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# Effect of moxonidine on blood pressure and sympathetic tone in conscious spontaneously hypertensive rats

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**Abstract**

The effects of moxonidine on blood pressure, heart rate and sympathetic tone were studied in conscious spontaneously hypertensive rats. Intravenous moxonidine (80 nmol) transiently increased blood pressure without affecting heart rate or splanchnic nerve activity. Moxonidine (20–80 nmol) given into the fourth cerebral ventricle dose-dependently lowered mean arterial pressure, heart rate and sympathetic outflow (maximally by 60 ± 3 mm Hg, 148 ± 10 beats $min^{-1}$ and 15 ± 3 μV). Moxonidine was more effective by this route than after the injection into the lateral ventricle. Clonidine (20–80 nmol) produced an initial pressor response after both intracerebroventricular routes of administration. A decrease in blood pressure was observed only when clonidine was given into the fourth ventricle. Clonidine decreased heart rate and splanchnic nerve activity similarly like moxonidine when the substances were given into the fourth ventricle. The data imply that the hypotensive effect of moxonidine is related to central sympathoinhibition. The main site of this action appears to be in the brainstem region. 

*Keywords:* Moxonidine; Clonidine; Blood pressure; Heart rate; Sympathetic nerve activity; Spontaneously hypertensive rat (SHR), conscious

## 1. Introduction

Moxonidine is a new antihypertensive agent which is structurally related to clonidine, an $\alpha_2$-adrenoceptor agonist (Armah et al., 1988). Both substances also bind with a high affinity to a new class of receptors, non-adrenergic imidazoline $I_1$ receptors (Ernsberger et al., 1993; Buccafusco et al., 1995). Several recent reports have provided evidence suggesting that the hypotensive effect of clonidine and moxonidine is mediated, at least partly, by activation of these imidazoline receptors (Ernsberger et al., 1993; Haxhiu et al., 1994; Buccafusco et al., 1995; Chan et al., 1996). Of these two agents, moxonidine has a higher selectivity for imidazoline $I_1$ receptors than for $\alpha_2$-adrenoceptors in radioligand binding studies (Ernsberger et al., 1993; Buccafusco et al., 1995).

Moxonidine is generally regarded as centrally active antihypertensive drug (Armah et al., 1988; Haxhiu et al., 1994; Buccafusco et al., 1995). Reduction of the central sympathetic outflow is considered to be the main factor underlying the clonidine-induced fall in blood pressure (Timmermans and Van Zwieten, 1982; Luft et al., 1985). Similarly, inhibition of the sympathetic tone by moxonidine, as evidenced by decreased circulating levels of catecholamines, was reported in both men and animals (Armah et al., 1988; Kirsch et al., 1990; Szabo and Urban, 1997). Moxonidine-induced sympathoinhibition has also been demonstrated by sympathetic nerve recordings in anaesthetized cats (Ramage and Wilkinson, 1989) and in conscious rabbits (Urban et al., 1995a). However, it has recently been suggested that peripheral presynaptic inhibition contributes to the overall reduction in sympathetic tone produced by moxonidine and that the central action is perhaps not sufficient for the blood pressure decrease (Urban et al., 1995b).

The effects of moxonidine on sympathetic nerve recordings have not been studied in hypertensive animal models so far. Therefore, we intended to evaluate the effects of centrally and peripherally administered moxonidine on

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sympathetic tone by recording the activity of the splanchnic sympathetic nerve in conscious, chronically instrumented spontaneously hypertensive rats (SHR). Blood pressure, heart rate, and plasma catecholamines were also measured. The effects of moxonidine were compared to those of clonidine in order to find out whether the cardiovascular effects of the two drugs reflect the differences in their selectivity for imidazoline $I_1$ receptors shown in radioligand binding studies.

## 2. Materials and methods

Adult 14–18 week old male spontaneously hypertensive (SHR) and age-matched normotensive Wistar-Kyoto (WKY) rats obtained from Charles River Wiga (Sulzfeld, Germany) were used. The rats were housed under controlled conditions at 24°C with 12 h light/dark cycle. The experiments were performed in accordance with the German national animal protection law.

