Ca^{2+}-free HCS solution (Fig. 6). Therefore, the mechanism by which Dex increases depolarization-induced contraction of the pulmonary artery vascular smooth muscle is not facilitation of CICR from the Ca^{2+} reservoir. Rather, the increase is likely to result from facilitated influx of extracellular Ca^{2+} via VDCC. Alpha-2 receptor-induced contraction of human subcutaneous resistance arteries depends, at least in part, on Ca^{2+} influx via L-type VDCC [10]. Alpha-2 receptor stimulants directly promote VDCC by a mechanism that depends on a G protein associated with protein kinase C activation [11]. It has also been reported that α_2-receptor stimulation in rat saphenous vein vascular smooth muscle results from depolarization of the cell membrane, which indirectly enhances Ca^{2+}-dependent contraction and Ca^{2+} sensitivity through VDCC activation [12]. Because Dex has an imidazole group, it is believed to act not only on the α_2 receptor but also on imidazoline receptors [13]. We therefore administered imidazoline, which is an imidazoline-receptor stimulant, and compared its effects with those of Dex. Imidazoline enhanced high KCl-induced contraction in a concentration-dependent manner. This result suggests that

imidazoline receptor stimulation may increase the contraction resulting from depolarization with high KCl. Imidazoline had weaker effects than Dex on cell membrane depolarization (Fig. 2).

The α_2-receptor stimulant Dex, imidazoline-receptor stimulant imidazoline, and α_2-receptor antagonists yohimbine and rauwolscine produced concentration-dependent decreases in contraction induced by the α_1/α_2-receptor stimulant adrenaline in the pulmonary artery vascular smooth muscle. Dex and imidazoline suppressed contraction resulting from adrenaline. This finding suggests that receptor stimulants containing an imidazoline group inhibit receptor stimulation involving both α_1 and α_2.

In the present study, adrenaline-induced contraction was suppressed by the α_2-receptor stimulant Dex, the imidazoline-receptor stimulant imidazoline, and the α_2-receptor antagonists yohimbine and rauwolscine. These findings suggest that the effect of Dex on adrenaline-induced contraction is attributable to its α_2-receptor-blocking action.

Dex inhibited RACC and IICR, but not CICR. Cell membrane Ca^{2+} channels regulated by receptor stimulation include RACC, which is a receptor that has a channel function coupled with receptor stimulants and which mediates the influx of extracellular Ca^{2+}. Receptor stimulants activate phospholipase C by activating G protein-coupled receptors on the cell membrane, resulting in the production of IP_3 from phosphatidylinositol, one of the lipid components of the cell membrane. IP_3 production leads to the activation of IICR, Ca^{2+} release from the intracellular reservoir [19]. Influx of extracellular Ca^{2+} and IP_3 activate ryanodine receptors on the ER, causing CICR of the Ca^{2+} reservoir. Both IP_3 and ryanodine receptors are present on the ER and play an important role in the regulation of Ca^{2+} release [20]. Vascular smooth muscle contraction is regulated by changes in the Ca^{2+} sensitivity of contraction proteins through phospholipase C activation by receptor stimulation [21]. The present study showed that Dex reduced the increases in contraction tension induced by the receptor stimulant adrenaline, suggesting that it suppressed RACC-mediated influx of extracellular Ca^{2+}, IICR, CICR, or all three (Fig. 4). Dex's suppression of adrenaline-induced increases in contraction tension after depletion of Ca^{2+} suggest that Dex reduces the RACC-mediated influx of extracellular Ca^{2+} (Fig. 5). Dex's suppression of adrenaline-induced increases in contraction tension in the absence of extracellular Ca^{2+} suggest that Dex suppresses IICR and/or CICR (Fig. 6). In the absence of extracellular Ca^{2+}, Dex did not affect caffeine-induced increases in contraction tension (Fig. 6). Caffeine stimulation activates ryanodine receptors on the ER and promotes CICR to induce contraction [9]. This mechanism suggests that Dex suppresses IICR, because it did not suppress CICR. We conducted experiments with histamine to confirm that Dex suppresses IICR. Receptor stimulation by histamine is coupled with phospholipase C via Gq, a G protein-mediated seven-transmembrane receptor. Ca^{2+} is recruited via IP_3 as a second messenger; contraction then occurs through diacylglycerol-mediated activation of protein kinase C [17]. Thus, histamine is believed to act specifically on IICR [18]. Our previous study showed that receptor stimulation in the absence of Ca^{2+} in the extracellular fluid and following depletion of the Ca^{2+} reservoir with caffeine and ryanodine did not cause any changes in contraction tension [19]. This finding indicates that IP_3 receptor

