Further Characterization of the Receptor Mechanism Involved in the Antidysrhythmic Effect of Dexmedetomidine on Halothane/Epinephrine Dysrhythmias in Dogs

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Background: α2 Adrenoceptors in the central nervous system mediate various physiologic processes, including cardiovascular control. Recently, some of these actions have been reported to be mediated by a nonadrenergic receptor, namely an imidazoline receptor. The authors previously reported that dexmedetomidine, a selective α2 agonist, prevents the genesis of halothane-epinephrine dysrhythmias through a central mechanism. Because dexmedetomidine also binds to imidazoline receptors, we performed the current study to examine the precise receptor mechanism involved in the antidysrhythmic property of dexmedetomidine.

Methods: Adult mongrel dogs were anesthetized with halothane (1.3%) and monitored continuously for systemic arterial pressure and premature ventricular contractions. The dysrhythmogenic dose of epinephrine was defined as the smallest dose producing four or more premature ventricular contractions within 15-s period. We examined the antidysrhythmic action of dexmedetomidine in the presence of two kinds of α2 antagonists, that is, agents that label imidazoline receptors and exert a pharmacologic action through imidazoline receptors (idazoxan and atipamezole) and agents that are nonimidazoline compounds and are lacking in pharmacologic action through imidazoline receptors (rauwolscine and I-659,066).

Results: Idazoxan and atipamezole significantly inhibited the antidysrhythmic action of dexmedetomidine, whereas rauwolscine and I-659,066 did not.

Conclusions: Because α2 antagonists having imidazoline or imidazole structures inhibited the antidysrhythmic action of dexmedetomidine, and the inhibition produced by the nonimidazoline α2 antagonists was not significant, imidazoline receptors in the central nervous system are more responsible for the antidysrhythmic action of dexmedetomidine than are α2 adrenoceptors. (Key words: Anesthetics, volatile: halothane. Heart: dysrhythmias. Receptors: α2-adrenergic; imidazoline. Sympathetic nervous system: α2 agonist; α2 antagonist; atipamezole; catecholamines; dexmedetomidine; epinephrine; idazoxan; I-659,066; rauwolscine.)

ADMINISTRATION of α2-adrenergic agonists during anesthesia is associated with sedation, analgesia, hemodynamic stability, and reduced anesthetic requirements.1 Although these effects are believed to be mediated through activation of α2 adrenoceptors that are widely distributed in the brain and involved in regulation of several physiologic processes,2 investigations have documented that some of the above agonists also interact with the imidazoline receptor, which binds agents, such as imidazoles (e.g., medetomidine), imidazolines (e.g., clonidine, idazoxan), some guanidines (e.g., guanabenz, amiloride), and oxazoles (rilmenidine) but have little affinity for agonists or antagonists without the above structures, such as epinephrine, yohimbine, and rauwolscine.3–8 We reported that dexmedetomidine, a highly selective α2 agonist,9 prevents the halothane/epinephrine-induced dysrhythmias via
an action within the central nervous system, and a later study suggested the involvement of imidazoline receptors in the modulation of halothane-epinephrine dysrhythmias. Dexmedetomidine contains an imidazoline in its chemical structure and has an affinity for imidazoline receptors despite weak affinity compared with that for α2 adrenoceptors. Thus, it may be possible that the imidazoline receptor contributes to the antisympathetic effect of dexmedetomidine. In the current study, using α2 antagonists with or without affinity for imidazoline receptors, we sought to identify the receptor in the central nervous system involved in the antisympathetic property of dexmedetomidine.

Materials and Methods

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

Eighty-seven adult mongrel dogs of either sex, weighing 7.3–12.5 kg, were used in 113 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 experimental group. Two dysrhythmogenic doses obtained in the same dog in separate experiments were considered two different observations. Anesthesia was induced with halothane alone and maintained at an end-tidal concentration of 1.3%, which was monitored continuously by an anesthetic gas analyzer (Datex model AA-102-30-00, Helsinki, Finland). The trachea of each dog was intubated with a cuffed tracheal tube, and the lungs were mechanically ventilated (Aika R60, Tokyo, Japan). The end-tidal carbon dioxide concentration was continuously monitored with an expired gas monitor (Minato 1H 21A, Osaka, Japan) and maintained at a level of 35–40 mmHg. A heating lamp and circulating water blanket were used to maintain the esophageal temperature at 36.5–38.5°C.

