Anesthesiology
75:113–117, 1991

Dexmedetomidine Prevents Epinephrine-induced Arrhythmias Through Stimulation of Central α_2 Adrenoceptors in Halothane-anesthetized Dogs

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Since α_2-adrenergic agonists have important effects on the adrenergic system that have recently been applied to the anesthetic setting, we investigated the effect of stimulation of α_2 adrenoceptors on epinephrine-induced arrhythmias in halothane-anesthetized dogs. The arrhythmogenic threshold for epinephrine was determined during halothane anesthesia in the presence of dexmedetomidine, a selective α_2 agonist, and L-medetomidine, a stereoisomer of medetomidine that lacks α_2-agonist activity. Dexmedetomidine increased the arrhythmogenic threshold for epinephrine in a dose-dependent manner during halothane anesthesia. At the highest dose of dexmedetomidine, 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, there was a three-fold increase in both the arrhythmogenic dose of epinephrine and the plasma epinephrine concentration that was reached at this dose. On the other hand, L-medetomidine over the same dose range did not effect the arrhythmogenic dose of epinephrine. Atipamezole, a central α_2 antagonist that crosses the blood–brain barrier, blocked the antiarrhythmic action of dexmedetomidine. L-659,066 a peripheral α_2 antagonist that does not penetrate the blood–brain barrier, did not affect the antiarrhythmic action of dexmedetomidine. Thus, dexmedetomidine's antiarrhythmic effect on epinephrine-induced arrhythmias during halothane anesthesia appears to be mediated at least in part by stimulation of central α_2 adrenoceptors. (Key words: Anesthetics, volatile: halothane. Heart: arrhythmias. Receptors: α_2 -adrenergic. Sympathetic nervous system: catecholamines; epinephrine, α_2 agonist; dexmedetomidine α_2 antagonist; atipamezole; L-659,066.)

EPINEPHRINE EXERTS ITS ACTION by activating the adrenergic receptor effector mechanism. We and others have used highly selective adrenoceptor agonists and antagonists to identify the myocardial adrenergic receptor that mediates epinephrine arrhythmias during halothane anesthesia.[1–4] Thus far, we have elucidated a pivotal role for both myocardial α_1 and β_1 adrenoceptors in the genesis of these arrhythmias.[2–4] Furthermore, with the halothane–epinephrine arrhythmia model, we have characterized an indirect protective effect of β_2-adrenergic receptors.[5] The α_2-adrenergic agonists have potent effects on the adrenergic system both peripherally and centrally. Since these compounds are used in the anesthetic paradigm, we sought to define their effect on halothane–epinephrine arrhythmias that are mediated by the adrenergic system. Furthermore, α_2 agonists have been reported to prevent other types of arrhythmias.[6,7] Therefore, using selective α_2 agonists and antagonists we sought to characterize the modulating role of central and peripheral α_2-adrenergic receptors in the mediation of halothane–epinephrine arrhythmias.

Materials and Methods

The studies were conducted under guidelines provided by the Animal Care Committee of Osaka University Medical School.

Forty-five adult mongrel dogs of either sex, weighing 7.5–13.0 kg, were used in 58 experiments. Whenever different experiments were performed with the same dog, more than 7 days elapsed between experiments. The same dog was not used more than once in the same experiment group. Two arrhythmogenic doses (ADs) obtained in the same dog in separate experiments were considered two independent observations. Anesthesia was induced with halothane alone and maintained at an end-tidal concentration of 1.3%, which was continuously monitored by an anesthetic gas analyzer (model AA-102-30-00, Datex®, Helsinki, Finland). After tracheal intubation the lungs of each animal were mechanically ventilated to maintain the end-tidal CO_2 concentration (model 1H 21A, Minato®, Osaka, Japan) at 35–40 mmHg. A heating lamp and circulating water blanket were used to maintain the esophageal temperature at 37.0–38.5°C. A femoral artery catheter was inserted for both pressure monitoring and blood gas and serum electrolyte sampling. Lead II of the electrocardiogram was monitored continuously. A femoral vein was cannulated for administration both of drugs

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and of lactated Ringer's solution, which was infused at a rate of 10 ml·kg^{-1} h^{-1}. Serum K^+ was maintained between 3.5 and 4.5 mEq/ml by infusing K^+ at a rate of 1–10 mEq/h. Arterial *p*H, oxygen tension (Pa_{O_2}), and serum Na^+ were maintained within the ranges of 7.35–7.45, 85–100 mmHg, and 135–150 mEq/l, respectively.

