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Involvement of central α_1- and α_2-adrenoceptors on cardiovascular responses to moxonidine

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Abstract

In the present study we compared the effects produced by moxonidine (α_2-adrenoceptor/imidazoline agonist) injected into the 4th cerebral ventricle and into the lateral cerebral ventricle on mean arterial pressure, heart rate and on renal, mesenteric and hindquarter vascular resistances, as well as the possible action of moxonidine on central α_1- or α_2-adrenoceptors to produce cardiovascular responses. Male Holtzman rats (n=7–8) anesthetized with urethane (0.5 g/kg, intravenously — i.v.) and α-chloralose (60 mg/kg, i.v.) were used. Moxonidine (5, 10 and 20 nmol) injected into the 4th ventricle reduced arterial pressure (−19±5, −30±7 and −43±8 mmHg vs. vehicle: 2±4 mmHg), heart rate (−10±6, −16±7 and −27±9 beats per minute — bpm, vs. vehicle: 4±5 bpm), and renal, mesenteric and hindquarter vascular resistances. Moxonidine (5, 10 and 20 nmol) into the lateral ventricle only reduced renal vascular resistance (−77±17%, −85±13%, −89±10% vs. vehicle: 3±4%), without changes on arterial pressure, heart rate and mesenteric and hindquarter vascular resistances. Pre-treatment with the selective α_2-adrenoceptor antagonist yohimbine (80, 160 and 320 nmol) injected into the 4th ventricle attenuated the hypotension (−32±5, −25±4 and −12±6 mmHg), bradycardia (−26±11, −23±5 and −11±6 bpm) and the reduction in renal, mesenteric and hindquarter vascular resistances produced by moxonidine (20 nmol) into the 4th ventricle. Pre-treatment with yohimbine (320 nmol) into the lateral ventricle did not change the renal vasodilation produced by moxonidine (20 nmol) into the lateral ventricle. The α_1-adrenoceptor antagonist prazosin (320 nmol) injected into the 4th ventricle did not affect the cardiovascular effects of moxonidine. However, prazosin (80, 160 and 320 nmol) into the lateral ventricle abolished the renal vasodilation (−17±4, −6±9 and 2±11%) produced by moxonidine. The results indicate that the decrease in renal vascular resistance due to moxonidine action in the forebrain is mediated by α_1-adrenoceptors, while the cardiovascular effects produced by moxonidine acting in the brainstem depend at least partially on the activation of α_2-adrenoceptors.

Keywords: Arterial pressure; Vascular resistance; α_1- and α_2-adrenoceptors; Hypotension; Anti-hypertensive; Sympathetic activity

1. Introduction

Moxonidine, an α_2-adrenoceptor and imidazoline receptor agonist, is a centrally acting anti-hypertensive drug that reduces arterial pressure by inhibiting sympathetic activity (Ernsberger et al., 1993, 1994, 1997). The rostral ventrolateral medulla (RVLM) that contains the sympathetic pre-motor neurons involved in cardiovascular regulation (Barman and Gebber, 1989; Guyenet et al., 1989; Guyenet, 2006) has been implicated as one of the most important central sites for the anti-hypertensive action of moxonidine. The α_2-adrenoceptors and imidazoline receptors have been shown to exist in the RVLM (Feldman et al., 1998) and microinjections of α_2-adrenoceptor/imidazoline agonists into the RVLM produce hypotension and bradycardia (Gomez et al., 1991; Haxhiu et al., 1994; Ernsberger and Haxhiu, 1997; Tolentino-Silva et al., 2000). Although α_2-adrenoceptors have been shown to be involved in the hypotension produced by clonidine (Guyenet, 1997), the anti-hypertensive responses induced by moxonidine have been suggested to depend on the activation of imidazoline receptors located in the RVLM (Gomez et al., 1991; Haxhiu et al., 1994; Ernsberger et al., 1997; Tolentino-Silva et al. 2000). The importance of the brainstem mechanisms for the hypotensive responses to moxonidine is also suggested by the reductions in splanchnic sympathetic nerve activity induced by moxonidine

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injected into the 4th cerebral ventricle in spontaneously hypertensive rats (SHR) (Nurminen et al., 1998).