Lead II of the electrocardiogram was monitored continuously. A femoral artery catheter was inserted for pressure monitoring and blood gas and serum electrolyte sampling. A right femoral vein was cannulated for the administration of drugs 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·l⁻¹ by infusing K⁺ at a rate of 1–10 mEq·h⁻¹. Arterial pH, oxygen tension, and serum Na⁺ were maintained within the ranges of 7.35–7.45, 85–100 mmHg, and 135–150 mEq·l⁻¹, respectively.

The dysrhythmia threshold was achieved when four or more premature ventricular contractions occurred within 15 s. The dysrhythmogenic dose of epinephrine was defined as the smallest dose that produced dysrhythmias. According to our previous method, the dysrhythmogenic dose of epinephrine was determined with logarithmically spaced infusions of epinephrine lasting 3 min. Recovery periods of 10–30 min were allowed between infusions until the hemodynamic parameters (arterial blood pressure and heart rate) returned to the basal levels. The infusion was started at the minimum dose of 0.67 μg·kg⁻¹·min⁻¹, and the dose was increased by $e^{0.4}$ ($e = 2.72$) until the dysrhythmia threshold was achieved. If dysrhythmias occurred at one of these doses, a smaller dysrhythmogenic dose, divided by $e^{0.2}$, was tested. When the criterion for dysrhythmogenic dose had been satisfied, an arterial blood sample was collected to measure the plasma concentration of epinephrine. The epinephrine concentration was measured in a fully automated high-performance liquid chromatography-fluorometric system (Tosoh model HLC-8030 Catecholamine Analyzer, Tokyo, Japan) using a diphenylethylendiamine condensation method. This assay method has a limit of sensitivity of 10 pg·ml⁻¹ for epinephrine. The inter- and intraassay variations were less than 3%.

Our previous study demonstrated that continuous intravenous administration of dexmedetomidine, 0.5 μg·kg⁻¹·min⁻¹, significantly prevents epinephrine-induced dysrhythmias during halothane anesthesia. Therefore, in the current study, we first reconfirmed the antisympathetic effect of continuous intravenous administration of dexmedetomidine at this dose in the presence of cerebroventricular saline, using the method in our previous report and examined whether the property of dexmedetomidine was inhibited by four α2 antagonists. The antagonists were diluted in 0.9% saline and administered into the cisterna magna through a 20-G needle percutaneously to elucidate the comparative involvement of α2 adrenoceptors and imidazoline receptors in the central nervous system as the site of action of antisympathetic effect of dexmedetomidine. The four α2 antagonists used in this study were as follows: (1) idazoxan, an imidazoline compound, which has almost same affinity for imidazoline receptors as for α2 adrenoceptors and exerts α2 antagonistic potency similar to that of rauwolscine and yohimbine; (2) atipamezole, an imidazoline compound, which also has some activity at imidazoline
receptors\textsuperscript{11,18}\textsuperscript{*} and whose $\alpha_2$ antagonistic potency is 10 times as potent as idazoxan\textsuperscript{19,20}; (3) rauwolscine, a nonimidazoline $\alpha_2$ antagonist that has little affinity for imidazoline receptors\textsuperscript{5,15} and whose $\alpha_2$ antagonistic potency is similar to that of yohimbine\textsuperscript{21}; and (4) L-659,066, a nonimidazoline $\alpha_2$ antagonist that is lacking in pharmacologic action through imidazoline receptors\textsuperscript{11} and whose $\alpha_2$ antagonistic activity is about a tenth of that of atipamezole and almost equivalent to that of rauwolscine.\textsuperscript{22,23} According to the previous data above described, the doses of each antagonist were determined to share roughly equieffective $\alpha_2$ antagonistic potency, that is, the dose ranges tested of idazoxan, atipamezole, rauwolscine, and L-659,066 were 5–20, 0.5–2.0, 10–40, and 10–40 $\mu$g·kg\textsuperscript{-1}, respectively. The cerebroventricular administration of these antagonists, including the saline and the intravenous dexmedetomidine infusion, were scheduled 25 and 30 min before starting epinephrine infusions, respectively. In these antagonistic studies, the dysrhythmogenic threshold of epinephrine in the presence of dexmedetomidine, 0.5 $\mu$g·kg\textsuperscript{-1}·min\textsuperscript{-1}, and with no antagonist (saline only) was shared as a value at dose 0 in each experiment.