The arrhythmia threshold was achieved when four or more premature ventricular contractions occurred within 15 s. The AD of epinephrine was defined as the lowest dose that produced the arrhythmias. According to a method we have reported previously,[8] the AD of epinephrine was determined with standardized logarithmically spaced infusions of epinephrine lasting 3 min with 10–30-min recovery periods between infusions. The infusion was started at the minimum dose of 0.67 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and the dose was increased by $e^{0.4}$ (e = 2.72) until the arrhythmia threshold was achieved. If arrhythmias did occur at one of these doses, a smaller arrhythmic dose, divided by $e^{0.2}$, was tested. At the time when the criterion for AD had been satisfied, an arterial blood sample was collected to measure the plasma concentration of epinephrine, as described previously.[9] This assay is based on the trihydroxyindole reaction; it has a limit of sensitivity of 5 pg/ml for epinephrine and an inter- and intraassay variation of less than 3%.

The AD of epinephrine was determined in the presence of dexmedetomidine 0, 0.1, 0.2, and 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, a highly selective α_2 agonist,[10–13] or in the presence of L-medetomidine 0.2 and 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, a stereoisomer of medetomidine that is inactive as an α_2 agonist.[12,13]

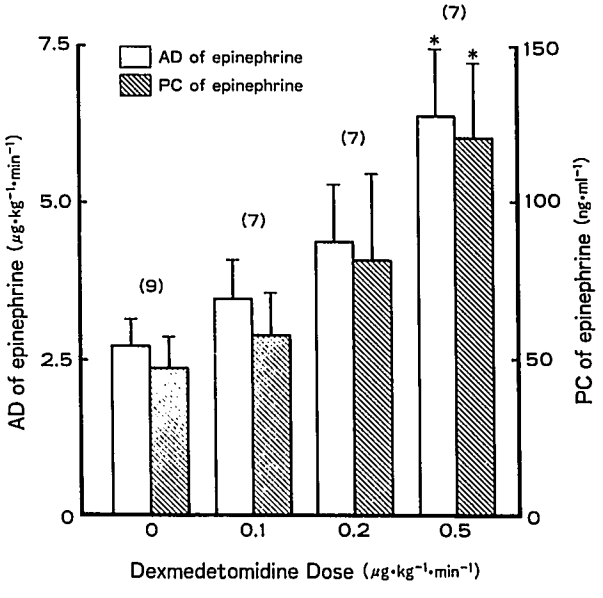

FIG. 1. Arrhythmogenic doses (AD) and plasma concentrations (PC) of epinephrine in the presence of dexmedetomidine 0, 0.1, 0.2, and 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ during halothane anesthesia in dogs (mean ± SEM; number of observations is shown in parentheses). *$P < 0.05$, compared with the 0 dose.

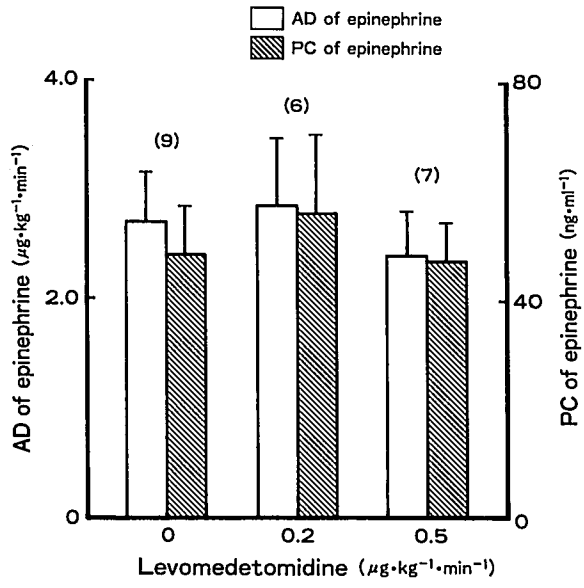

FIG. 2. The arrhythmogenic threshold of epinephrine in the presence of L-medetomidine during halothane anesthesia in dogs (mean ± SEM; number of observations is shown in parentheses). AD = arrhythmogenic dose; PC = plasma concentration.

In order to determine the site of action of dexmedetomidine, the ADs for epinephrine were also examined in the presence of dexmedetomidine 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, combined with either atipamezole 10 $\mu g \cdot kg^{-1}$, an α_2 antagonist which crosses the blood–brain barrier,[14] or L-659,066 100 $\mu g \cdot kg^{-1}$, an α_2 antagonist that does not cross the blood–brain barrier.[15]

Hemodynamic parameters (heart rate and systolic and diastolic arterial pressures) were recorded at the time the AD was achieved under the different treatment conditions.

The results of multiple groups were analyzed by one-way analysis of variance, and comparison between groups were assessed by Scheffé's test. $P < 0.05$ was considered statistically significant.