Moxonidine injected into the 4th ventricle reduces mean arterial pressure, heart rate and mesenteric, hindquarter and renal vascular resistances (Moreira et al., 2004, 2006), while injected into the lateral cerebral ventricle moxonidine produces no effect on arterial pressure and heart rate (Nurminen et al., 1998; Moreira et al., 2003). However, injection of moxonidine into the lateral ventricle increases salivary gland vascular resistance and renal sodium and water excretion and inhibits water and sodium intake (Moreira et al., 2003; Penner and Smyth, 1994; Menani et al., 1999, 2006).

Reduction in renal sympathetic nerve activity is the mechanism proposed for the increase in renal sodium and water excretion by moxonidine injected into the lateral ventricle. However, no study has investigated possible changes on renal vascular resistance produced by moxonidine injected into the lateral ventricle. Although the involvement of α_2-adrenoceptors and/or imidazoline receptors on cardiovascular responses to moxonidine acting in the brainstem is still controversial, the inhibition of water and sodium intake by moxonidine in the forebrain depends on α_2-adrenoceptor activation (de Oliveira et al., 2003). Furthermore, renal responses to moxonidine in the forebrain are suggested to depend on imidazoline receptors (Smyth and Penner, 1999).

Besides the action on α_2-adrenoceptors and imidazoline receptors (Gomez et al., 1991; Haxhiu et al., 1994; Guyenet, 1997; Ernsberger and Haxhiu, 1997; Tolentino-Silva et al., 2000; de Oliveira et al., 2003; Menani et al., 1999, 2006), few studies have also reported effects of moxonidine on α_1-adrenoceptors (Raasch et al., 2000; George et al., 2004; Kennedy et al., 2006). Therefore, in the present study we investigated the effects produced by moxonidine injected into the 4th ventricle or into the lateral ventricle alone or combined with α_1- or α_2-adrenoceptor antagonists (prazosin and yohimbine, respectively) on mean arterial pressure, heart rate and mesenteric, hindquarter and renal vascular resistances.

2. Materials and methods

2.1. Animals

All experiments were performed in accordance with the Brazilian National Health and Medical Research Council code of practice for the care and use of animals for scientific purposes and were approved by the Animal Experimentation Ethics Committee of the Federal University of São Paulo, School of Medicine. Experiments were performed on adult male Holtzman rats weighing 300 to 350 g.

2.2. Surgical procedure

General anesthesia was induced with 5% halothane in 100% oxygen. The rats received a tracheostomy and artificial ventilation with 2% halothane in 100% oxygen was maintained throughout surgery. A catheter (PE-10 connected to PE-50) was inserted into the femoral artery for the measurement of pulsatile arterial pressure, mean arterial pressure and heart rate. A femoral vein catheter was used for the administration of drugs. To record pulsatile arterial pressure, mean arterial pressure and heart rate, the arterial catheter was connected to a P23 Db pressure transducer (Statham Gould) coupled to a pre-amplifier (model ETH-200 Bridge Bio Amplifier, CB Sciences) connected to a Powerlab computer recording system (Powerlab 16SP, ADInstruments). Upon completion of surgical procedures, halothane was replaced by a mixture of urethane (0.5 g/kg) and α-chloralose (60 mg/kg) slowly administered intravenously (i.v.) All rats were ventilated with 100% oxygen throughout the experiments. Rectal temperature (maintained at 37 °C) was also monitored throughout the experiments with a thermostatically controlled heating pad. After injection of the intravenous anesthetic mixture, the adequacy of anesthesia was monitored during a 20 min stabilization period by testing for the absence of withdrawal response and lack of arterial pressure change to firm toe pinch. After these criteria were satisfied, the muscle relaxant pancuronium was administered at the initial dose of 1 mg/kg i.v. and the adequacy of anesthesia was thereafter gauged solely by the lack of increase in arterial pressure to firm toe pinch. Approximately hourly supplements of one-third of the initial dose of chloralose–urethane were needed to satisfy these criteria during the course of the recording period.

Immediately after vein and artery catheterization, a midline laparotomy was performed and miniature pulsed Doppler flow probes were placed around the renal artery, superior mesenteric artery and low abdominal aorta for measurement of renal, mesenteric and hindquarter blood flows, respectively. The probes were fixed to the surrounding tissues with suture thread. Data from animals in which the probes moved during the experiment were not considered for analysis.