Hemodynamic parameters (heart rate and systolic and diastolic arterial blood pressures) were recorded at the time the dysrhythmogenic dose was achieved under the different treatment conditions. The data were expressed as mean ± SEM. The results of multiple groups were analyzed by one-way analysis of variance, followed by post hoc Scheffé’s test for multiple comparison. A comparison of two groups was assessed by Student’s $t$ test. We considered $P < 0.05$ to be statistically significant.

**Results**

Dexmedetomidine affected basal hemodynamic variables (the data just before the epinephrine infusion), i.e., it reduced basal heart rate and increased basal blood pressure. However, pretreatment of various cerebroventricular $\alpha_2$ antagonist did not significantly modify these hemodynamic effects of dexmedetomidine. Dexmedetomidine treatment (0.5 $\mu$g·kg\textsuperscript{-1}·min\textsuperscript{-1}) significantly increased both the dysrhythmogenic dose and the plasma concentration of epinephrine at which dysrhythmias occurred (fig. 1). The effects of idazoxan, atipamezole, rauwolscine, and L-659,066 on the antidysrhythmic action of dexmedetomidine are shown in figures 2–5, respectively. Idazoxan significantly blocked the antidysrhythmic action of dexmedetomidine at all doses examined (fig. 2). Similarly, atipamezole did so dose-dependently and achieved a significant inhibition at the medium dose, whereas the high dose of atipamezole showed a slight reversal of the effect instead of further inhibition (fig. 3). On the other hand, the inhibition of nonimidazole $\alpha_2$ antagonists (rauwolscine and L-659,066) were not significant (figs. 4 and 5). The hemodynamic parameters at the genesis of the dysrhythmias are shown in tables 1–4. These antagonists, except L-659,066, decreased systolic arterial pressure significantly at the onset of the dysrhythmias, whereas the changes of diastolic blood pressure and heart rate were not so remarkable.

**Discussion**

The current results demonstrate that dexmedetomidine prevents epinephrine-induced dysrhythmias in

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure.png}
\caption{Dysrhythmogenic dose (DD) and plasma concentration (PC) of epinephrine in the presence of 0.5 $\mu$g·kg\textsuperscript{-1}·min\textsuperscript{-1} dexmedetomidine during halothane anesthesia in dogs (mean ± SEM; number of observations shown in parentheses). \textsuperscript{*}$P < 0.05$, compared with no dexmedetomidine treatment (dexmedetomidine dose = 0).}
\end{figure}


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**Fig. 2.** The effect of idazoxan on the dysrhythmgogenic threshold of epinephrine in the presence of 0.5 μg·kg⁻¹·min⁻¹ dexmedetomidine during halothane anesthesia in dogs (mean ± SEM; number of observations shown in parentheses). *P < 0.05, compared with dexmedetomidine alone (idazoxan dose = 0). DD = dysrhythmgogenic dose; PC = plasma concentration.

**Fig. 3.** The effect of atipamezole on the dysrhythmgogenic threshold of epinephrine in the presence of 0.5 μg·kg⁻¹·min⁻¹ dexmedetomidine during halothane anesthesia in dogs (mean ± SEM; number of observations shown in parentheses). *P < 0.05, compared with dexmedetomidine alone (atipamezole dose = 0). DD = dysrhythmgogenic dose; PC = plasma concentration.

**Fig. 4.** The effect of rauwolscine on the dysrhythmgogenic threshold of epinephrine in the presence of 0.5 μg·kg⁻¹·min⁻¹ dexmedetomidine during halothane anesthesia in dogs (mean ± SEM; number of observations shown in parentheses). DD = dysrhythmgogenic dose; PC = plasma concentration.

**Fig. 5.** The effect of L-659,066 on the dysrhythmgogenic threshold of epinephrine in the presence of 0.5 μg·kg⁻¹·min⁻¹ dexmedetomidine during halothane anesthesia in dogs (mean ± SEM; number of observations shown in parentheses). DD = dysrhythmgogenic dose; PC = plasma concentration.
Table 1. Hemodynamic Data at the Time Dysrhythmias Were Induced with Epinephrine in the Presence of Dexmedetomidine (0.5 μg·kg⁻¹·min⁻¹) and Various Doses of Idazoxan during Halothane Anesthesia

<table>
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<tr>
<th>Dose of Idazoxan (μg·kg⁻¹)</th>
<th>N</th>
<th>SAP (mmHg)</th>
<th>DAP (mmHg)</th>
<th>HR (beats/min)</th>
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<tr>
<td>0</td>
<td>8</td>
<td>289 ± 13</td>
<td>143 ± 6</td>
<td>91 ± 6</td>
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<td>10</td>
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<td>7</td>
<td>225 ± 6*</td>
<td>118 ± 8</td>
<td>88 ± 7</td>
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Data are mean ± SEM.
N = number of observations; SAP = systolic arterial pressure; DAP = diastolic arterial pressure; HR = heart rate.
* P < 0.05 versus control (dexametomidine alone).

halothane-anesthetized dogs, and this action is significantly inhibited by an α₂ antagonist with an imidazoline or a related structure and an affinity for imidazoline receptors (i.e., idazoxan and atipamezole). The inhibition produced by a nonimidazoline α₂ antagonist (L-659,066 and rauwolscine) is not significant (figs. 2–5).

