Sympathoinhibitory effects of rilmenidine may be mediated by sites located below the brainstem

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1 To determine the site of action of rilmenidine, we examined its effects on arterial blood pressure (BP), heart rate (HR) and postganglionic renal sympathetic nerve activity (RSNA) after intracerebroventricular (i.c.v.) administration ($300 \mu\text{g kg}^{-1}$), in groups (all $n = 6$) of conscious and freely moving, pentobarbitone-anaesthetized and pentobarbitone-anaesthetized and spinally transected, fifteen week-old male spontaneously hypertensive rats (SHRs).

2 In conscious SHRs, which exhibited a low sympathetic nerve activity (RSNA: $3.4 \pm 0.9 \mu\text{V}$), rilmenidine was inactive on systolic BP (SBP), diastolic BP (DBP), HR and RSNA.

3 In intact pentobarbitone-anaesthetized SHRs, which exhibited an elevated sympathetic nerve activity (RSNA: $10.6 \pm 0.9 \mu\text{V}$), rilmenidine exerted potent antihypertensive (ΔSBP : $-37 \pm 4\%$; ΔDBP : $-43 \pm 6\%$), bradycardic (ΔHR : $-32 \pm 3\%$) and sympathoinhibitory (ΔRSNA : $-68 \pm 9\%$) activities.

4 In pentobarbitone-anaesthetized SHRs with cervical spinal cord transection, BP was markedly decreased and sympathetic nerve activity (RSNA: $10.3 \pm 3.1 \mu\text{V}$) returned to the level observed in conscious SHRs (RSNA: $3.6 \pm 0.5 \mu\text{V}$). In these conditions, rilmenidine remained sympathoinhibitory (ΔRSNA : $-74 \pm 5\%$).

5 In conclusion, we have shown that pentobarbitone-anaesthesia enhances the peripheral sympathetic tone by a central action, as the spinal cord transection allows RSNA to return to normal levels and that, spinal or ganglionic structures could be a major site of the sympathoinhibitory action of rilmenidine.

Keywords: α_2 -Adrenoceptors; blood pressure; intracerebroventricular; renal sympathetic nerve activity; rilmenidine; spinal transection; spontaneously hypertensive rats; sympathetic nervous system

Introduction

For clonidine and related drugs like rilmenidine, several sites of action (for review see Jarrott *et al.*, 1987; Jarrott, 1988) have been proposed: brainstem (Bousquet & Guertzenstein, 1973; Bousquet *et al.*, 1981; Punnen *et al.*, 1987), spinal cord (Connor *et al.*, 1981; Solomon *et al.*, 1989) and/or peripheral presynaptic α_2 -adrenoceptors (Timmermans *et al.*, 1981). Moreover, although one mechanism proposed for the antihypertensive action of rilmenidine in spontaneously hypertensive rats (SHRs) has been a reduction in peripheral sympathetic tone (Van Zwieten, 1988), to our knowledge, no studies have been able to demonstrate the direct action of rilmenidine on the peripheral sympathetic nervous system activity in anaesthetized or conscious SHRs. Otherwise, previous studies in conscious unrestrained (Sannajust *et al.*, 1989; 1992) and pentobarbitone-anaesthetized (Sannajust *et al.*, 1992) SHRs suggested that rilmenidine did not act primarily and exclusively on the central nervous system (forebrain/brainstem) to lower arterial blood pressure (BP) and heart rate (HR).

Therefore, the aim of the present study was to determine whether or not these drugs could exert their sympathoinhibitory effect by acting on sites located outside the brain. Consequently, we measured the arterial BP and the renal sympathetic nerve activity (RSNA) after i.c.v. injections of rilmenidine in conscious, pentobarbitone-anaesthetized and, pentobarbitone-anaesthetized and spinal cord transected SHRs.

Methods

Eighteen 15 week-old male SHRs (IFFA-Credo, Les Oncins, France) weighing 290 to 337 g, were used in these experiments.

Preparation of the animals (for details see Sannajust *et al.*, 1992)

In all animals, one week before experimentation, a stainless-steel guide cannula was implanted. After a 5-day period of recovery, two polyethylene catheters were inserted into the left femoral artery and vein for BP measurement and drug administrations, respectively. On the day of the experiment, the arterial line of conscious and pentobarbitone-anaesthetized SHRs was connected to a pressure transducer coupled to a recorder. The body temperature of anaesthetized animals was maintained at $37 \pm 1^\circ\text{C}$ by means of a heating pad and the trachea was cannulated for artificial ventilation with room air ($10 \text{ ml kg}^{-1} \times 65 \text{ min}^{-1}$).