The flow probes were connected to a Doppler flowmeter (Department of Bioengineering, University of Iowa, Iowa City, IA, USA) coupled to a Powerlab computer recording system (model Powerlab 16SP, ADInstruments) for blood flow recording. Details of the Doppler flow recording technique, including the reliability of the method for estimation of flow velocity, have been described previously by Haywood et al. (1981). Relative renal, mesenteric and hindquarter vascular resistance changes were calculated as the ratio of mean arterial pressure and Doppler shifts.

After the fixation of the flow probes, animals were placed in a stereotaxic apparatus in prone position. Injections into the 4th ventricle and lateral ventricle were made using a 10 μl Hamilton syringe connected by a polyethylene tubing (PE-10) to an injection cannula (0.3 mm o.d.). For injections into the 4th ventricle the injection cannula was positioned 12.7 mm caudal to bregma, 0.0 mm lateral to midline and 7.0 mm below the dura mater. For injections into the lateral ventricle the injection cannula was positioned 0.3 mm caudal to bregma, 1.5 mm lateral to midline and 3.6 mm below the dura mater. The volume of injections into the 4th ventricle and lateral ventricle was 1 to 3 μl.

2.3. Drugs

Moxonidine hydrochloride (5, 10 and 20 nmol/μl), a gift from Solvay Pharma (Germany), was injected into the 4th

ventricle and lateral ventricle. Yohimbine hydrochloride (80 nmol in 2 μl, 160 and 320 nmol in 3 μl) or prazosin hydrochloride (80, 160 and 320 nmol in 2 μl) was injected into the 4th ventricle and lateral ventricle. Yohimbine and prazosin were purchased from Sigma Chemical Co., USA. Moxonidine, yohimbine and prazosin were dissolved in a mix of propylene glycol/water 2:1. The mix of propylene glycol/water 2:1 was used as vehicle for moxonidine, yohimbine and prazosin.

2.4. Histology

At the end of the experiment, a 2% solution of Evans blue was microinjected into the 4th ventricle or lateral ventricle (1 μl). The animals were killed by an overdose of urethane (1.8 g/kg of body weight i.v.). Saline followed by 10% buffered formalin was perfused through the heart. The brains were frozen, cut coronally into 50 μm sections and stained with Neutral red. Only animals with injections into the 4th ventricle or lateral ventricle were considered for statistical analysis.

2.5. Statistical analysis

Statistical analysis was done with Sigma Stat version 3.0 (Jandel Corporation, Point Richmond, CA). Data are reported as means ± standard error of the mean. One-way parametric ANOVA followed by the Newman–Keuls multiple comparisons test was used as appropriate. Significance was set at $P < 0.05$.

2.6. Experimental protocols

All studies were performed in rats anesthetized with urethane and α-chloralose. Blood flows, mean arterial pressure and heart rate were continuously recorded during 80 min, starting 20 min after the connection of the arterial line to the pressure transducer. Control (baseline) values were recorded for 10 min and were analyzed immediately before the first treatment (first central vehicle or drug injection). These values were used as reference to calculate the changes produced by the treatments.