### 2.1. Experimental procedure

For the intracerebroventricular injections, polypropylene cannulae (PP 20) were implanted under chloral hydrate (400 mg $kg^{-1}$ i.p.) anaesthesia 1–2 week before the experiments as described previously (Unger et al., 1981). The coordinates for the left lateral cerebral ventricle and the fourth cerebral ventricle were (relative to the bregma): 0.6 mm caudal, 1.3 mm lateral and 5 mm vertical from the surface of the skull, and 10.2 mm caudal at the sagittal midline and 6.8 mm vertical, respectively. Verification of the placement of the cannula in the lateral ventricle was made 2–3 days after the operation by checking the typical drinking behaviour induced by intracerebroventricular injection of angiotensin II (50 ng). The correct placement of the cannula in the fourth ventricle was verified by a post-mortem examination of the diffusion of Evans blue, which was injected into the fourth ventricle at the end of the experiments. The dye was observed in the fourth ventricle as well as on the ventral surface of the medulla.

For the measurements of mean arterial pressure and heart rate, a catheter (PP10 in PP 50) was inserted into the abdominal aorta through the femoral artery under chloral hydrate anaesthesia 2–3 days prior the experiments. The femoral vein was cannulated (PP 50) for intravenous (i.v.) injections. The catheters were tunnelled under the skin and exteriorized at the back of the neck.

Efferent sympathetic nerve activity was recorded with chronic electrodes implanted on the splanchnic nerve 1–2 days before the experiments under methohexital anaesthesia (Brevimytal®, Lilly). After an initial bolus dose of methohexital (10 mg $kg^{-1}$ i.v.), repeated injections were given when required. The surgical procedures have been described in detail elsewhere (Unger et al., 1984). Briefly, the area of the left splanchnic nerve was exposed retroperitoneally via a flank incision. A splanchnic nerve branch between the coeliac ganglion and the suprarenal plexus was placed on a thin bipolar electrode. When an optimal signal was obtained, the nerve on the electrode was insulated and attached with silicone rubber (Wacker-Chemie, München, Germany). The transmission line to the amplifier was exteriorized via a miniature connector at the neck of the rat.

Mean arterial pressure, heart rate and splanchnic nerve activity were monitored while the animals were conscious and unrestrained in individual cages. The arterial cannula was connected to a Statham P23Dc pressure transducer connected to a Gould Brush blood pressure computer and a Gould Brush 2400 recorder. For the measurement of splanchnic nerve activity, the nerve signal was amplified, rectified and displayed on a Gould Brush 2400 recorder. All parameters were recorded at least for 30 min before the injections of the drugs to obtain stable basal values. Moxonidine and clonidine (20–80 nmol) were administered into the lateral or into the fourth cerebral ventricle. The injection volume was 5 μl (1 μl drug flushed with 4 μl isotonic saline). Control animals received an equivalent volume of saline. After the injection, mean arterial pressure, heart rate and splanchnic nerve activity were monitored over a period of 60 min. Only one dose of moxonidine or clonidine was tested in each rat.

### 2.2. Estimation of plasma catecholamine concentrations

The plasma concentrations of adrenaline and noradrenaline were determined in conscious SHR after injection of moxonidine and clonidine (40 nmol) into the fourth cerebral ventricle. For blood sampling, the femoral arterial catheter was connected to an extension catheter (PP 50) with a syringe filled with heparinized saline. Blood samples (0.3 ml) were collected before and 5, 15, 30 and 60 min after the administration of the drugs. Samples were centrifuged at $5000 \times g$ in a refrigerated centrifuge. A 150 μl portion of plasma was deproteinated by the addition of an equal volume of 0.6 M perchloric acid. Plasma samples were vortexed, centrifuged at $10\,000 \times g$ for 20 min, and the supernatant was kept frozen (−75°C) until assayed for catecholamine content by a radioenzymatic method (Da Prada and Zürcher, 1976).

### 2.3. Drugs

Moxonidine was a generous gift from H.-J. Mest (Beiersdorf-Lilly, Hamburg, Germany). Clonidine hydrochloride was purchased from Fluka Chemie (Buchs, Switzerland).