stimulation results in no Ca^{2+} release from the Ca^{2+} reservoir when ryanodine receptors are fixed in the open state. The experiment showed that histamine-induced increases in contraction tension was reduced in the absence of extracellular Ca^{2+}, suggesting that Dex suppresses IICR (Fig. 6).

Dex at high doses activates $\alpha_{2\beta}$ receptors distributed in vascular smooth muscle, causing hypertension resulting from contraction of the vascular smooth muscle. At low doses, Dex causes hypotension resulting from vasodilation and bradycardia resulting from parasympathetic dominance [20].

Studies have found that the addition of Dex to local anesthetics, for example during spinal anesthesia, extended the duration of anesthesia [3]. Another study found that the administration of 100 μg of Dex to the brachial plexus for brachial nerve block significantly extended the duration of effect of local anesthetics [2]. Significantly reduced blood flow was reported in guinea pigs that received 1.0 μM Dex trans dermally [5], and a prolonged duration of action of local anesthetic was observed when 0.1 to 1.0 μM Dex was administered, findings that are pertinent to the field of dentistry [4]. Anti-inflammatory effects have also been observed in mice that received Dex concentrations ≥0.1 μM [6]. One clinical report also suggested that at high doses ($>10^{-8}$ mol/L) Dex increases peripheral vascular resistance, leading to an increase in blood pressure [21]. A previous report investigating the effect of mepivacaine on the isolated rat aorta found that verapamil and calcium-free Krebs solution attenuated mepivacaine-induced contraction of the endothelium-denuded aorta [22]. Thus, calcium influx via voltage-operated calcium channel (VOCC) activation by low concentrations of mepivacaine may trigger the initial contraction [22]. If the situation may be mediated by VDCC activation, it may be possibility that at large doses ($> 10^{-6}$ M) Dex demonstrates the vasoconstrictor effects on the pulmonary artery. It is unclear whether the 5 μM Dex concentration used in the present study is optimal for addition to local anesthetics. The optimal concentration should be explored in the future, based on these previous reports.

Conclusions

Dex increased the contraction tension resulting from depolarization stimulation by high KCl in a concentration-dependent manner in porcine pulmonary artery vascular smooth muscle. The enhancement of high KCl-induced contraction with Dex addition was completely antagonized by the α_2-receptor antagonists yohimbine and rauwolscine, therefor this enhancing effect of Dex was mediated by α_2 receptors. Dex suppressed increases in contraction tension induced by receptor stimulation with adrenaline, also in a concentration-dependent manner. Dex inhibited RACC and IICR, but not CICR. Elucidating the effects and mechanisms of action of Dex in the central arteries is likely to be useful as basic data for creating Dex-containing local anesthetics.

Abbreviations

HBSS: Hank's balanced salt solution; VDCC: Voltage-dependent Ca^{2+} channel; RACC: Receptor-activated Ca^{2+} channel; IICR: phosphatidylinositol-1,4,5-triphosphate (IP_3)-induced Ca^{2+} release; CICR: Ca^{2+}-induced

Ca^{2+} release

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Committee on the Ethics of Animal Experiments of Iwate Medical University. All experiments were conducted in accordance with the Institutional Animal Care and Use Committee guidelines (Ethical number is 26-010).