Results

Dexmedetomidine treatment significantly increased both the AD and the plasma concentration of epinephrine in a dose-dependent fashion (as determined by one-way analysis of variance), achieving statistical significance at 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, the highest dose tested (fig. 1). L-medetomidine at the doses tested did not affect the AD or the plasma concentration of epinephrine (fig. 2). The systolic arterial pressure was significantly increased, the heart rate significantly decreased, and the diastolic pressure unchanged at the time that the arrhythmic threshold was achieved in the dexmedetomidine-treated animals (table 1). Hemodynamic parameters were unaffected by L-medetomidine at the time of arrhythmias (table 2). Ati-

TABLE 1. Hemodynamic Data During Arrhythmias in the Presence of Dexmedetomidine during Halothane Anesthesia

Dose of Dexmedetomidine ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	n	SAP (mmHg)	DAP (mmHg)	HR (beats per min)
0	9	223 ± 12.4	127 ± 6.08	148 ± 12.3
0.1	7	226 ± 14.0	133 ± 8.10	114 ± 9.50
0.2	7	257 ± 17.3	149 ± 11.7	105 ± 6.35
0.5	7	301 ± 14.2*	155 ± 7.63	88 ± 8.08*

Data are mean ± SEM.
* $P < 0.05$ compared with dexmedetomidine 0.

pamezole, a central α_2 antagonist, blocked the antiarrhythmic action of dexmedetomidine, whereas L-659,066, a peripheral α_2 antagonist, did not change the threshold (fig. 3). Both the central (atipamezole) and peripheral (L-659,066) α_2-adrenoceptor antagonists attenuated the hemodynamic response to dexmedetomidine 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (table 3).

Discussion

The current study demonstrated that dexmedetomidine, a highly selective α_2 agonist, inhibits the arrhythmogenic effect of epinephrine during halothane anesthesia and that this response is blocked by atipamezole, a selective α_2 antagonist that partitions with great facility into the brain.

The L-enantiomer of medetomidine did not affect the epinephrine dose for arrhythmias with halothane in the range of medetomidine doses we tested. Although a larger dose of L-medetomidine might have some beneficial effect, our data suggest that dexmedetomidine, in the dose range of the current study, is acting at stereospecific binding sites. The nature and location of these binding sites were addressed in this study by using the α_2-adrenoceptor antagonists atipamezole and L-659,066. Atipamezole is a potent α_2 antagonist that readily crosses the blood–brain barrier[14]; L-659,066, in contrast, does not penetrate the blood–brain barrier.[15] Using doses that are equipotent[15–17] and in which a comparable peripheral cardiovascular effect was exerted (table 3), we found that only the centrally active compound blocked the antiarrhythmic effect of dexmedetomidine. These data suggest that dexmedetomidine exerts its antiarrhythmic effect *via* stimulation of central α_2 adrenoceptors and that its effect is independent of changes in hemodynamic parameters.

TABLE 2. Hemodynamic Data During Arrhythmias in the Presence of L-medetomidine during Halothane Anesthesia

Dose of L-medetomidine ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	n	SAP (mmHg)	DAP (mmHg)	HR (beats per min)
0	9	223 ± 12.4	127 ± 6.08	148 ± 12.3
0.2	6	226 ± 13.1	122 ± 8.76	145 ± 11.0
0.5	7	219 ± 13.1	116 ± 4.07	144 ± 12.7

Data are mean ± SEM.

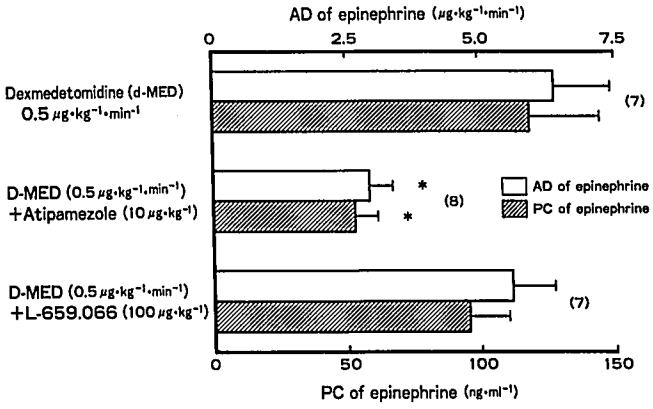

FIG. 3. The effect of atipamezole (10 $\mu g \cdot kg^{-1}$) and L-659,066 (100 $\mu g \cdot kg^{-1}$) on the arrhythmogenic threshold of epinephrine in the presence of dexmedetomidine (D-MED) 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ during halothane anesthesia in dogs (mean ± SEM; number of observations is shown in parentheses). *$P < 0.05$ compared to dexmedetomidine alone. AD = arrhythmogenic dose; PC = plasma concentration.