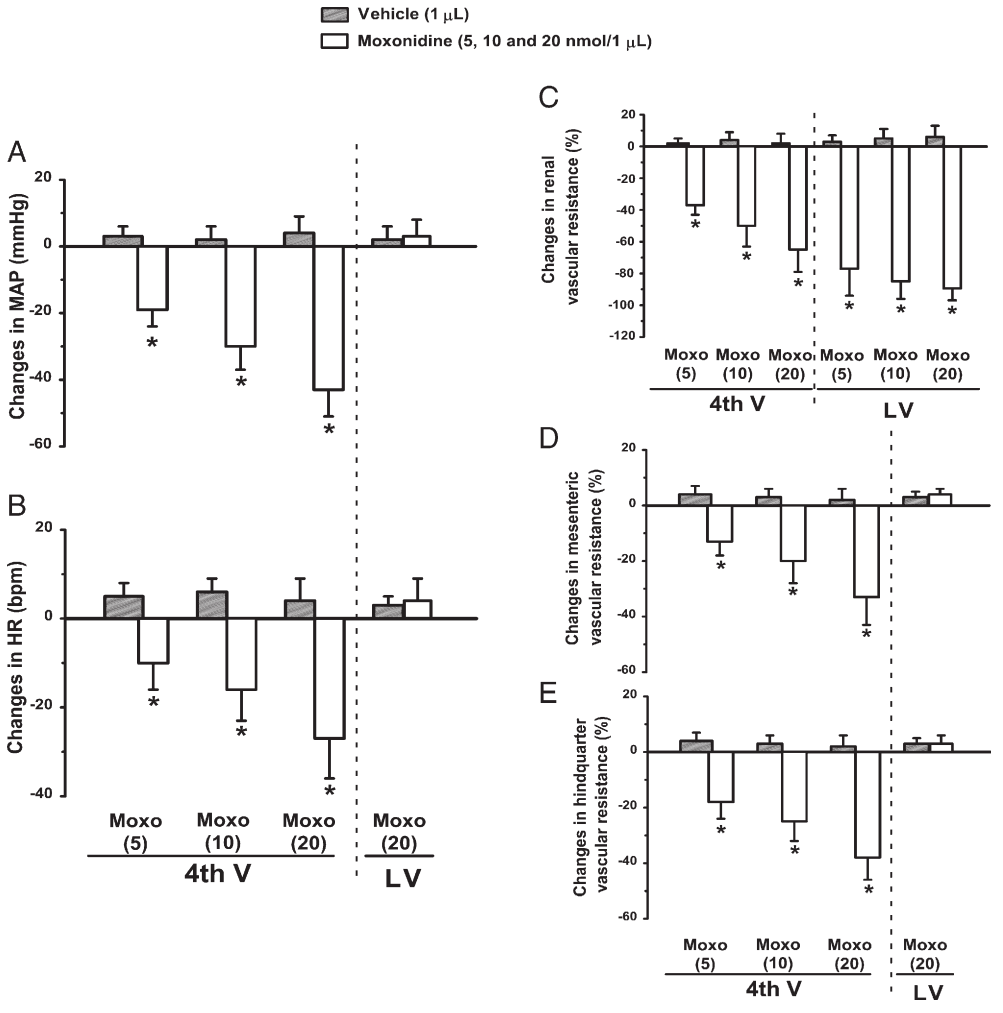

Fig. 1. Cardiovascular effects produced by central injections of moxonidine. Changes in (A) mean arterial pressure (MAP), (B) heart rate (HR), (C) renal, (D) mesenteric and (E) hindquarter vascular resistances produced by moxonidine (5, 10 and 20 nmol/μl) or vehicle injected into the 4th ventricle or lateral ventricle. The results are represented as means ± SEM. $n = 8$/group of rats. *Different from vehicle (Student–Newman–Keuls test, $P < 0.01$).

2.6.1. Effects of moxonidine injected into the 4th ventricle or lateral ventricle on mean arterial pressure, heart rate and regional vascular resistances

Two groups of animals were used in order to investigate the cardiovascular effects of central injection of moxonidine:

1) Vehicle into the 4th ventricle or lateral ventricle (control);
2) Moxonidine into the 4th ventricle or lateral ventricle.

The three doses of moxonidine (5, 10 and 20 nmol/μl) or vehicle were injected into the 4th ventricle or lateral ventricle in a random sequence at 30 min intervals.

2.6.2. Effects of the combination of yohimbine and moxonidine injected into the 4th ventricle or lateral ventricle on mean arterial pressure, heart rate and regional vascular resistances

Moxonidine (20 nmol/μl) or vehicle was injected into the 4th ventricle or lateral ventricle 15 min after the injection of yohimbine or vehicle in the same place. Four groups of animals for each area (4th ventricle or lateral ventricle) were used in order to investigate the cardiovascular effects produced by the combination of central injections of yohimbine and moxonidine:

1) Vehicle into the 4th ventricle (or lateral ventricle) followed by vehicle into the 4th ventricle (or lateral ventricle) (control group);
2) Vehicle into the 4th ventricle (or lateral ventricle) followed by moxonidine into the 4th ventricle (or lateral ventricle);
3) Yohimbine into the 4th ventricle (or lateral ventricle) followed by vehicle into the 4th ventricle (or lateral ventricle);
4) Yohimbine into the 4th ventricle (or lateral ventricle) followed by moxonidine into the 4th ventricle (or lateral ventricle).