Consent for publication

All authors have read the final manuscript and consent to publication in BMC Anesthesiology.

Availability of data and materials

The datasets during and/or analyzed during current study available from the corresponding author on reasonable request.

Competing interests

The author declare that they have no competing interests.

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There was no founding in this manuscript.

Authors' contributions

MC contributed to data collection, data analysis, and manuscript preparation; approved the final manuscript; and attests to the integrity of the original data and the analysis reported in this manuscript. KS contributed to study design, data collection, data analysis, and manuscript preparation; approved the final manuscript, and attests to the integrity of the original data and the analysis reported in this manuscript.

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Figures

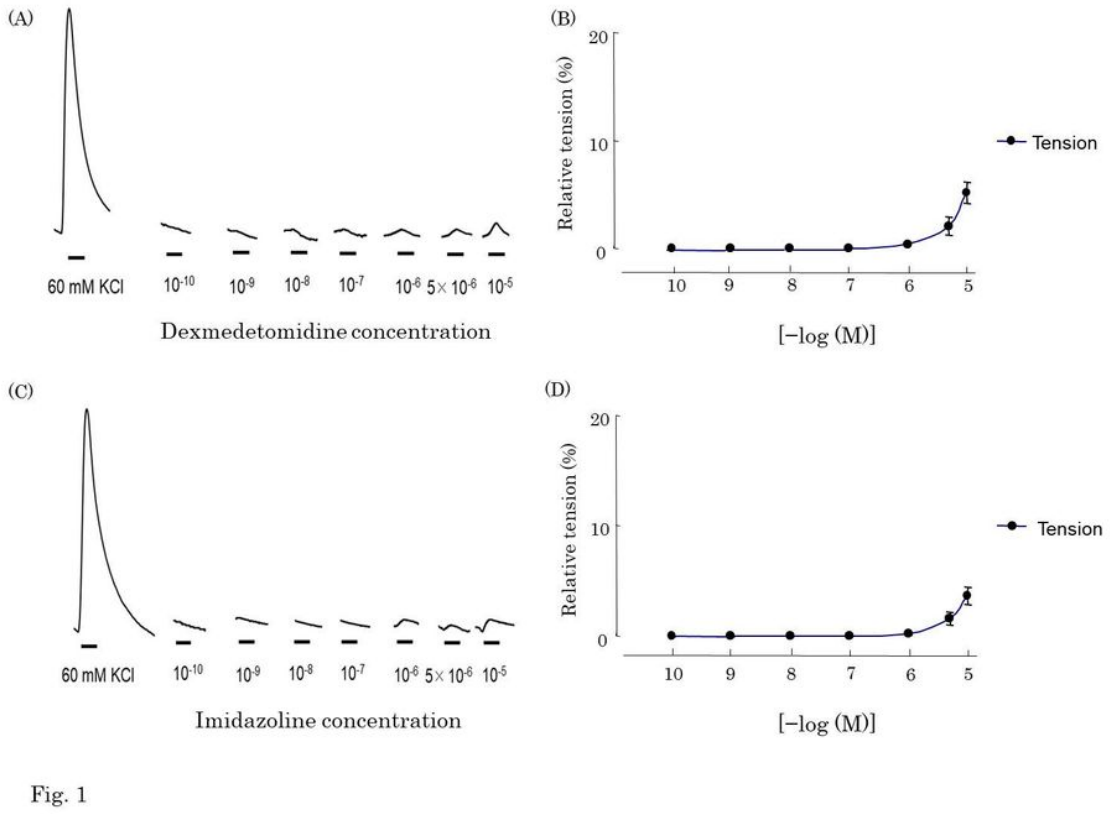

Fig. 1

Figure 1

Direct effects of various concentrations of dexmedetomidine (Dex) and imidazoline on pulmonary artery vascular smooth muscle. Representative traces showing the effects of Dex (A) and imidazoline (B) on contraction tension. (C and D) Analyzed data. In the pulmonary artery samples, addition of Dex at concentrations of 10−6, 5 × 10−6, and 10−5 M caused contraction tension to increase by 0.4±0.1%, 2.1±0.8%, and 5.2±1%, respectively. The addition of imidazoline at concentrations of 10−6, 5 × 10−6, and 10−5 M caused contraction tension to increase in the pulmonary artery samples by 0.2±0.1%, 1.6±0.6%, and 3.6±0.8%, respectively. Six samples of artery were tested under each condition.