Renal sympathetic nerve activity measurement

Efferent renal sympathetic nerve activity was measured by the technique described by Thoren & Ricksten (1979), with minor modifications. Briefly, under methohexitone-anaesthesia (i.v. injection of a 3% solution of methohexitone, adapted for each animal when required) for conscious SHRs or under pentobarbitone-anaesthesia (60 mg kg^{-1} , i.p.) for anaesthetized SHRs, the renal sympathetic nerve was approached dorso-laterally through an incision in the left flank extending from the latissimus dorsalis muscle to the level of the sternum. Ventral retraction of the spleen and the kidney allowed for the dissection of nerves located along the left renal artery. The left renal nerve was isolated and carefully freed from surrounding tissue with the aid of a stereoscopic dissecting microscope. A thin platinum-iridium bipolar electrode was placed around the nerve and insulated with silicone rubber (Wacker Silgel 604, Adrian, U.S.A.). The electrode cable was sutured to the surrounding muscles, and the free end was passed subcutaneously to the back of the neck, exteriorized, and sutured in place. The rats were allowed a 2 h period to recover from anaesthesia before starting the experiment. The nerve signals were amplified ($\times 50,000$) by a Grass P511.J. amplifier (Grass Instr. Co., Quincy, U.S.A.) with a low- and high-frequency

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Table 1 Effects of pentobarbitone-anaesthesia on the baseline values of the parameters recorded in fifteen week-old male SHR

	Conscious (n = 6)	Pentobarbitone-anaesthetized	
		Intact (n = 6)	Before transection (n = 6)
SBP (mmHg)	178 ± 8	155 ± 11†	121 ± 14**††
DBP (mmHg)	118 ± 10	114 ± 11	87 ± 13**††
HR (b.p.m.)	375 ± 15	393 ± 11	325 ± 12**††
RSNA (μV)	3.4 ± 0.9	10.6 ± 0.9††	10.3 ± 3.1††

Data are mean ± s.e.mean

* $P < 0.05$; ** $P < 0.01$; vs intact-anaesthetized SHR.

(Mann-Whitney-U-test).

† $P < 0.05$; †† $P < 0.01$; vs conscious SHR (Mann-Whitney-U-test).

cut-off set at 100 and 1,000 Hz, respectively. The amplified nerve activity was displayed on a Gould oscilloscope DSO-1602 (Gould Instr. S.A.F., Paris, France). For the integration of discharges the nerve signals appearing at the oscilloscope outputs were rectified and displayed along with arterial BP and HR on a computer MOTOROLA SYS-3304/NY/082 (Motorola Co., Tempe, U.S.A.) (Gustin *et al.*, 1990). The background non neural activity was taken as the activity recorded after injection of a ganglionic blocker (trimethaphan camsilate: 10 mg kg^{-1} , i.v.). This background activity was determined at the end of the experiment and subtracted from the total integrated activity to allow the quantitative estimation of sympathetic nerve activity.

Spinal cord transection

Six pentobarbitone-anaesthetized animals were subjected to spinal transection at the level of the fifth cervical (C5) segment. The spinal cord was exposed via a dorsal laminectomy from cervical level C1 to C6, then the vertebral disk between C4 and C5 segments was removed to allow visualization of the dorsal surface of the cord. Once the dura was perforated, the exposed spinal cord was kept moist with warm mineral oil. The spinal cord was completely transected at C5 level, first, with a scalpel blade and second, in order to ensure the completeness of the transection with a dental hand-drill. Immediately, a disk of gel foam (Spongel*, Lab. Houde, Paris, France), approximately 1 mm in width, was placed into the sectional spinal cord space, the muscles were sutured and the incision was closed.

Blood pressure, heart rate and renal sympathetic nerve activity signals processing

Systolic BP (SBP), diastolic BP (DBP), heart rate (HR) and rectified nerve signals of RSNA were continuously recorded in freely moving and anaesthetized groups of animals by a computerized technique (Gustin *et al.*, 1990).