2.6.3. Effects of the combination of prazosin and moxonidine injected into the 4th ventricle or lateral ventricle on mean arterial pressure, heart rate and regional vascular resistances

Moxonidine (20 nmol/μl) or vehicle was injected into the 4th ventricle or lateral ventricle 15 min after the central

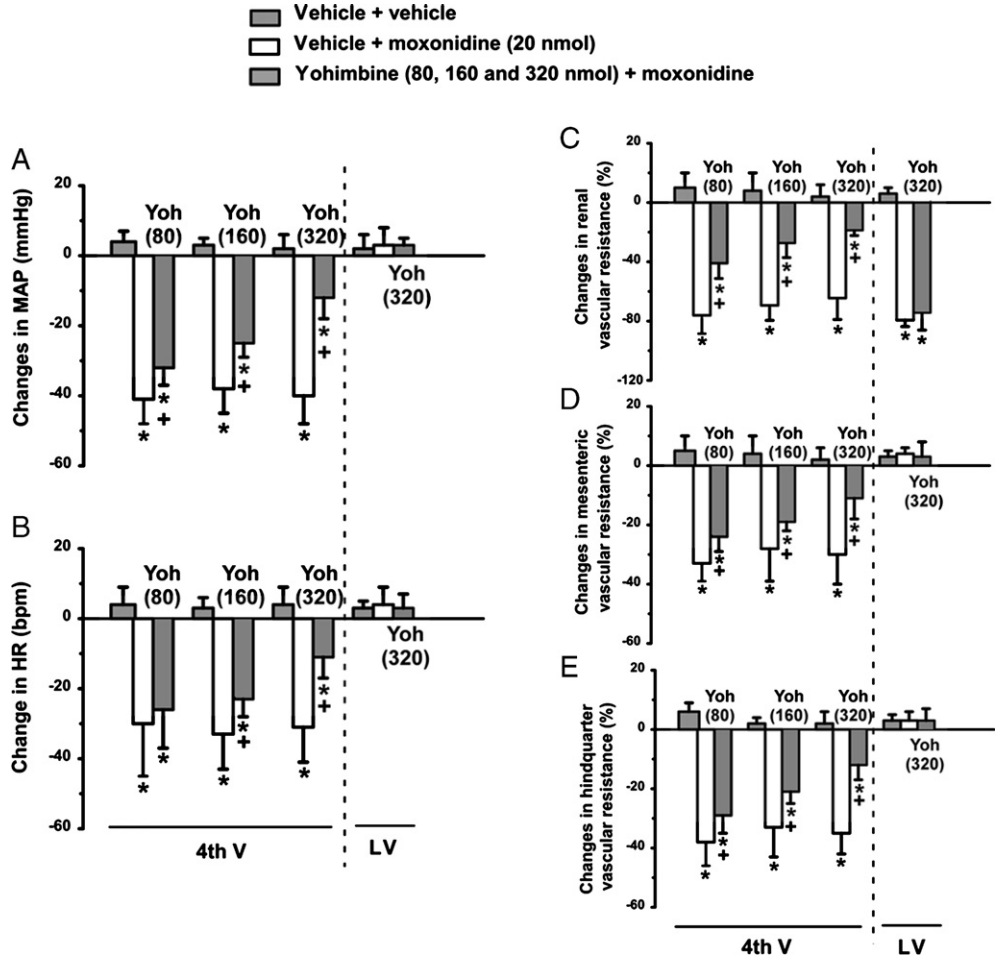

Fig. 2. Effects of the combination of central injection of yohimbine and moxonidine on mean arterial pressure, heart rate and regional vascular resistance. Changes in (A) mean arterial pressure (MAP), (B) heart rate (HR), (C) renal, (D) mesenteric and (E) hindquarter vascular resistance produced by yohimbine (80 nmol/2 μl, 160 and 320 nmol/3 μl) or vehicle followed by moxonidine (20 nmol/μl) or vehicle injected into the 4th ventricle or lateral ventricle. The results are represented as means ± SEM. $n = 8$/group of rats. *Different from vehicle + vehicle; $^{+}$different from vehicle + moxonidine (Student–Newman–Keuls test, $P < 0.01$).

injection of prazosin or vehicle. Four groups of animals for each area 4th ventricle or lateral ventricle were used in order to investigate the cardiovascular effects of the combination of central injections of prazosin and moxonidine:

1) Vehicle into the 4th ventricle (or lateral ventricle) followed by vehicle into the 4th ventricle (or lateral ventricle) (control group);
2) Vehicle into the 4th ventricle (or lateral ventricle) followed by moxonidine 4th ventricle (or lateral ventricle);
3) Prazosin into the 4th ventricle (or lateral ventricle) followed by vehicle into the 4th ventricle (or lateral ventricle);
4) Prazosin into the 4th ventricle (or lateral ventricle) followed by moxonidine into the 4th ventricle (or lateral ventricle).