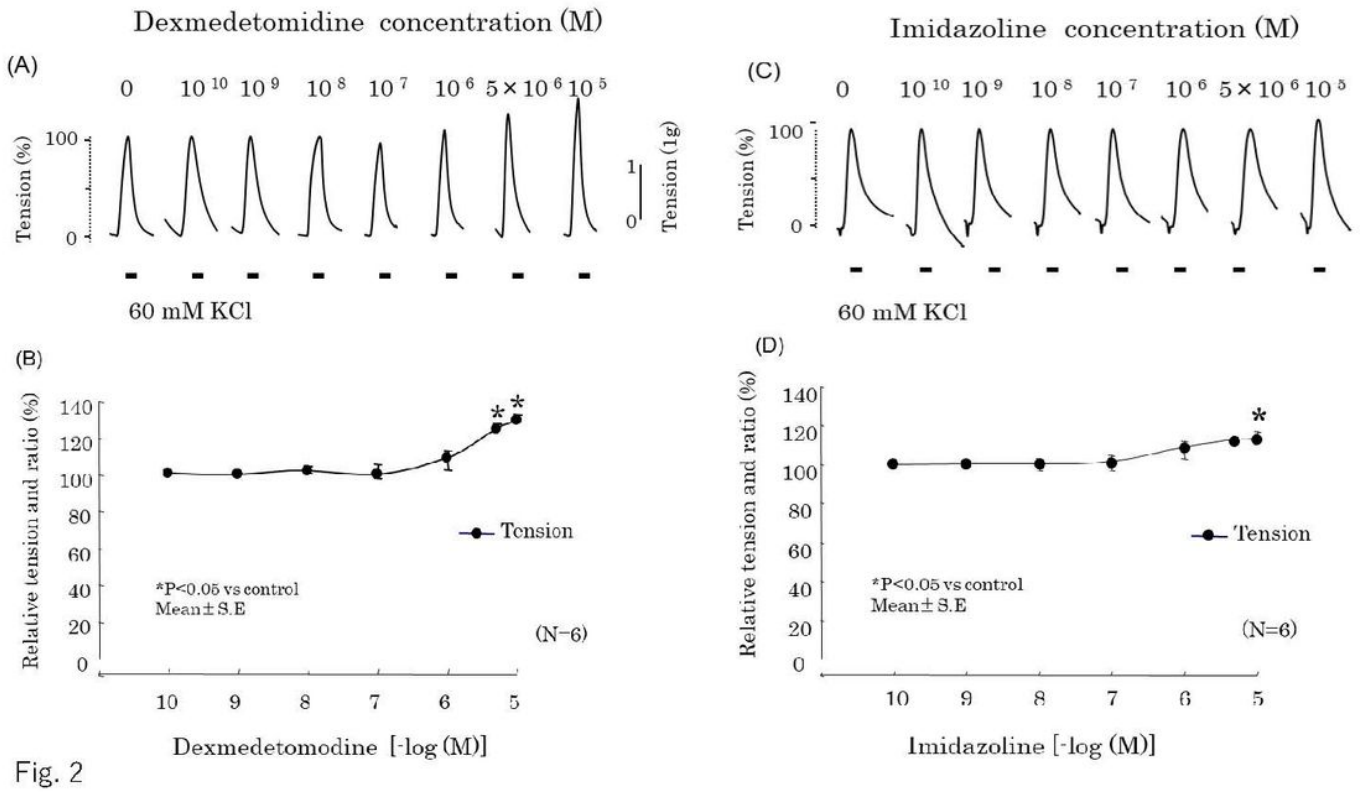

Fig. 2

Figure 2

Effects of dexmedetomidine and imidazoline on contraction tension with 60 mM KCl. Representative traces showing the effects of dexmedetomidine and imidazoline on contraction tension in endothelium-denuded porcine pulmonary artery (A and C) induced with 60 mM KCl. (B and D) Analyzed data. The contraction tension are normalized to 60 mM KCl within each set and expressed as a relative value in percentage. Each bar and accompanying line indicate the mean and SE of the group. Six samples are included in each group. *P<0.05 compared with 60 mM KCl.