Experimental protocols

In all groups of SHR, i.c.v. cannula and, arterial and venous catheters were implanted one week and 48 h, respectively, before the start of the recording sessions. Injection volumes were $2 \mu\text{l}$ per animal for i.c.v. and 0.5 ml kg^{-1} for i.v. injections. In conscious and unrestrained animals, the i.c.v. and i.v. polyethylene tubes were extended outside the registration cage to avoid stressing the animals. Finally, at the end of each experiment, i.v. injections of the ganglionic blocker trimethaphan camsilate (10 mg kg^{-1}) were used to estimate the background noise level of the nerve activity.

Conscious SHR (n = 6) Each awake rat was placed in a cylindrical cage and connected to the BP recording system for a 0.5 to 1.0 h control period. Then, under methohexitone-anaesthesia, the renal nerve bipolar electrode was implanted

and spike activity was monitored. After a 2 h period which allowed the animal to recover from anaesthesia and the cardiovascular parameters to stabilize, BP, HR and RSNA were continuously recorded for 5 to 6 h. After a 1 h control period, each animal received one i.c.v. injection of artificial cerebrospinal fluid (CSF) followed by one i.c.v. injection of rilmenidine ($300 \mu\text{g kg}^{-1}$).

Pentobarbitone-anaesthetized SHR (n = 6) After connection to the BP recording system, implantation of the renal nerve bipolar electrode and cannulation of the trachea, each animal was placed in a stereotaxic frame, for an equilibration period which allowed the cardiovascular parameters, blood gases and pH to stabilize. Then, BP, HR and RSNA were recorded continuously for a 1 h control period and a 3–4 h period during which, each animal received one i.c.v. injection of artificial CSF followed by one of rilmenidine ($300 \mu\text{g kg}^{-1}$).

Pentobarbitone-anaesthetized and spinally-transected SHR (n = 6) The animals were prepared as described above for anaesthetized SHR. Then, they were mounted on a stereotaxic frame in order to hold the head steady whilst the spinal cord was dissected and BP, HR and RSNA were continuously recorded. When the cardiovascular parameters returned to control values, the spinal cord was completely transected at C5 level and they were monitored for a 3–4 h period. Twenty to thirty min after transection, when all the cardiovascular parameters were stabilized, each animal received one i.c.v. injection of artificial CSF followed by one of rilmenidine ($300 \mu\text{g kg}^{-1}$).

Assessment of the guide-cannula implantation and of spinal transection

At the end of each experiment, the guide-cannula position was assessed as previously described in Sannajust *et al.* (1992). The spinal transection was confirmed *post-mortem* by dissection of the site of lesion.

Statistical evaluation

Data are expressed as mean ± standard error of the mean (s.e.mean). At any given time of the recording, the significance of the differences was assessed by means of a Mann-Whitney-U-test. Wilcoxon's signed rank-test for paired differences was used when appropriate. The interpretation of multiunit nerve recordings has several problems, as it is function of the number of active fibres, their firing frequency and of the contact between the nerve bundle and the electrode. However, since great care was taken to standardize the mechanical preparation of nerve bundles only slight differences were observed among the various SHR and we, therefore, compared RSNA between groups.

Drugs and solutions

Rilmenidine [N-(dicyclopropylmethyl)-amino-2A2-oxazoline] phosphate (I.R.I. Servier, France) was dissolved in artificial CSF (Palaic *et al.*, 1967) and maintained in sealed vials at 37°C and adjusted to pH 7.3 just before injection. [Val⁵]-angiotensin II acetate and trimethaphan camsilate were obtained from Sigma Chemical Company (St-Louis, U.S.A.) and Hoffmann-La-Roche Lab., (Basle, Switzerland) respectively.

Results

Effects of i.c.v. administration of rilmenidine in conscious SHR

In freely moving, quietly resting SHR, basal SBP, DBP, HR and RSNA (average of the 20 min of control period preceding i.c.v. administrations) are indicated in Table 1. As shown in Figure 1, artificial CSF as well as rilmenidine ($300 \mu\text{g kg}^{-1}$,

Figure 1 Systolic (SBP), diastolic (DBP) blood pressure, heart rate (HR) and renal sympathetic nerve activity (RSNA) before and after i.c.v. injection of cerebrospinal fluid (CSF) and rilmenidine ($300 \mu\text{g kg}^{-1}$) in one conscious (a) and one pentobarbitone-anaesthetized spontaneously hypertensive rat (b). Each point of the graph is the mean of the values recorded during 60 s periods. The background noise of RSNA has been subtracted.

i.c.v.) did not affect these parameters. On the other hand, the ganglionic blocker given at the end of experiment, markedly reduced SBP, DBP, HR and RSNA.

