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Antiarrhythmic action of rilmenidine on adrenaline-induced arrhythmia via central imidazoline receptors in halothane-anaesthetized dogs

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1 To elucidate the role of central imidazoline receptors in the genesis of adrenaline-induced arrhythmias under halothane anaesthesia, we investigated the effects of rilmenidine, a selective agonist at imidazoline receptors, on this type of arrhythmia in dogs. Rilmenidine (1, 3, 10 $\mu g\ kg^{-1}$, i.v.) did not affect basal haemodynamic parameters (heart rate and blood pressure), but dose-dependently inhibited adrenaline-induced arrhythmias under halothane anaesthesia.

2 Although, rilmenidine has a weak affinity for α_2-adrenoceptors, pretreatment with idazoxan (10 $\mu g\ kg^{-1}$, intracisternally i.c.), an imidazoline receptor antagonist which has also α_2-adrenoceptor blocking potency, blocked the antiarrhythmic effect of rilmenidine (10 $\mu g\ kg^{-1}$, i.v.). In contrast, pretreatment with rauwolscine (20 $\mu g\ kg^{-1}$, i.c.), a classical α_2-adrenoceptor antagonist with little affinity for imidazoline receptors, did not affect the effect of rilmenidine (10 $\mu g\ kg^{-1}$, i.v.). Furthermore, bilateral vagotomy completely blocked the antiarrhythmic action of rilmenidine (10 $\mu g\ kg^{-1}$, i.v.).

3 It is suggested that the antiarrhythmic action of rilmenidine is due to the activation of central imidazoline receptors and that vagal tone is critical for this action of rilmenidine.

Keywords: Halothane anaesthesia; arrhythmias; imidazoline receptor; autonomic nervous system; vagus nerve; sympathetic neural activity; rilmenidine

Introduction

It is well known that the arrhythmogenic action of adrenaline is enhanced in the presence of the inhalation hydrocarbon anaesthetic halothane, although the precise mechanism of this phenomenon remains unknown (Reynolds, 1984; Atlee & Bosnjak, 1990; Hayashi *et al.*, 1991c). Several previous reports have shown that the central nervous system (CNS) affects the genesis of different types of arrhythmias including this type (Waxman *et al.*, 1989; Podrid *et al.*, 1990; Chen *et al.*, 1991; Hayashi *et al.*, 1991a,c). Recently, we demonstrated that an α_2-adrenoceptor agonist dexmedetomidine, which has a weak affinity for imidazoline receptors (Wikberg & Uhlén, 1990; Wikberg *et al.*, 1991), inhibits adrenaline-induced arrhythmia under halothane anaesthesia through its action on the CNS (Hayashi *et al.*, 1991b). Furthermore, our subsequent studies suggested that central imidazoline receptors are involved in the genesis of halothane-adrenaline-induced arrhythmia (Hayashi *et al.*, 1993a), and that the inhibition of sympathetic neural activity is protective against this type of arrhythmia (Kamibayashi *et al.*, 1992; 1995).

On the other hand, the activation of central imidazoline receptors is known to inhibit sympathetic neural activity, and this property could be responsible for the hypotensive action of imidazoline receptor agonists such as clonidine (Ernsberger *et al.*, 1990; Feldman *et al.*, 1990; Tibirica *et al.*, 1991; Michel & Ernsberger, 1992). These findings imply that activation of central imidazoline receptors affects the genesis of this type of arrhythmia by altering sympathetic neural activity.

The present study was designed to elucidate the role of central imidazoline receptors in halothane-adrenaline-induced arrhythmia by the use of rilmenidine, an oxazoline analogue of clonidine and a selective imidazoline receptor agonist (Bricca *et al.*, 1989; 1993; 1994; Ernsberger *et al.*, 1993; Vos *et al.*, 1994). We investigated whether rilmenidine inhibits the adrenaline-induced arrhythmia in halothane-anaesthetized dogs, and attempted to define the role of the imidazoline receptors in the CNS by central treatment with the antagonists: idazoxan, an imidazoline receptor antagonist with an affinity for an α_2-adrenoceptor, and rauwolscine, a classical α_2-adrenoceptor antagonist with little affinity for imidazoline receptors (Lehmann *et al.*, 1989). Furthermore, to elucidate the role of vagal tone, we investigated the effect of bilateral vagotomy on the action of rilmenidine.