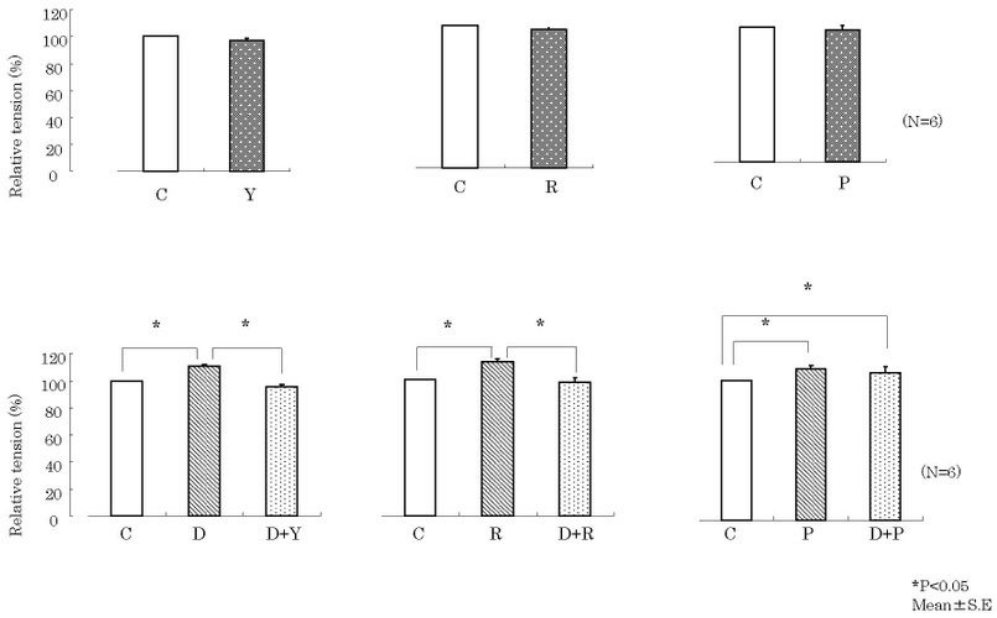

Fig. 3

Figure 3

Effects of yohimbine, rauwolscine, and prazosin on contraction tension induced with 60 mM KCl and with dexmedetomidine (Dex)-enhanced responses to 60 mM KCl. Each drug is used at a concentration of 5 × 10−6 M. Changes in contraction tension are normalized to 60 mM KCl within each set and expressed as a relative value in percentage. Each bar and accompanying line indicate the mean and SE of a group. Six samples are included per group. *P<0.05 compared with 60 mM KCl or Dex. C, control; Y, yohimbine; R, rauwolscine; P, prazosin; D, dexmedetomidine.