### 2.4. Statistical analysis

The results are expressed as mean ± S.E.M. The data were analysed by one-way analysis of variance and the

pairwise comparisons between the SHR groups were assessed with the Tukey's test. To analyse the influence of moxonidine and clonidine on plasma catecholamines at different time points, comparisons to the initial baseline levels were performed by Student's paired *t* test adjusted by the Bonferroni correction for multiple comparisons (Ludbrook, 1994). Kruskall–Wallis test was used for evaluation of differences between SHR and WKY. Differences were considered significant when $P < 0.05$.

## 3. Results

The initial baseline values for mean arterial pressure, heart rate and splanchnic nerve activity in various groups of SHR and WKY are shown in Table 1. There were no significant differences in baselines among the SHR groups, whereas the baseline mean arterial pressure was significantly lower in WKY than in SHR. Basal values for heart rate and splanchnic nerve activity were not significantly different between the strains.

### *3.1. Effects of moxonidine and clonidine on blood pressure, heart rate and splanchnic nerve activity*

In conscious SHR, moxonidine (20–80 nmol) administered into the fourth cerebral ventricle caused a dose-dependent decrease in mean arterial pressure, heart rate and splanchnic nerve activity with a maximal reduction from $140 \pm 3$ to $80 \pm 2$ mm Hg, from $319 \pm 7$ to $171 \pm 7$ beats $min^{-1}$, and from $39 \pm 4$ to $24 \pm 4$ μV, respectively, at the 80 nmol dose (Fig. 1). When moxonidine was given into the lateral cerebral ventricle, a significant decrease in mean arterial pressure, heart rate and splanchnic nerve activity from $138 \pm 4$ to $100 \pm 6$ mm Hg, from $297 \pm 17$ to $228 \pm 14$ beats $min^{-1}$, and from $35 \pm 3$ to $28 \pm 3$ μV, respectively, was observed only at the highest dose (80 nmol) (Fig. 2). The hypotensive effect of this dose of moxonidine injected into the lateral ventricle was preceded by a transient initial increase in mean arterial pressure (by $23 \pm 2$ mm Hg), which peaked 1 min after the injection and lasted less than 3 min. The reductions in mean arterial pressure, heart rate and splanchnic nerve activity after moxonidine 40 and 80 nmol were significantly larger when the substance was administered into the fourth ventricle than into the lateral ventricle ($P < 0.05$).

Clonidine (20–80 nmol) given into the fourth ventricle produced a biphasic blood pressure response. A dose-dependent initial pressor effect, which lasted less than 5 min, was followed by a decrease in mean arterial pressure at the two lower doses (20 and 40 nmol) (Fig. 1). The reduction in mean arterial pressure was maximal 15–20 min after 20 nmol clonidine (from $139 \pm 9$ to $101 \pm 4$ mm Hg), and no further reduction was observed at higher doses. The initial pressor effect of clonidine at the dose of 80 nmol (maximally by $55 \pm 4$ mm Hg) was long-lasting (15–20 min) and stronger than that induced by the same dose of moxonidine ($P < 0.05$). No significant decrease in mean arterial pressure was observed during the 60 min post-injection period after the largest dose of clonidine (80 nmol). At the two lower doses (20 and 40 nmol), there were no significant differences in the hypotensive effects of clonidine and moxonidine, whereas the largest dose (80 nmol) of moxonidine produced a more pronounced hypotension ($P < 0.01$). Clonidine decreased heart rate and splanchnic

Table 1
Baseline values of mean arterial pressure, heart rate and splanchnic nerve activity prior to drug administration