Methods

Experimental preparation

This study was conducted according to the guidelines approved by the Animal Care Committee of Osaka University, Faculty of Medicine. Adult mongrel dogs of either sex weighing 8–12 kg were used. Anaesthesia was induced and maintained with halothane alone. After tracheal intubation, the lungs were ventilated mechanically (Aika R60, Tokyo, Japan) to maintain the end-tidal CO_2 concentration at 35–40 mmHg and the end-tidal concentration of halothane was maintained at 1.3%, which was monitored continuously with an anaesthetic gas analyser (Datex, model AA 102-30-00, Helsinki, Finland). Both a heating lamp and a circulating water blanket were used to maintain oesophageal temperature at 37–38.5°C. Lead II of the electrocardiogram was monitored continuously. A femoral artery catheter was inserted for both blood sampling and pressure monitoring with a pressure transducer (Nihon Kohden AC611G, Tokyo, Japan). The

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electrocardiogram and arterial blood pressure were recorded with a thermal array recorder (Nihon Kohden WS-641G, Tokyo, Japan). A femoral vein was also cannulated for administration of both drugs and lactated Ringer 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 (PaO_2), and serum Na^+ were also maintained within the ranges of 7.35–7.45, 85–100 mmHg, and 135–150 mEq l^{-1}, respectively.

Determination of the arrhythmogenic doses of adrenaline

After preparation, an initial period of 45–60 min was allowed for stabilization, and adrenaline was infused intravenously for 3 min using standardized logarithmically spaced infusions (Hayashi *et al.*, 1991c). Infusion of adrenaline was performed with a constant volume infusion pump (Terumo, STG-502, Tokyo, Japan). The dose of adrenaline was begun at the minimum dose of 0.67 $\mu g\ kg^{-1}\ min^{-1}$, and increased by a factor of $e^{0.4}$($e=2.72$) (1.0, 1.49, 2.23, 3.32, 4.95, 7.39, 11.0 $\mu g\ kg^{-1}\ min^{-1}$) until the arrhythmia was produced. If arrhythmia occurred at one of these doses, a lower dose, reduced by a factor of $e^{0.2}$, was tested. For example, if arrhythmia occurred at 1.0 $\mu g\ kg^{-1}\ min^{-1}$, a dose of 0.82 $\mu g\ kg^{-1}\ min^{-1}$ ($1.0/e^{0.2}$) was tested subsequently. Similarly, in case of 1.49, 2.23, 3.32, 4.95, 7.39 or 11.0 $\mu g\ kg^{-1}\ min^{-1}$, a smaller dose of 1.22, 1.82, 2.72, 4.06, 6.05, or, 9.03 $\mu g\ kg^{-1}\ min^{-1}$ was tested, respectively. We defined the arrhythmogenic dose of adrenaline as the lowest dose which produced arrhythmia. Between infusions, recovery periods of 10–30 min were allowed until the haemodynamic parameters (heart rate and blood pressure) became stable.

During adrenaline infusion, arrhythmias were observed and we defined arrhythmia as four or more continuous or intermittent premature ventricular contractions occurring within 15 s and other arrhythmias which were not of ventricular origin (e.g. premature atrial contractions, junctional rhythms) were neglected.

Determination of plasma adrenaline concentration

At the time when the criterion for arrhythmogenic dose had been satisfied, 4 ml arterial blood samples were collected to measure the plasma concentration of adrenaline. The blood samples were added to precooled plastic tubes containing 40 μl 0.2 M EDTA-2 Na and 0.2 M $Na_2S_2O_5$ and centrifuged at 4,000 r.p.m. for 10 min at 2°C to separate the plasma. Then, 1 ml of plasma was acidified with 0.5 ml of 2.5% perchloric acid to precipitate protein and the samples were stored at −40°C until analysis. The plasma concentration of adrenaline was determined by an h.p.l.c. fluorometric method, as described previously (Hayashi *et al.*, 1993b). This assay has a limit of sensitivity of 5 pg ml^{-1} for adrenaline and inter- and intraassay variations of less than 3%.