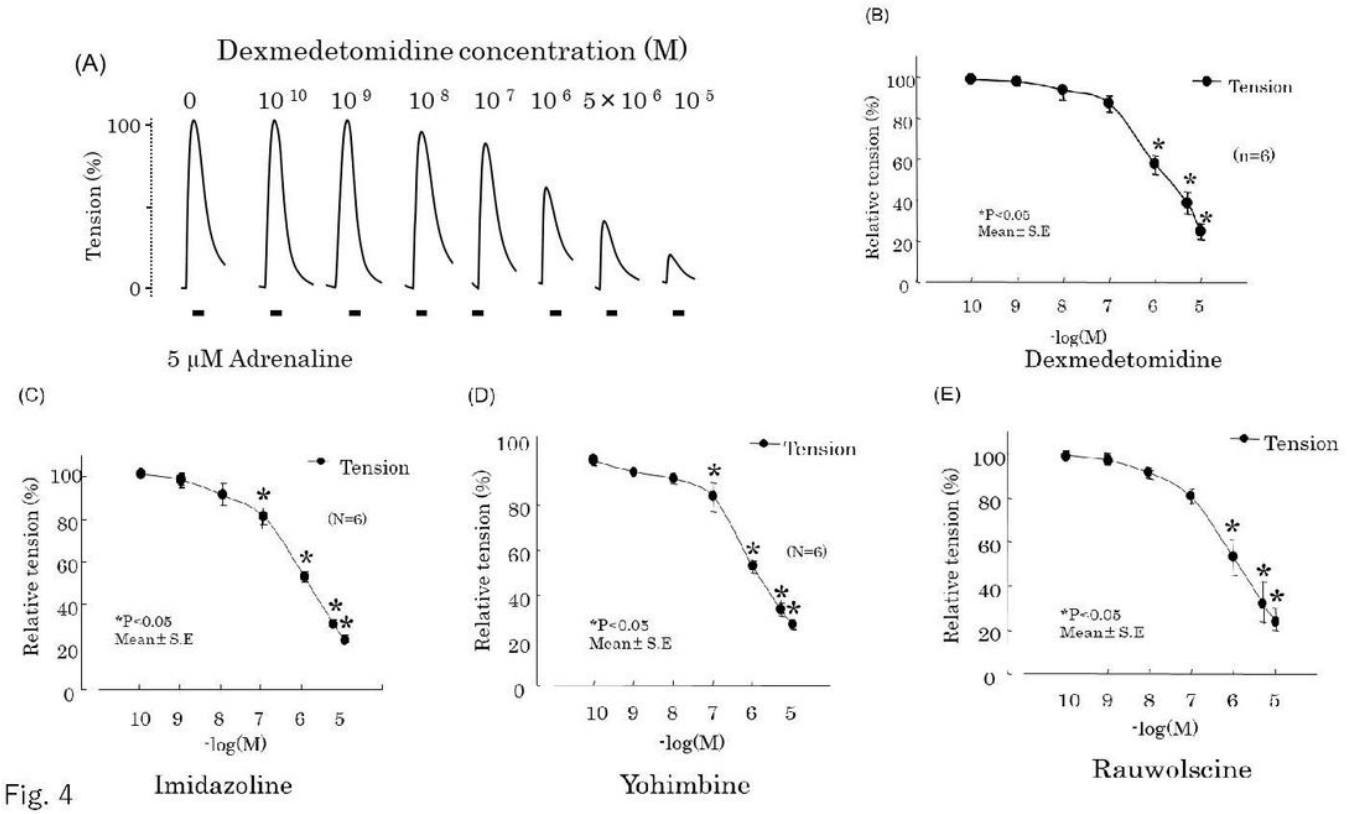

Fig. 4

Figure 4

Effects of dexmedetomidine (Dex), imidazoline, yohimbine, and rauwolscine on contraction tension induced with 5 μM adrenaline. (A) Representative traces showing the effects of Dex on tension. (B, C, D and E) Analyzed data. Changes in contraction tension are normalized to 5 μM adrenaline within each set and expressed as a relative value in percentage. Each bar and accompanying line indicate the mean and SE of a group. There are six samples per group. *P<0.05 compared with 5 μM adrenaline.