| Strain | Route | Drug | Dose (nmol) | Mean arterial pressure (mm Hg) | Heart rate (beats $min^{-1}$) | Splanchnic nerve activity (μV) |
|---|---|---|---|---|---|---|
| SHR | fourth ventricle | saline | 5 μl | $138 \pm 3$ (6) | $303 \pm 19$ (6) | $34 \pm 3$ (6) |
| | | moxonidine | 20 | $139 \pm 7$ (6) | $306 \pm 14$ (6) | $41 \pm 7$ (5) |
| | | | 40 | $140 \pm 2$ (8) | $327 \pm 9$ (8) | $40 \pm 3$ (6) |
| | | | 80 | $140 \pm 3$ (7) | $319 \pm 7$ (7) | $39 \pm 4$ (5) |
| | | clonidine | 20 | $139 \pm 9$ (5) | $293 \pm 15$ (5) | $34 \pm 3$ (5) |
| | | | 40 | $134 \pm 2$ (5) | $320 \pm 22$ (5) | $37 \pm 3$ (5) |
| | | | 80 | $133 \pm 3$ (5) | $268 \pm 12$ (5) | $35 \pm 6$ (5) |
| SHR | lateral ventricle | saline | 5 μl | $139 \pm 7$ (6) | $277 \pm 12$ (6) | $40 \pm 4$ (6) |
| | | moxonidine | 20 | $134 \pm 9$ (5) | $288 \pm 13$ (5) | $45 \pm 4$ (5) |
| | | | 40 | $133 \pm 3$ (6) | $284 \pm 17$ (6) | $40 \pm 4$ (4) |
| | | | 80 | $138 \pm 4$ (7) | $297 \pm 17$ (7) | $35 \pm 3$ (6) |
| | | clonidine | 20 | $134 \pm 3$ (6) | $294 \pm 15$ (6) | $33 \pm 3$ (5) |
| | | | 40 | $135 \pm 8$ (6) | $295 \pm 11$ (6) | $34 \pm 3$ (6) |
| | | | 80 | $134 \pm 8$ (6) | $293 \pm 12$ (6) | $39 \pm 4$ (5) |
| SHR | intravenous | saline | 200 μl | $136 \pm 7$ (6) | $318 \pm 22$ (6) | $34 \pm 4$ (4) |
| | | moxonidine | 80 | $137 \pm 10$ (5) | $322 \pm 13$ (5) | $37 \pm 4$ (5) |
| WKY | fourth ventricle | saline | 5 μl | $88 \pm 1$[a] (6) | $317 \pm 12$ (6) | $33 \pm 3$ (6) |
| | | moxonidine | 80 | $93 \pm 3$[a] (6) | $304 \pm 18$ (6) | $30 \pm 4$ (4) |

Values are expressed as means ± S.E.M. from number of animals indicated in parentheses.
[a] $P < 0.05$ WKY vs. SHR, Kruskal–Wallis test.