Drugs and administration

Rilmenidine (2-[N-(dicyclopropylmethyl) amino] oxazoline) was a kind gift from Institut de Recherches Servier (France). Other chemicals were obtained from the sources indicated: halothane (Takeda Chemical, Osaka, Japan), idazoxan hydrochloride (RBI, MA, U.S.A.), rauwolscine hydrochloride (RBI), (−)-adrenaline (Wako chemical, Osaka, Japan). Rilmenidine was dissolved in saline to the desired concentration such that each dog received a dose as 1 ml bolus injection. Idazoxan and rauwolscine were dissolved in saline at concentrations of 100 $\mu g\ ml^{-1}$ and 200 $\mu g\ ml^{-1}$, respectively. In each dog, a 20-gauge spinal needle (Terumo, Tokyo, Japan) was inserted percutaneously between the spinal processes of C1 and C2 and advanced into the cisterna magna, and these antagonists were then administered intracisternally through the needle. Adrenaline was dissolved in 0.2 ml HCl (1 N) and diluted with saline to a concentration of 300 $\mu g\ ml^{-1}$. We used physiological saline (0.9% w/v % sodium chloride: Terumo, Tokyo, Japan) to dissolve or dilute the chemicals.

Experimental protocols

Experiment 1 The effect of rilmenidine on the halothane-adrenaline-induced arrhythmia ($n=30$) The arrhythmogenic doses and plasma concentrations of adrenaline were determined in the presence of rilmenidine (0, 1, 3, 10 $\mu g\ kg^{-1}$, i.v.). Rilmenidine or vehicle was administered intravenously and then 30 min later the first infusion of adrenaline was started.

Experiment 2 Antagonistic activity of idazoxan and rauwolscine on the effect of rilmenidine ($n=28$) The arrhythmogenic doses and plasma concentrations of adrenaline were determined in the presence of rilmenidine (10 $\mu g\ kg^{-1}$, i.v.) pretreated with intracisternal vehicle (1 ml of saline), idazoxan (10 $\mu g\ kg^{-1}$) or rauwolscine (20 $\mu g\ kg^{-1}$), respectively. The doses of idazoxan and rauwolscine were determined to be approximately equal with regard to α_2-adrenoceptor blockade (Perry *et al.*, 1981; Boyajian *et al.*, 1987; Illeus *et al.*, 1990). In these groups, the intracisternal injections of the antagonist were made 5 min before intravenous rilmenidine and then 30 min later the first infusion of adrenaline was started.

Experiment 3 Effects of bilateral vagotomy on the effects of rilmenidine ($n=15$) The arrhythmogenic doses and plasma concentrations of adrenaline were determined with or without rilmenidine in the bilaterally vagotomized dogs. In these groups, bilateral vagotomy was performed by sectioning both vagus nerves at the level of the fourth cervical vertebra. After haemodynamic stability was achieved, intravenous rilmenidine (10 $\mu g\ kg^{-1}$, i.v.) or vehicle (1 ml of saline, i.v.) was injected and 30 min later the first infusion of adrenaline was started.

In each experiment, haemodynamic parameters (heart rate, arterial blood pressures) at the basal period and at the time of arrhythmia were recorded.

Data analysis

All data were expressed as means ± s.e.mean. The results of multiple groups (Experiments 1–3) were analysed by one way analysis of variance (ANOVA), and comparisons between groups were assessed by Scheffe's test. To compare the haemodynamic data between the groups receiving 10 $\mu g\ kg^{-1}$ of rilmenidine with or without bilateral vagotomy, comparisons were made by Student's unpaired t test. In these comparisons, $P<0.05$ was considered statistically significant.

Results

Under halothane anaesthesia, rilmenidine (1, 3, 10 $\mu g\ kg^{-1}$, i.v.) altered neither the basal mean arterial pressure nor heart rate 30 min after administration (Table 1) and the haemodynamic data obtained at the onset of arrhythmia were not significantly different in each group (Table 2). However, intravenous administration of rilmenidine increased both the arrhythmogenic doses and plasma concentration of adrenaline in a dose-dependent manner (Figure 1). Furthermore, at the time of arrhythmia, arterial blood pressure tended to increase and heart rate tended to decrease in the rilmenidine-treated animals despite the higher plasma concentration of adrenaline (Table 2, Figure 1).

Although, neither intracisternal idazoxan (10 $\mu g\ kg^{-1}$) nor intracisternal rauwolscine (20 $\mu g\ kg^{-1}$) affected the basal haemodynamic parameters (data not shown) under halothane anaesthesia, idazoxan but not rauwolscine blocked the antiarrhythmic effect of rilmenidine (10 $\mu g\ kg^{-1}$, i.v.) (Figure 2). Mean arterial pressure and heart rate at the time of arrhythmia in both groups were not significantly different compared with rilmenidine alone (10 $\mu g\ kg^{-1}$, i.v.) (Table 3).