Effects of pentobarbitone-anaesthesia (see Table 1)

Pentobarbitone-anaesthesia significantly ($P < 0.05$) lowered SBP and markedly (3 fold) increased RSNA. The surgical preparation required for the spinal cord transection slightly reduced BP and HR, but did not affect the RSNA level. Figure 2 indicates that the bursts of spikes of the renal nerve were more marked and exhibited a more clear-cut rhythmicity in pentobarbitone-anaesthetized (b) than in conscious (a) SHRs.

Effects of i.c.v. administration of rilmenidine in pentobarbitone-anaesthetized SHRs

In anaesthetized intact SHRs, rilmenidine ($300 \mu\text{g kg}^{-1}$, i.c.v.) induced rapid, marked and long-lasting decreases in SBP, DBP, HR and RSNA (Figure 1). The maximum effects appeared around 90 min after i.c.v. injection, and were as follows: SBP ($-37 \pm 4\%$), DBP ($-43 \pm 6\%$), HR ($-32 \pm 3\%$) and RSNA ($-68 \pm 9\%$). As shown in Figure 1, 5 min after injection, HR, SBP and DBP were significantly ($P < 0.05$) decreased ($-11 \pm 2\%$, $-8 \pm 2\%$ and $-9 \pm 4\%$ respectively) while RSNA remained stable. Then SBP, DBP, HR and RSNA decreased in parallel to reach the maximal effect within 90 min.

Figure 2 Typical oscilloscope recordings of the signals of renal sympathetic nerve activity (RSNA) in (a) one conscious, (b) one pentobarbitone-anaesthetized spontaneously hypertensive rat, (c) during baseline after spinal cord transection, (d) after i.c.v. injection of rilmenidine ($300 \mu\text{g kg}^{-1}$) and (e) after ganglionic blockade.

Effects of spinal cord transection

As indicated in Table 1 and Figure 3, the spinal cord dissection prior to the transection induced significant decreases in SBP and HR, but did not affect RSNA which was identical to that of pentobarbitone-anaesthetized intact SHR. Acute spinal cord transection at C5 level, markedly ($P < 0.05$) and irreversibly reduced SBP, DBP, HR and RSNA ($-48 \pm 4\%$; $-52 \pm 4\%$; $-18 \pm 6\%$ and $-56 \pm 8\%$ respectively) (see Figures 2 and 3). Only 2 out of 6 animals in this experiment responded to the transection with a rapid and very short-lasting initial increase in BP, HR and RSNA, but, immediately after the end of transection, SBP, DBP, HR and RSNA decreased to levels significantly below control period. HR was less markedly reduced than BP. Interestingly, the spinal cord transection did not completely abolish RSNA as (see Figure 4) its level ($3.6 \pm 0.5 \mu\text{V}$) returned to that of conscious SHR ($3.4 \pm 0.9 \mu\text{V}$), but as shown in Figure 2b suppressed its rhythmicity.

Effects of i.c.v. administration of rilmenidine in pentobarbitone-anaesthetized and spinally transected SHRs

After spinal transection, average SBP, DBP, HR and RSNA were $61 \pm 4 \text{ mmHg}$; $40 \pm 4 \text{ mmHg}$; $267 \pm 24 \text{ b.p.m.}$ and

$3.6 \pm 0.5 \mu\text{V}$ respectively. In these new basal conditions (Figure 3), artificial CSF was devoid of effect and rilmenidine ($300 \mu\text{g kg}^{-1}$, i.c.v.), did not alter BP but, significantly ($P < 0.05$) decreased HR ($-6 \pm 1\%$) and RSNA ($-22 \pm 4\%$) 5 min after the administration. The maximum effects (HR: $-16 \pm 3\%$; RSNA: $-74 \pm 5\%$) were obtained 50 min after the injection. Interestingly as indicated in Figure 4, the rilmenidine-induced relative decrease in RSNA was identical in intact and in spinal cord-transected SHRs.