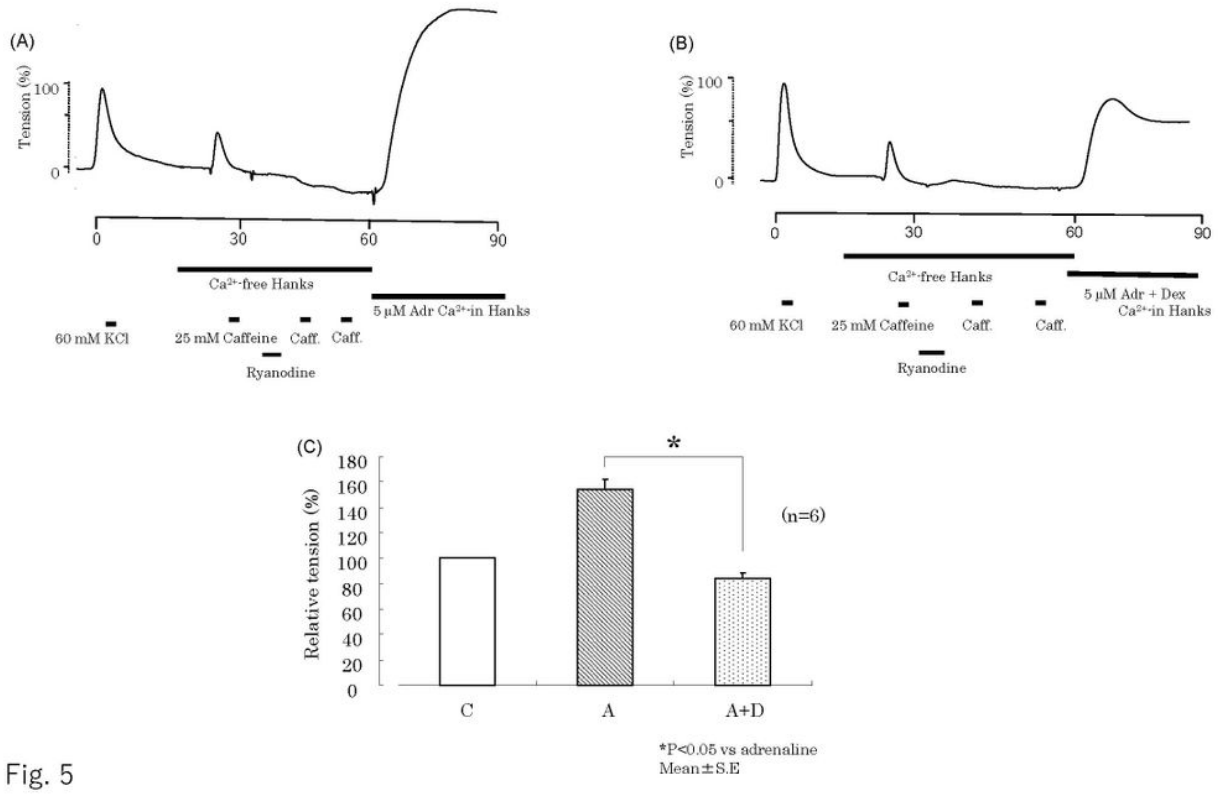

Fig. 5

Figure 5

Effects of dexmedetomidine on contraction tension induced with 5 μM adrenaline in Ca2+-containing Hanks solution after depletion of the intracellular Ca2+ store and extracellular Ca2+. Representative traces showing the effects of dexmedetomidine on contraction tension in endothelium-denuded pulmonary artery (A and B) induced with 5 μM adrenaline. (C) Analyzed data. After the Ca2+ reservoir is depleted, a Ca2+-containing HCS solution containing 5 × 10−6 M adrenaline or Ca2+-containing HCS solution containing 5 × 10−6 M adrenaline supplemented with 5 × 10−6 M Dex was administered for approximately 15 min, as indicated below the contraction traces. Changes in contraction tension are normalized to 60 mM KCl within each set and expressed as a relative value in percentage. Each bar and accompanying line indicate the mean and SE of a group. Six samples are included in each group. *P<0.05 compared with adrenaline. C, control; A, adrenaline; D, dexmedetomidine; Caff, Caffeine.