Table 1 The effects of rilmenidine on basal haemodynamic parameters under halothane anaesthesia

Doses of rilmenidine ($\mu g\ kg^{-1}$, i.v.)	n	*Before administration* MAP (mmHg)	HR (beats min^{-1})	*After administration* MAP (mmHg)	HR (beats min^{-1})
0	7	74±5	115±8	72±4	115±6
1	7	73±4	121±9	74±7	116±8
3	8	73±7	113±8	91±7	122±12
10	8	70±5	108±9	77±5	106±8

Values are expressed as means±s.e.mean, n=number of observations, MAP=mean arterial pressure, HR=heart rate.

Table 2 Haemodynamic data at the onset of arrhythmias in the presence of rilmenidine

Dose of rilmenidine ($\mu g\ kg^{-1}$, i.v.)	n	MAP (mmHg)	HR (beats min^{-1})
0	7	155±10	138±13
1	7	147±9	116±20
3	8	158±13	120±25
10	8	172±6	98±15

Values are expressed as mean±s.e.mean, n=number of observations, MAP=mean arterial pressure, HR=heart rate.

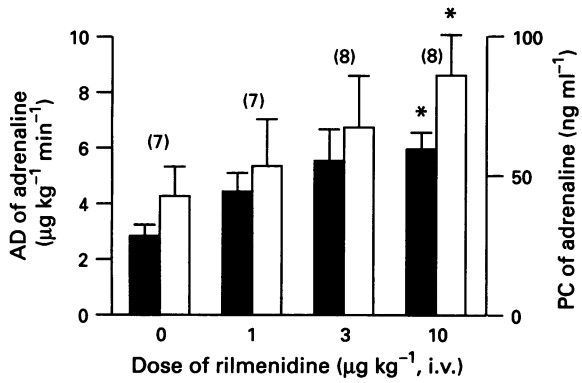

Figure 1 Arrhythmogenic dose (AD, solid columns) and plasma concentrations (PC, open columns) of adrenaline in the presence of rilmenidine (0, 1, 3, 10 $\mu g\ kg^{-1}$, i.v.) under halothane anaesthesia in dogs. The values are expressed as mean±s.e.mean and number of observations is shown in parentheses. Statistical significance: *$P<0.05$ compared with dose 0.

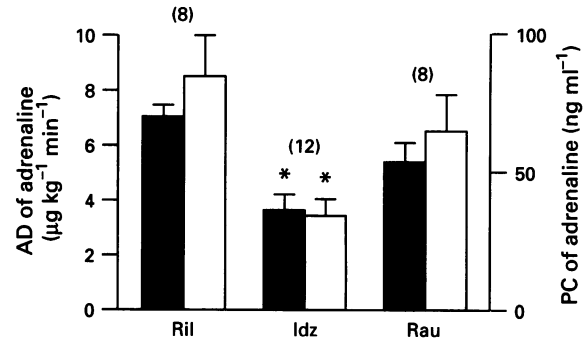

Figure 2 Arrhythmogenic dose (AD, solid columns) and plasma concentrations (PC, open columns) of adrenaline in the presence of rilmenidine pretreated with vehicle, idazoxan or rauwolscine under halothane anaesthesia in dogs. The values are expressed as mean± s.e.mean and number of observations is shown in parentheses. Ril: vehicle (i.c.)+rilmenidine (10 $\mu g\ kg^{-1}$, i.v.), Idz: idazoxan (10 $\mu g\ kg^{-1}$, i.c.)+rilmenidine (10 $\mu g\ kg^{-1}$, i.v.), Rau: rauwolscine (20 $\mu g\ kg^{-1}$, i.c.)+rilmenidine (10 $\mu g\ kg^{-1}$, i.v.), Statistical significance: *$P<0.05$ compared with Ril.

Table 3 Haemodynamic data at the onset of arrhythmias in the antagonistic experiments

	n	MAP (mmHg)	HR (beats min^{-1})
Ril	8	172±6	98±15
Ril+Idz	12	158±10	110±10
Ril+Rau	8	168±6	114±10

Values are expressed as mean±s.e.mean, Ril: rilmenidine (10 $\mu g\ kg^{-1}$, i.v.), Idz: idazoxan (10 $\mu g\ kg^{-1}$, i.c.), Rau: rauwolscine (20 $\mu g\ kg^{-1}$, i.c.). n=number of observations, MAP=mean arterial pressure, HR=heart rate.