3. Results

3.1. Changes in arterial pressure, heart rate and regional vascular resistances produced by moxonidine injected into the 4th ventricle or lateral ventricle

Moxonidine (5, 10 and 20 nmol/μl) injected into the 4th ventricle reduced arterial pressure (−19±5, −30±7 and −43±8 mmHg vs. vehicle: 2±4 mmHg) [$F(7, 49)=150.03$, $P<0.01$] and heart rate (−10±6, −16±7 and −27±9 beats per minute — bpm vs. vehicle: 4±5 bpm), [$F(7, 49)=267.32$, $P<0.01$] (Fig. 1A and B). Moxonidine into the 4th ventricle also reduced renal (−37±6, −50±13 and −65±14% vs. vehicle: 2±6%), [$F(11, 84)=99.216$, $P<0.01$] (Fig. 1C), mesenteric (−13±5, −20±8 and −33±10% vs. vehicle: 2±4%), [$F(7, 49)=435.26$, $P<0.01$] (Fig. 1D) and hindquarter

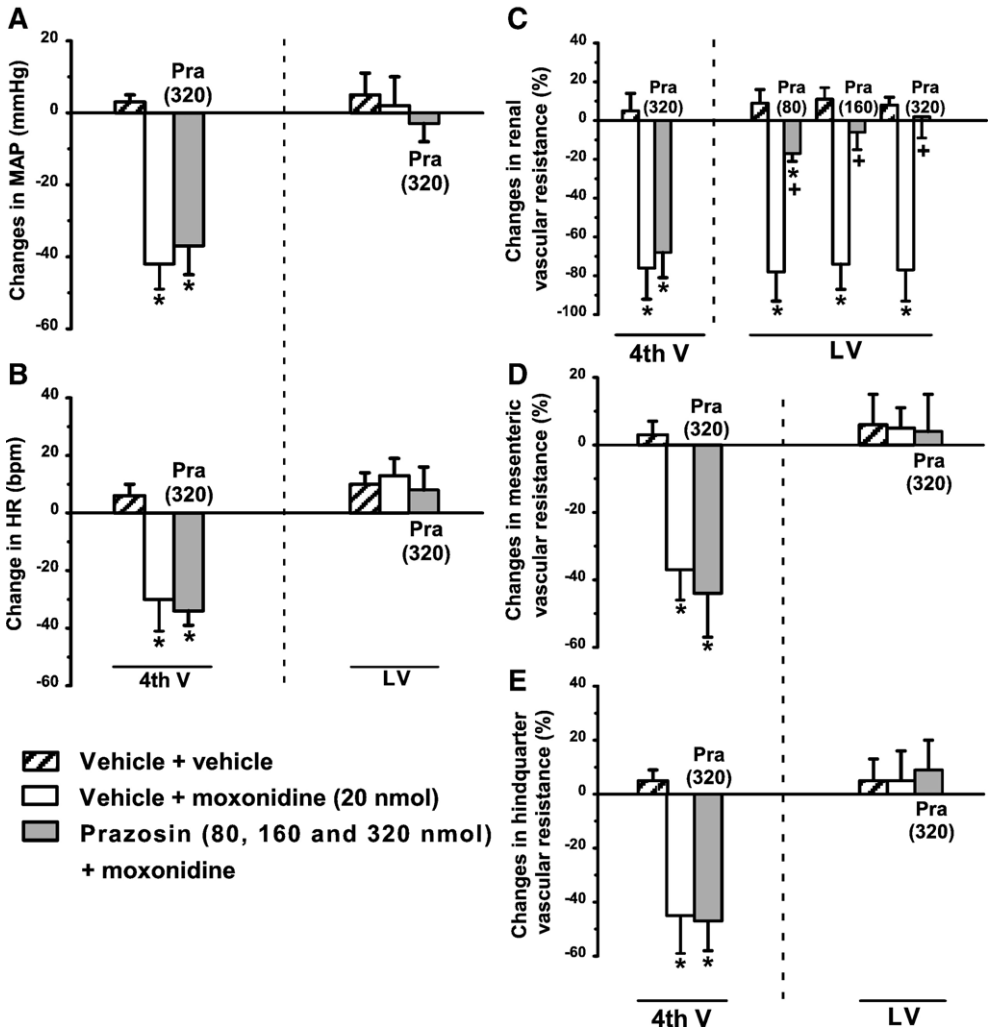

Fig. 3. Effects of the combination of central injection of prazosin and moxonidine on mean arterial pressure, heart rate and regional vascular resistance. Changes in (A) mean arterial pressure (MAP), (B) heart rate (HR), (C) renal, (D) mesenteric and (E) hindquarter vascular resistance produced by prazosin (80, 160 and 320 nmol/2 μl) or vehicle followed by moxonidine (20 nmol/μl) or vehicle injected into the 4th ventricle or lateral ventricle. The results are represented as means±SEM. $n=7$/group of rats. *Different from vehicle+vehicle; $^{+}$different from vehicle+moxonidine (Student–Newman–Keuls test, $P<0.01$).

vascular resistance (−18±6, −25±7 and −38±8% vs. vehicle: 4±3%), [$F(7, 49)=387.54$, $P<0.01$] (Fig. 1E).

Differently from 4th ventricle injections, moxonidine (20 nmol/μl) injected into the lateral ventricle produced no change on arterial pressure (2±4 mmHg vs. vehicle: 3±5 mmHg) and heart rate (3±2 bpm vs. vehicle: 4±5 bpm), (Fig. 1A and B), as well in mesenteric (3±2% vs. vehicle: 4±2) (Fig. 1D) and hindquarter vascular resistances (3±2% vs. vehicle: 3±3%) (Fig. 1E). However, moxonidine (5, 10 and 20 nmol/μl) into the lateral ventricle reduced renal vascular resistance (−77±17%, −85±13%, −89±10% vs. saline: 3±4%) (Fig. 1C).