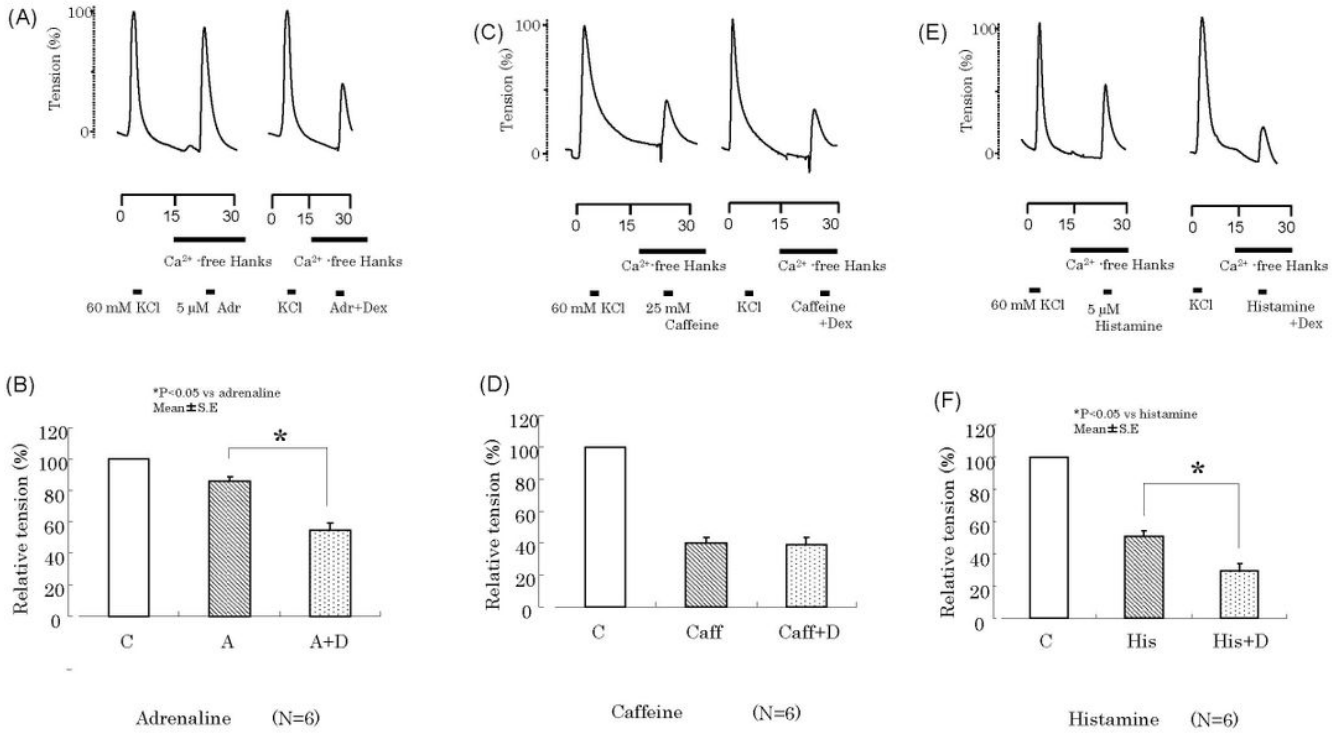

Fig. 6

Figure 6

Effects of dexmedetomidine (Dex) on contraction tension induced with 5 μM adrenaline, histamine and 25 mM caffeine with depletion of extracellular Ca2+. (A, C and E) Representative traces showing the effects of dexmedetomidine on contraction tension. (B, D and F) Analyzed data. Changes in contraction tension are normalized to 60 mM KCl within each set of experiments and expressed as a relative value in percentage. Each bar and accompanying line indicate the mean and SE of a group. Six samples are included in each group. *P<0.05 compared with adrenaline, histamine. C, control; A, adrenaline; D, dexmedetomidine; Caf, caffeine; H; histamine.