Bilateral vagotomy did not affect the arrhythmogenic doses or plasma concentrations of adrenaline compared with intact dogs (Figure 3). However, the antiarrhythmic effects of rilmenidine (10 $\mu g\ kg^{-1}$, i.v.) were totally abolished in the bilaterally vagotomized animals (Figure 3). At the time of arrhythmia, the bilateral vagotomy did not affect the mean arterial pressure but increased the heart rate in the presence of rilmenidine (10 $\mu g\ kg^{-1}$, i.v.) (Table 4).

Discussion

Receptor mechanism of the antiarrhythmic action of rilmenidine

Rilmenidine, a centrally acting antihypertensive agent, binds selectively to imidazoline receptors in the CNS (Bricca *et al.*, 1989; 1994; Vos *et al.*, 1994) and this property was considered to be responsible for the antihypertensive action of this agent (Ernsberger *et al.*, 1990; Feldman *et al.*, 1990; Gomez *et al.*, 1991). In the present study, rilmenidine increased the dose of adrenaline required to induce ventricular arrhythmia under halothane anaesthesia and it is conceivable that the activation of central imidazoline receptors is responsible for the antiarrhythmic effect of rilmenidine observed in our study. However, rilmenidine also interacts weakly with α_2-adrenoceptors (Ernsberger *et al.*, 1993) and Urban *et al.* (1994) reported that α_2-adrenoceptors rather than imidazoline receptors are likely to be responsible for the sympathoinhibitory action of rilmenidine. Thus, it is important to identify which receptor is responsible for the antiarrhythmic effect of rilmenidine. In our study, centrally administered idazoxan, but not rauwolscine, blocked the antiarrhythmic effect of rilmenidine. Idazoxan is known to have high affinity for imidazoline receptors (Lehmann *et al.*, 1989) whereas its α_2-antagonistic potency is similar to that of rauwolscine (Feldman *et al.*, 1990; Illeus & Nören-

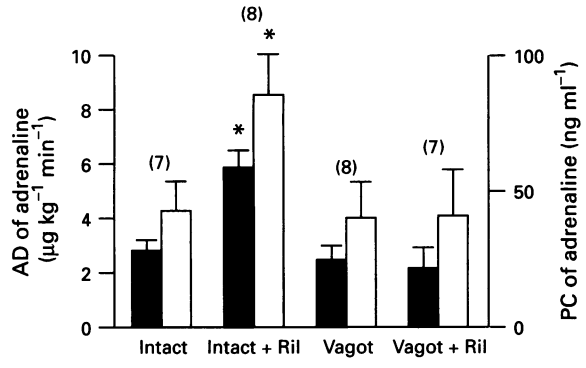

Figure 3 Arrhythmogenic dose (AD, solid columns) and plasma concentrations (PC, open columns) of adrenaline in the intact or bilaterally vagotomized dogs under halothane anaesthesia. The values are expressed as mean ± s.e.mean and number of observations is shown in parentheses. Intact: intact vagus + vehicle alone (i.v.), Intact + Ril: intact vagus + rilmenidine (10 μg kg^{-1}, i.v.), Vagot: bilateral vagotomy + vehicle (i.v.), Vagot + Ril: bilateral vagotomy + rilmenidine (10 μg kg^{-1}, i.v.). Statistical significance: $*P<0.05$ compared with intact.

Table 4 Haemodynamic data at the onset of arrhythmias in the presence of rilmenidine with or without bilateral vagotomy

	n	*MAP* (mmHg)	*HR* (beats min^{-1})
Ril	8	172 ± 6	98 ± 15
Ril + Vagot.	7	160 ± 9	174 ± 29*

Values are expressed as mean ± s.e.mean, n = number of observations, MAP = mean arterial pressure, HR = heart rate. Ril: rilmenidine (10 μg kg^{-1}, i.v.), Vagot: bilaterally vagotomized dogs, $*P<0.05$ compared with Ril.

berg, 1990; Tibirica *et al.*, 1991). On the other hand, rauwolscine shows little affinity for imidazoline receptors as compared with its α_2-agonist potency (Lehmann *et al.*, 1989; Brown *et al.*, 1990). We determined the doses of idazoxan and rauwolscine so that these antagonists exerted approximately equal effects in blocking α_2-adrenoceptors (Perry *et al.*, 1981; Boyajian *et al.*, 1987; Illeus & Nörenberg, 1990). Intracisternal injection of these agents did not affect the basal haemodynamic parameters under halothane anaesthesia, and we could not speculate on the degree of α_2-adrenoceptor and imidazoline receptor blockade by these agents in our study. However, rilmenidine is a selective imidazoline receptor agonist (the imidazoline/α_2-adrenoceptor affinity ratio is approximately 30) (Ernsberger *et al.*, 1993), and the doses of rilmenidine used here were very small. Thus, we consider that the doses of both antagonists were sufficient to block the α_2-adrenoceptor potency of rilmenidine and the dose of idazoxan was appropriate for imidazoline receptor blockade in our experiments. These findings indicate that the activation of central imidazoline receptors is responsible for the antiarrhythmic effect of rilmenidine.