Two reports by Bousquet’s group demonstrated that the imidazoline receptor is involved in the hypotensive effect of clonidine, which was previously believed to be exerted through activation of α₂ adrenoceptors. Later, the imidazoline receptor was documented to be responsible for other several pharmacologic properties of α₂ agonists. More recently, the protein of this receptor has been isolated from bovine adrenal chromaffin cells, and evidence has accumulated suggesting that this type of receptor is distinct from an α₂ adrenoceptor and its signal transduction is different from that of α₂ adrenoceptors. Considering that dexametomidine has an imidazole structure and possesses an affinity for imidazoline receptor, we thought it important to identify the receptor mechanism involved in the antidysrhythmic actions of dexametomidine. The current findings suggest that the imidazoline receptors play a more important role than α₂ adrenoceptors in inhibition by dexametomidine of the genesis of halothane-epinephrine dysrhythmias.

When we compared the inhibitory property of the four α₂ antagonists we tested, idazoxan had the most definite inhibitory action. Idazoxan has an imidazoline in its chemical structure, and previous work demonstrated that idazoxan bound to imidazoline receptor with high affinity and acts as an antagonist at the receptors. In comparison, atipamezole is a imidazole compound. Wikberg and Uhen reported that imidaz-

Table 2. Hemodynamic Data at the Time Dysrhythmias Were Induced with Epinephrine in the Presence of Dexmedetomidine (0.5 μg·kg⁻¹·min⁻¹) and Various Doses of Atipamezole during Halothane Anesthesia

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<tr>
<th>Dose of Atipamezole (μg·kg⁻¹)</th>
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<th>DAP (mmHg)</th>
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<td>91 ± 6</td>
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<tr>
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<td>244 ± 13</td>
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<td>1.0</td>
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<td>2.0</td>
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<td>241 ± 9*</td>
<td>131 ± 8</td>
<td>91 ± 6</td>
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</table>

Data are mean ± SEM.
N = number of observations; SAP = systolic arterial pressure; DAP = diastolic arterial pressure; HR = heart rate.
* P < 0.05 versus control (dexametomidine alone).

Table 3. Hemodynamic Data at the Time Dysrhythmias Were Induced with Epinephrine in the Presence of Dexmedetomidine (0.5 μg·kg⁻¹·min⁻¹) and Various Doses of Rauwolscine during Halothane Anesthesia

<table>
<thead>
<tr>
<th>Dose of Rauwolscine (μg·kg⁻¹)</th>
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<td>247 ± 8</td>
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<td>7</td>
<td>234 ± 11*</td>
<td>134 ± 10</td>
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<td>40</td>
<td>7</td>
<td>235 ± 6*</td>
<td>138 ± 6</td>
<td>84 ± 11</td>
</tr>
</tbody>
</table>

Data are mean ± SEM.
N = number of observations; SAP = systolic arterial pressure; DAP = diastolic arterial pressure; HR = heart rate.
* P < 0.05 versus control (dexametomidine alone).

Table 4. Hemodynamic Data at the Time Dysrhythmias Were Induced with Epinephrine in the Presence of Dexmedetomidine (0.5 μg·kg⁻¹·min⁻¹) and Various Doses of L-659,066 during Halothane Anesthesia

<table>
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<th>Dose of L-659,066 (μg·kg⁻¹)</th>
<th>N</th>
<th>SAP (mmHg)</th>
<th>DAP (mmHg)</th>
<th>HR (beats/min)</th>
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</thead>
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<td>262 ± 14</td>
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<td>84 ± 6</td>
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<td>123 ± 6</td>
<td>80 ± 6</td>
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<td>40</td>
<td>10</td>
<td>259 ± 13</td>
<td>135 ± 6</td>
<td>97 ± 11</td>
</tr>
</tbody>
</table>

Data are mean ± SEM.
N = number of observations; SAP = systolic arterial pressure; DAP = diastolic arterial pressure; HR = heart rate.