Discussion

The major finding of this study is that rilmenidine acts to lower BP by reducing peripheral sympathetic nervous system (SNS) activity and that the site of this sympathoinhibitory effect is not only located in the brainstem but also in the spinal or ganglionic structures.

Rilmenidine is an amino-oxazoline, structurally related to imidazolines such as clonidine, which exhibits α_2 -adrenoceptor agonist activities (Laubie *et al.*, 1985) and antihypertensive properties. Although the mechanism proposed for the antihypertensive action of rilmenidine in SHRs is a reduction in peripheral sympathetic tone (Van Zwieten, 1988), to our knowledge, no studies have demonstrated its direct action on the peripheral SNS activity in anaesthetized or conscious SHRs.

Previous studies in conscious, unrestrained (Sannajust *et al.*, 1989) and pentobarbitone-anaesthetized (Sannajust *et al.*, 1992) SHRs have shown that the ability of rilmenidine and clonidine to lower BP could be related to the level of the sympathetic drive and conversely to the integrity of the cardiac baroreflex. The absence of antihypertensive effects of rilmenidine or clonidine administered by the i.c.v. route in conscious SHRs, suggests that these drugs could interact with central structures like forebrain (Klevans *et al.*, 1973; Van den Buuse *et al.*, 1990) and brainstem (Gomez *et al.*, 1990), which play an activator or inhibitor role of sympathetic tone, respectively (Head, 1991). Therefore, in this study we examined in conscious unrestrained, pentobarbitone-anaesthetized and pentobarbitone-anaesthetized and spinally transected SHRs, the effects of rilmenidine administered by i.c.v. route, on BP, HR and postganglionic efferent RSNA. We have chosen to record the nerve traffic in the renal nerve because it represents a major sympathetic nerve implicated in the BP regulation. The renal nerve is well known to influence cardiovascular resistance, Na^+ and water reabsorption and renin secretion (DiBona, 1982). Under these conditions, in conscious SHRs, the absence of RSNA change after i.c.v. administered rilmenidine ($300 \mu\text{g kg}^{-1}$ chosen from the dose-response curves obtained in previous experiments, Sannajust *et al.*, 1992) rules out a possible compensation, by other pressor systems, of the BP effects of rilmenidine. On the other hand, it seems unlikely that the lack of effect of rilmenidine on RSNA could depend on a balance of the two components (pressor and depressor) and that the vasomotor influence of the forebrain structures would be quantitatively opposed to the vasoinhibitory influence of the brainstem. This is in accordance with the recent demonstration by Gomez *et al.* (1990) that midcollicular decerebration did not affect the hypotensive effect of rilmenidine microinjected into the vasomotor centre (C1 area) of the rostral ventrolateral medulla; therefore, forebrain structures are not implicated in the mechanism of the antihypertensive action of rilmenidine.

In a second set of experiments, we administered rilmenidine by the i.c.v. route in pentobarbitone-anaesthetized SHRs. These experiments were designed to confirm the increase in SNS activity previously hypothesized (Sannajust *et al.*, 1992) on the basis of indirect evidence such as the great hypotensive effect of the ganglionic blocker, trimethaphan and to demonstrate whether the ability of rilmenidine to lower BP could be related to the degree of central sympathetic drive. It is generally accepted (Zimpfer *et al.*, 1982; Murthy *et al.*, 1982; Matsukawa & Ninomiya, 1989) that barbiturate-anaesthesia

Figure 3 Systolic (SBP), diastolic (DBP) blood pressure, heart rate (HR) and renal sympathetic nerve activity (RSNA) before and after spinal cord transection then, after i.c.v. injection of cerebrospinal fluid (CSF) and of rilmenidine ($300 \mu\text{g kg}^{-1}$) in one pentobarbitone-anaesthetized spontaneously hypertensive rat. Each point of the trace is the mean of the values recorded during 60 s periods. The background noise of RSNA has been subtracted.

increases the SNS activity and we have observed that the anaesthetized SHRs present a 3 fold higher RSNA level than the conscious SHRs. Interestingly, by using our technique of continuous recording of the different cardiovascular parameters we observed that RSNA decreased after the onset of the BP and HR decreases. This delay (2–3 min) demonstrates that the decrease in BP could result firstly from a sympathetic-independent decrease in HR, possibly mediated by vagal stimulation, and secondly from a reduction in sympathetic nerve activity which would induce an additional decrease in HR and a reduction in the cardiac output. Therefore, we have to consider that, like clonidine (Bonham *et al.*, 1984), rilmenidine may act at least, on two different sites, one controlling HR and the other controlling RSNA. Moreover, these results demonstrate that rilmenidine diminishes the electrical activity of postganglionic sympathetic fibres and provides direct evidence of a preganglionic or ganglionic site of action. Nevertheless, although we had quantified the sympathoinhibitory effect of i.c.v. rilmenidine we have yet to determine whether the effect is of central or peripheral origin.