Effects of rilmenidine on the haemodynamic parameters

An interesting finding in this study was that rilmenidine increased the arrhythmogenic dose of adrenaline, whereas no hypotensive effect was noted in the dose ranges we tested. When we reviewed previous reports of animal studies, much larger doses of intravenous rilmenidine were used to investigate the hypotensive effect of rilmenidine (Mayorov *et al.*, 1993; Boucher *et al.*, 1994; Urban *et al.*, 1994), and therefore this phenomenon would be due to the doses of rilmenidine administered. In addition, the inhalational anaesthetic, halothane, itself is known to reduce cardiac output (Eger *et al.*, 1970) and decrease blood pressure at the concentration used here (Hayashi *et al.*, 1991c). Considering that the haemodynamic data in these papers were recorded in conscious animals or in animals under intravenous anaesthesia, the effect of halothane on the circulation might mask the haemodynamic action of rilmenidine in our experiments. The reasons for neither idazoxan nor rauwolscine effecting the basal haemodynamic parameters might also be due to the same reason.

On the other hand, our haemodynamic data showed that the blood pressure and heart rate at the onset of arrhythmia did not increase significantly despite the increase in plasma concentration of adrenaline in the rilmenidine-treated groups and bilateral vagotomy completely blocked the antiarrhythmic action of rilmenidine. In the bilaterally vagotomized dogs, the heart rate increased at the onset of arrhythmia despite the presence of rilmenidine, suggesting impairment of the baroreflex. Rilmenidine is known to enhance the baroreflex response to the rise in blood pressure (Spiers *et al.*, 1990). In our experiment, rilmenidine could have potentiated the baroreflex following adrenaline infusion, resulting in attenuation of the hypertensive action of adrenaline. The elevation of arterial blood pressure has been suggested to facilitate the occurrence of halothane-adrenaline-induced arrhythmia (Reynolds, 1984; Atlee & Bosnjak, 1990) and we consider that this property of rilmenidine contributes to its antiarrhythmic action. In addition, it is suggested that the antiarrhythmic action of rilmenidine may be much more potent than its hypotensive action under halothane anaesthesia.

Autonomic neural activity and the antiarrhythmic action of rilmenidine

Previous binding studies showed that imidazoline receptors are located predominantly in the rostral ventrolateral medulla oblongata (RVLM) (Bricca *et al.*, 1994), and imidazoline receptors in the C1 area of the RVLM are considered to be responsible for the hypotensive action of imidazoline receptor ligands such as clonidine and rilmenidine (Gomez *et al.*, 1991). The neurones of the C1 area project to excite sympathetic preganglionic neurones of the spinal cord (Ruggiero *et al.*, 1989). In addition, nucleus tractus solitarii (NTS) and the C1 area are functionally connected to control the sympathovagal activity (Ross *et al.*, 1985). The NTS contains the afferent terminals of the vagus nerve and regulates activity of the dorsal motor nucleus of the vagus where efferent parasympathetic nerves originate (Ross *et al.*, 1985). Thus, the C1 area is considered to be an important area for sympathovagal vasomotor control. On the other hand, it has been demonstrated that sympathetic blockade as well as vagal stimulation can attenuate the arrhythmogenic potency of adrenaline in the presence of halothane (Zink *et al.*, 1975; Waxman *et al.*, 1989; Kamibayashi *et al.*, 1995). Therefore, the present study suggests that rilmenidine attenuates sympathetic neural activity or enhances vagal input at the C1 area via activation of imidazoline receptors and thus inhibits halothane-adrenaline-induced arrhythmia.

In conclusion rilmenidine dose-dependently inhibited halothane-adrenaline-induced arrhythmia, and it is suggested that central imidazoline receptors are involved in the antiarrhythmic effect of this agent. In addition, inhibition of the sympathetic neural activity is likely to be involved in this effect and the vagal nerve is critical for the antiarrhythmic action of rilmenidine.

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