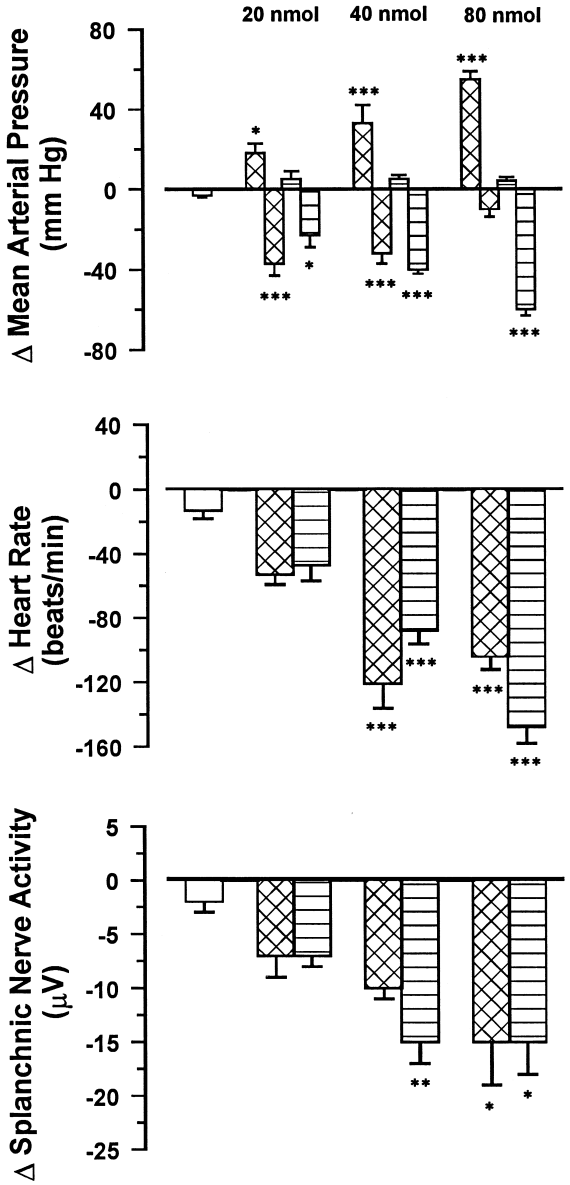


Fig. 1. Maximal effects of moxonidine and clonidine (40–80 nmol) administered into the fourth cerebral ventricle in mean arterial pressure, heart rate and splanchnic nerve activity in conscious SHR. The data is presented as mean ± S.E.M. Open bars represent saline injections, cross-hatched bars clonidine injections, and transversely hatched bars moxonidine injections. At the upper panel showing the results in mean arterial pressure, the bars above the zero line present the maximal initial pressor effect of clonidine and moxonidine, whereas the bars under the zero line represent the subsequent depressor effect of these drugs. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$ vs. saline (Tukey's test).

nerve activity in a similar manner as moxonidine when both substances were given into the fourth ventricle (Fig. 1).

After administration of clonidine into the lateral ventricle, a dose-dependent initial increase in mean arterial pressure without a subsequent hypotension was observed (Fig. 2). The duration of the pressor effect was less than 5 min after the two lower doses (20 and 40 nmol) and 20–25 min after the largest dose of clonidine (80 nmol). By this route of administration, all doses of clonidine reduced heart rate but did not significantly influence splanchnic nerve activity.

Fig. 3 shows the time-course of blood pressure, heart rate and splanchnic nerve activity responses after injection of an equipotent hypotensive dose of moxonidine and clonidine (40 nmol) into the fourth ventricle. The onset of

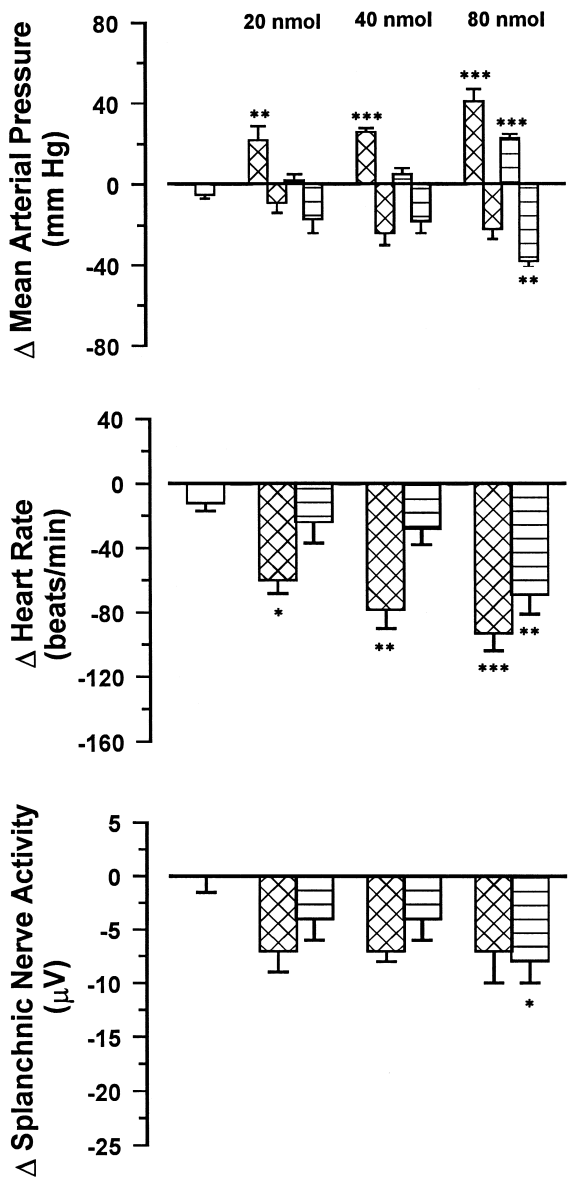


Fig. 2. Maximal effects of moxonidine and clonidine (40–80 nmol) administered into the lateral cerebral ventricle on mean arterial pressure, heart rate and splanchnic nerve activity in conscious SHR. The data is presented as mean ± S.E.M. Open bars represent saline injections, cross-hatched bars clonidine injections, and transversely hatched bars moxonidine injections. At the upper panel showing the results in mean arterial pressure, the bars above the zero line present the maximal initial pressor effect of clonidine and moxonidine, whereas the bars under the zero line represent the subsequent depressor effect of these drugs. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$ vs. saline (Tukey's test).