A final set of experiments was designed to determine whether or not the sympathoinhibitory effect of rilmenidine was due to an action within the brainstem or could be the result of a peripheral action. I.c.v. administered rilmenidine may reach peripheral sites either by leaking from the cerebral ventricles into the systemic circulation or by diffusing through the CSF to spinal sites (e.g. the intermediolateralis tractus: IML) controlling the peripheral SNS tone. For this reason, we performed an acute spinal cord transection at the C₅ cervical level in pentobarbitone-anaesthetized rats. As previously reported by Schramm & Livingstone (1987) and Taylor & Schramm (1987), the spinal cord transection profoundly and irreversibly decreased SBP and DBP but less markedly reduced HR. Interestingly, the spinal cord transection did not

completely abolish the RSNA which returned to the level observed in conscious SHRs, demonstrating that pentobarbitone-anaesthesia enhances the peripheral SNS tone by a central effect. Moreover, these observations suggest that the SNS activity in intact rats is generated not only by spinal or medullary centres, but also by interaction, at spinal levels, of excitatory and inhibitory information descending via multiple pathways. Spinal or ganglionic systems also contribute to the SNS tone (Schramm & Chornoboy, 1982). In these conditions, despite the normal RSNA level, i.c.v. rilmenidine was still able to decrease RSNA markedly to a degree similar to that observed in intact pentobarbitone-anaesthetized SHRs. This clearly demonstrates that this sympathoinhibition after spinal cord transection cannot be explained by a central effect of rilmenidine, but by action at sites situated below the C₅ level. As the measured RSNA is postganglionic, these sites may be located in the IML of the thoracolumbar spinal cord or in ganglionic structures. In addition, as rilmenidine has no effect in conscious SHRs with similar RSNA level, it must be emphasized that spinal cord transection has altered the mechanisms of control of the sympathetic tone. In that respect, Elghozi *et al.* (1989) have shown that the IML column receives noradrenergic fibres which have an important tonic inhibitory action on spinal preganglionic sympathetic motoneurons and non-adrenergic fibres which have an excitatory action on these same motoneurons; furthermore, these two kinds of fibres could, via stimulation of α_2 -adrenoceptors, influence the vasomotor tone and HR.

Taken together, the results of the present study lead to the hypothesis that, in conscious SHRs, the tonic influence of the inhibitory inputs from the arterial baroreceptors and the noradrenergic fibres could counteract the effects of rilmenidine which are mediated via stimulation of α_2 -adrenoceptors. Pentobarbitone-anaesthesia may only suppress the influence

Figure 4 Effects of i.c.v. injections of rilmenidine ($300 \mu\text{g kg}^{-1}$) on the renal sympathetic nerve activity (RSNA) in conscious (a), intact anaesthetized (b) or anaesthetized and spinal cord transected (c) spontaneously hypertensive rats. (Open columns: before injection; hatched columns: after injection). n = number of animals.

of inhibitory noradrenergic fibres, inducing an increase of the SNS activity and, as the cardiac baroreflex is abolished by pentobarbitone, anaesthesia could favour the action of rilmenidine. Similarly, in pentobarbitone-anaesthetized and spinally transected SHR, the influences of both noradrenergic and non-adrenergic fibres may be blocked, thereby explaining the identical RSNA basal level observed in conscious animals and, thus unmasking the ability of rilmenidine to exert its action by stimulation of unoccupied α_2 -adrenoceptors.

Such spinal or ganglionic sites of action obviously require further investigations of the location and nature of the recep-

tors involved. However, the present work demonstrates that pentobarbitone-anaesthesia enhances the peripheral sympathetic tone by a central action. The antihypertensive effects of rilmenidine are closely related to the pre-existing level of the sympathetic drive and the mechanism of the sympatho-inhibitory action of rilmenidine seems to involve sites located below the brainstem.

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