The cause of halothane–epinephrine arrhythmias remains unknown. Epinephrine acts on both postsynaptic α_1 and β_1 myocardial adrenoceptors to produce arrhythmias during halothane anesthesia.[2–4] No important role for myocardial β_2 adrenoceptors was demonstrated in our previous experiments.[5] The precise mechanisms involved in this antiarrhythmic action of α_2 agonists are not clear. If α_2 adrenoceptors were to exist in the heart, then stimulation of these receptors may be expected to produce identical second messenger effects, as is seen with β antagonists, which also are blockers of epinephrine-induced arrhythmias.[18] However, until now there have been no data to support the existence of postsynaptic α_2 adrenoceptors in the mammalian heart.[19,20] Also, our results with L-659,066, the peripheral α_2 antagonist, further refutes the existence of functional postsynaptic α_2 adrenoceptors in the heart (fig. 3).

Another possible mechanism for the antiarrhythmic effect of dexmedetomidine may involve its action on the peripheral vasculature. Arterial blood pressure has been

TABLE 3. Hemodynamic Data during Arrhythmias and Halothane Anesthesia

	n	SAP (mmHg)	DAP (mmHg)	HR (beats per min)
Dexmedetomidine alone	7	301 ± 14.2	155 ± 7.63	88 ± 8.08
Dexmedetomidine + atipamezole	8	216 ± 10.7	125 ± 6.80*	139 ± 15.0*
Dexmedetomidine + L-659,066	7	211 ± 11.7*	118 ± 7.78	129 ± 16.1*

Data are mean ± SEM.
* $P < 0.05$ compared with dexmedetomidine alone.

suggested to be an important factor in the genesis of halothane–epinephrine arrhythmias.[4,21,22] Stimulation of α_2 adrenoceptors in arterial vessels produces vasoconstriction, which increases systemic vascular resistance and thereby results in elevation of arterial blood pressure.[23] However, such a response to dexmedetomidine might be expected to potentiate halothane–epinephrine arrhythmias,[22] which is opposite to what was found (fig. 1). Again, our data with the peripheral antagonist (fig. 3) argues against a "vascular" explanation.

Another indirect mechanism by which α_2-adrenergic agonists may ameliorate epinephrine-induced arrhythmias during halothane anesthesia may be attributed to the bradycardia produced.[22] The mechanism of action for α_2-mediated bradycardia include enhancement of the baroreflex response to increase in blood pressure,[24] inhibition of norepinephrine release from its presynaptic storage site at the cardiac neuroeffector junction of the sinoatrial node,[25] and an increase in vagal tone.[26] However, it is unlikely that the α_2 agonist exerts its antiarrhythmic action by an indirect cardiovascular effect, since the peripheral α_2 antagonist "normalized" the hemodynamic changes seen with dexmedetomidine but did not block its antiarrhythmic action (fig. 3).

Our finding that atipamezole, but not L-659,066, blocked the antiarrhythmic effect of dexmedetomidine suggests a central site of action. The α_2 agonist potently inhibits neuronal firing rate from the locus ceruleus,[27] leading to a decrease in sympathetic outflow. This action may decrease the release of norepinephrine at the cardiac neuroeffector junction, mimicking the action of a class II antiarrhythmic drug.[28] In fact, other α_2-adrenergic agonist have been shown to exert an antiarrhythmic action in other arrhythmia models.[6,7]

In this halothane–epinephrine arrhythmia model, the α_2-adrenergic agonist increases the depth of the anesthetic state provided by halothane in dogs.[12] However, an increase in the depth of anesthesia does not appear to be important in attenuating epinephrine-induced arrhythmias during halothane anesthesia in dogs.[29] Thus, dexmedetomidine, acting *via* a central α_2 adrenoceptor, significantly reduces the likelihood of epinephrine-induced arrhythmias during halothane anesthesia. A question arising out of these findings is whether other centrally active drugs exert their attenuating or enhancing effects on halothane–epinephrine arrhythmias through action at central α_2 adrenoceptors. Thiopental, for example, modestly enhances halothane–epinephrine arrhythmias.[30,31] Therefore, it may be useful to explore this hypnotic drug's action on central α_2-adrenoceptors as a possible reason for its potentiating action. Finally, the apparent action of dexmedetomidine to oppose halothane–epinephrine arrhythmias could be further justification for inclusion of dexmedetomidine as preanesthetic medication for clinical general anesthesia.[32]

The authors thank Farmos Pharmaceutica (Turku, Finland) for supplying dexmedetomidine, levomedetomidine, and atipamezole. They also thank Merck Sharp & Dohme Research Laboratories (West Point, PA) for supplying L-659,066. They are grateful to K. Ishida, K. Yamaoka, T. Konishi, and Y. Furukawa for their assistance throughout this study.

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