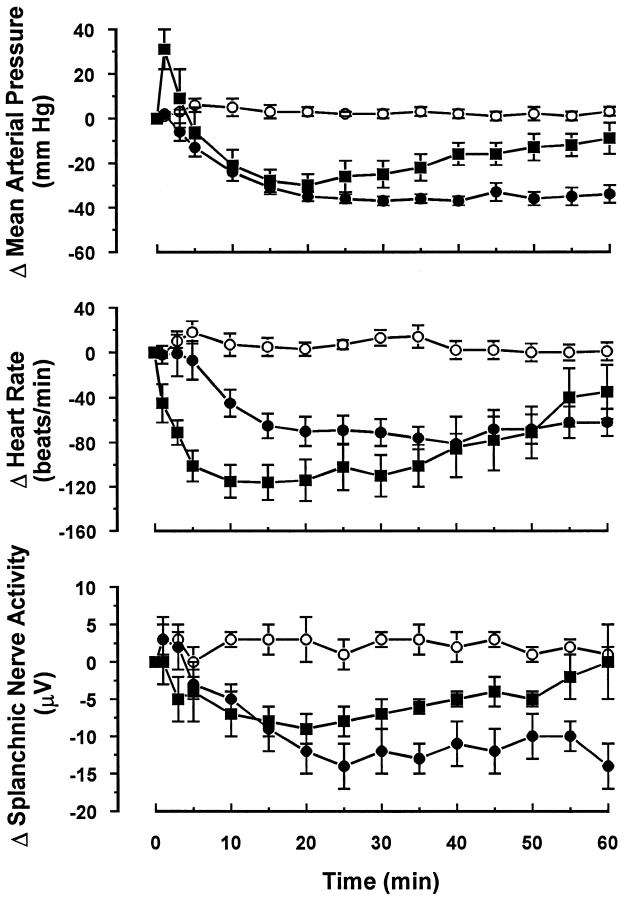


Fig. 3. Time-course in changes of mean arterial pressure, heart rate and splanchnic nerve activity after saline (5 μl; open circles), moxonidine (40 nmol; solid circles) and clonidine (40 nmol; solid squares) administered into the fourth cerebral ventricle at time point zero. The data is presented as mean ± S.E.M.

the hypotensive, bradycardic and sympathoinhibitory effects of moxonidine was within 5 min. The maximal reductions in mean arterial pressure, heart rate and splanchnic nerve activity appeared around 20 min, and the effects lasted more than 60 min. After clonidine, an increase in blood pressure was observed immediately after the injection and reached the maximum within 1 min. The subsequent hypotensive effect began 5–10 min after the injection of clonidine and was maximal between 15–20 min. The bradycardia after clonidine began within 1 min and was maximal around the 10th min. The onset of the decrease in splanchnic nerve activity was within 2–5 min and the maximal reduction was achieved within 15–20 min. The clonidine-induced reductions in mean arterial pressure, heart rate and splanchnic nerve activity diminished at the end of the 60 min observation period.

In WKY rats, the decreases in mean arterial pressure and heart rate after moxonidine (80 nmol) into the fourth ventricle were significantly smaller than those in SHR, the maximal reductions were from $93 \pm 3$ to $73 \pm 3$ mm Hg ($-20 \pm 3$ mm Hg, $P < 0.01$ vs. SHR) and from $304 \pm 18$ to $232 \pm 18$ beats min$^{-1}$ ($-73 \pm 10$ beats min$^{-1}$, $P < 0.01$ vs. SHR), respectively. The maximal decrease in splanchnic nerve activity was slightly but not significantly smaller in WKY than in SHR ($-8 \pm 2$ μV, $P = 0.08$ vs. SHR).

Intravenous moxonidine (80 nmol) caused an initial rise in blood pressure (from $137 \pm 10$ to $177 \pm 7$ mm Hg, $P < 0.01$ vs. saline i.v.) in SHR without any subsequent reduction in mean arterial pressure, heart rate or splanchnic nerve activity ($P > 0.05$). A significant reduction in blood pressure and heart rate after intravenous moxonidine was seen at a larger dose (400 nmol) (data not shown).