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oles have affinities for imidazoline receptors, and Miettinen et al. suggested that atipamezole has an affinity for imidazoline receptors. Therefore, some of the pharmacologic actions of atipamezole may be mediated through these receptors. In fact, we reported that atipamezole alone significantly potentiated dysrhythmogenicity of epinephrine by blocking imidazoline receptors, not \( \alpha_2 \) receptors. In contrast with these antagonists, neither L-659,066 nor rauwolscine contains imidazoline or a related structure, and imidazoline receptors may not be involved in their pharmacologic actions. Although nonimidazoline antagonists might have a slightly greater \( \alpha_2 \) antagonistic potency. However, pharmacokinetic data of the four antagonists in the cerebrospinal fluid have not been published, thus, it might be possible that larger doses of nonimidazoline compounds may be required to exert equipotent \( \alpha_2 \) antagonistic action to idazoxan and atipamezole. However, it may be unlikely. As shown in figures 4 and 5, rauwolscine and L-659,066 tended to inhibit the effect of dexmedetomidine, but the inhibition of each agent was reversed at the highest dose, suggesting that more concentrated nonimidazoline antagonists in the cerebrospinal fluid are not effective to exert further inhibition of the antidysrhythmic action of dexmedetomidine. Because the order of the inhibitory potency was idazoxan > atipamezole > rauwolscine = L-659,066 in the current results, we may deduce that the potency differences are dependent on the interaction with imidazoline receptors. Recent radioligand binding studies have suggested the pharmacologic classification of two imidazoline receptors, namely \( I_1 \) and \( I_2 \). Although one binding study suggested another nonadrenergic binding site that has high affinity for atipamezole in neonatal rat lung. Because the differences in the affinity of dexmedetomidine, idazoxan, and atipamezole are not well elucidated, we cannot identify the receptor subtype involved in the antidysrhythmic action of dexmedetomidine. However, if idazoxan and atipamezole differ in their receptor subtype selectivity, then differences in their inhibitory potency of the antidysrhythmic effect of dexmedetomidine might be due to blockade of separate subtypes. In addition, although neither the structure nor the physiologic role of the imidazoline receptors has been well clarified, previous biochemical data indicate that imidazoline receptors are separated from \( \alpha_2 \) adrenoceptors and facilitate different transduction passways. Thus, further studies are required to clarify the detailed intracellular mechanism following imidazoline receptors involved in the antidysrhythmic action of dexmedetomidine.

The precise site in the central nervous system involved in the antidysrhythmic action of dexmedetomidine has not been elucidated. Although the locus ceruleus is known to be a principal site of the hypnotic response of \( \alpha_2 \) agonists and the involvement of \( \alpha_{2A} \) adrenoceptors, not imidazoline receptors, was reported, the nucleus reticularis lateralis in the ventrolateral medulla, a region relatively rich in imidazoline receptors, was reported to be a site of the hypotensive action of clonidine. In the current results, imidazoline receptors are more responsible than \( \alpha_2 \) adrenoceptors for the antidysrhythmic action of dexmedetomidine, so the nucleus reticularis lateralis might be one region originating this action. This brain area is connected functionally with nucleus tractus solitarius, which modulates autonomic control, including vagal activity, which plays a critical role in the antidysrhythmic property of dexmedetomidine.

Hemodynamic parameters have been known to be an important factor in modulating the genesis of halothane-epinephrine dysrhythmias. Considering that imidazoline receptors are involved in central hypotensive action of imidazoline agents, including clonidine, the different profile concerning pharmacologic activity through imidazoline receptors between imidazoline and nonimidazoline compounds might affect the hemodynamic variables in the current study. However, this possibility is unlikely, because the strong hemodynamic action of the intravenous epinephrine used in this study is likely to mask any hemodynamic difference. In fact, as shown in tables 1-4, systolic blood pressures at the onset of the dysrhythmias correlated with dysrhythmogenic doses of epinephrine, indicating that the hemodynamic parameters were dependent on the epinephrine infusion doses in the current study.

In conclusion, the current data suggest that imidazoline receptors in the central nervous system may be involved in the antidysrhythmic effect of dexmedetomidine, and a major contribution of \( \alpha_2 \) adrenoceptors in this action is unlikely.

The authors thank Farmos Pharmaceutica (Turku, Finland), for supplying dexmedetomidine and atipamezole; and Merck Sharp & Dohme Research Laboratories (West Point, PA), for giving L-659,066.
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