In control animals which received intracerebroventricular or intravenous injections of saline, mean arterial pressure, heart rate and splanchnic nerve activity did not change significantly during the experiments.

### *3.2. Effects of moxonidine and clonidine on plasma catecholamines*

Catecholamines in plasma were determined at various time points after the injection of equipotent antihypertensive doses of moxonidine and clonidine (40 nmol) into the fourth ventricle in conscious SHR. The maximal reduction in plasma catecholamine levels was achieved 30 min after moxonidine injection (noradrenaline: $0.51 \pm 0.10$ pmol ml$^{-1}$ vs. $1.16 \pm 0.12$ pmol ml$^{-1}$ (basal); $P < 0.05$; adrenaline: $0.22 \pm 0.08$ pmol ml$^{-1}$ vs. $1.47 \pm 0.31$ pmol ml$^{-1}$ (basal); $P < 0.05$). Adrenaline levels remained reduced up to 60 min after moxonidine injection ($0.21 \pm 0.13$ pmol ml$^{-1}$; $P < 0.05$ vs. basal), whereas noradrenaline concentration at this time point ($0.89 \pm 0.25$ pmol ml$^{-1}$) was not significantly different from the basal level. The maximal reduction in plasma noradrenaline levels was achieved 15 min after clonidine injection ($0.19 \pm 0.08$ pmol ml$^{-1}$ vs. $1.32 \pm 0.25$ pmol ml$^{-1}$ (basal); $P < 0.05$), whereas adrenaline levels in plasma were maximally reduced 30 min after clonidine ($0.14 \pm 0.06$ pmol ml$^{-1}$ vs. $1.63 \pm 0.14$ pmol ml$^{-1}$ (basal); $P < 0.05$). Significant reduction in plasma noradrenaline and adrenaline levels was already observed in the 5th min post clonidine injection ($0.32 \pm 0.05$ and $0.34 \pm 0.06$ pmol ml$^{-1}$, respectively). Plasma adrenaline remained decreased 60 min after clonidine ($0.50 \pm 0.14$ pmol ml$^{-1}$; $P < 0.05$ vs. basal), whereas plasma noradrenaline levels gradually increased, and did not significantly differ from the basal levels at this time point ($0.68 \pm 0.23$ pmol ml$^{-1}$). There were no significant differences between the maximal responses of plasma catecholamines to moxonidine and clonidine. Control injections of isotonic saline did not produce any significant changes of plasma catecholamines during the experiments.

## 4. Discussion

In conscious SHR, intracerebroventricularly administered moxonidine produced a dose-dependent decrease in

efferent sympathetic nervous activity as directly recorded from the splanchnic nerve. The sympathoinhibitory effect paralleled with decreases in blood pressure and heart rate. Centrally given moxonidine also reduced the concentrations of circulating catecholamines. Moxonidine has previously been shown to decrease the sympathetic nervous activity in anaesthetized cats (Ramage and Wilkinson, 1989) and in conscious rabbits (Urban et al., 1995a). The present study demonstrates for the first time the sympathoinhibitory effect of moxonidine in a hypertensive animal model.

The lack of sympathoinhibitory and hypotensive responses to peripherally given moxonidine at a dose that was fully active after intracerebroventricular administration confirms the view that moxonidine acts primarily within the brain. This finding is in contrast with some previous studies in rabbits suggesting that peripheral inhibition of transmitter release contributes to the overall decrease in sympathetic tone by moxonidine (Urban et al., 1995a,b). Higher forebrain structures which can be targeted when moxonidine is injected into the lateral cerebral ventricle do not seem to be the predominant site of the sympathoinhibitory and hypotensive action since the substance was less effective via this route than after its administration into the fourth ventricle. Our results are in line with studies suggesting that the rostral ventrolateral medulla is a principal site of the vasodepressor action of moxonidine (Ernsberger et al., 1993; Haxhiu et al., 1994).

The effects of moxonidine and clonidine on blood pressure were different. Clonidine induced a dose-related initial pressor response after both intracerebroventricular routes of administration, whereas moxonidine elicited a slight increase in blood pressure only when the largest dose was given into the lateral ventricle. Sympathetic stimulation as an initiating factor for the pressor response is unlikely, since no increase in the splanchnic sympathetic nerve activity was observed. No hypotension was observed when the largest dose of clonidine (80 nmol) was administered into the fourth ventricle, even though the same degree of inhibition of splanchnic nerve activity as with moxonidine was recorded. We assume that the hypotensive action of the largest dose of clonidine was counterbalanced by the strong initial pressor response. The pressor response was long-lasting and still present at the time points during which the most pronounced hypotensive effects were recorded when the lower doses of clonidine were given. The different blood pressure responses to moxonidine and clonidine could also result from the differences in their selectivity for imidazoline $I_1$ receptors and $\alpha_2$-adrenoceptors as it was demonstrated in radioligand binding studies. There is some evidence suggesting an involvement of central $\alpha_2$-adrenoceptors in the forebrain (e.g., in the hypothalamic paraventricular nucleus) in the pressor effect of centrally given clonidine (Kawasaki et al., 1992; Ebihara et al., 1993). Moxonidine has lower affinity for $\alpha_2$-adrenoceptors than clonidine (Ernsberger et al., 1993; Buccafusco et al., 1995), which may explain why moxonidine did not produce marked pressor effect after the central administration. In addition to the differences in the affinity of these two drugs for $\alpha_2$-adrenoceptors, clonidine is more lipophilic and penetrates more readily cell membranes than moxonidine (Armah et al., 1988). Thus, when the compounds are administered into the fourth ventricle, the forebrain structures mediating the pressor effect are more easily accessible to clonidine than to moxonidine, which may explain the lack of the response when moxonidine was administered via this route. Moxonidine is at least 40-fold more selective for imidazoline $I_1$ receptors than for $\alpha_2$-adrenoceptors, whereas clonidine shows nearly equal affinities for both types of receptors (Ernsberger et al., 1993; Buccafusco et al., 1995). Studies with imidazoline $I_1$- and $\alpha_2$-receptor antagonists have indicated a preferential involvement of imidazoline $I_1$ receptors in the hypotensive action of moxonidine (Haxhiu et al., 1994; Chan et al., 1996; Nurminen et al., 1996; Szabo and Urban, 1997). However, since the $I_1$ receptor antagonists currently available retain some activity at $\alpha_2$-adrenoceptors, the cardiovascular effects mediated by imidazoline $I_1$ receptors and $\alpha_2$-adrenoceptors cannot be clearly distinguished at present.

Moxonidine and clonidine injected into the fourth ventricle produced a dose-dependent decrease in heart rate, which could be due to reduction of sympathetic outflow to the heart. Clonidine caused a substantial bradycardia after the administration into the lateral cerebral ventricle, even though the splanchnic nerve activity was not significantly reduced. In addition to the inhibition of the sympathetic outflow, clonidine is known to stimulate the cardiac vagal activity by central mechanisms (Badoer et al., 1983), which may explain the occurrence of the bradycardia without a reduction in sympathetic tone.

The effective central dose of moxonidine in SHR had little effect on blood pressure or sympathetic nerve activity in normotensive WKY. More prominent hypotension induced by moxonidine in hypertensive animals may result from a higher initial blood pressure. In addition, previous studies have shown differences in the electrophysiological properties of central cardiovascular neurones in the rostral ventrolateral medulla between SHR and normotensive rats (Chan et al., 1991).

The sympathetic nervous system is implicated in the pathophysiology of essential hypertension and its sequelae (Julius and Weder, 1989; Ferrario and Averill, 1991). Substances that reduce sympathetic outflow would be expected to provide a significant degree of protection of the peripheral organs, particularly the heart, from the deleterious effects of chronically elevated sympathetic tone. Treatment with moxonidine has been shown to cause a regression of left ventricular hypertrophy in hypertensive animals and patients (Amann et al., 1992; Motz and Strauber, 1994). Therefore, moxonidine may offer a new rational approach to the treatment of hypertension.

In conclusion, our study imply that in conscious SHR moxonidine lowers blood pressure and heart rate by central sympathoinhibition. Furthermore, brainstem structures accessible to moxonidine injected into the fourth cerebral ventricle appear to be major sites of this action.

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