3.2. Effects of the combination of yohimbine and moxonidine injected into the 4th V or LV on MAP, HR and regional vascular resistances

Yohimbine (80 nmol/2 μl, 160 and 320 nmol/3 μl) injected into the 4th ventricle produced no change in baseline arterial pressure (106±5, 110±5 and 104±8 mmHg, vs. vehicle: 109±5 mmHg), heart rate (321±14, 329±9 and 322±16 bpm, vs. vehicle: 326±11 bpm) and renal, mesenteric and hindquarter vascular resistance. The pre-treatment with yohimbine (80 nmol/2 μl, 160 and 320 nmol/3 μl) into the 4th ventricle reduced moxonidine-induced hypotension (−32±5, −25±4 and −12±6 mmHg), [$F(11, 77)=98.69$, $P<0.01$] and bradycardia (−26±11, −23±5 and −11±6 bpm), [$F(11, 77)=103.18$, $P<0.01$] (Fig. 2A and B), as well the reduction in renal (−40±8, −27±9 and −19±4%), [$F(11, 77)=232.21$, $P<0.01$] (Fig. 2C), mesenteric (−24±5, −19±3 and −11±7%), [$F(11, 77)=254.65$, $P<0.0.1$] (Fig. 2D) and hindquarter vascular resistance (−29±6, −21±4 and −12±5%), [$F(11, 77)=187.12$, $P<0.01$] (Fig. 2E).

Yohimbine (320 nmol/3 μl) injected into the lateral ventricle also produced no change in baseline arterial pressure (103±2 mmHg vs. vehicle: 101±6 mmHg), heart rate (319±11 bpm, vs. vehicle: 324±8 bpm) and renal, mesenteric and hindquarter vascular resistance. The pre-treatment with yohimbine (320 nmol/3 μl) into the lateral ventricle did not affect the renal vasodilation (−75±12%, $P>0.05$) produced by moxonidine into the lateral ventricle (Fig. 2C).

3.3. Effects of the combination of prazosin and moxonidine injected into the 4th lateral ventricle or lateral ventricle on arterial pressure, heart rate and regional vascular resistances

Prazosin (320 nmol/2 μl) injected into the 4th ventricle produced no change on baseline arterial pressure (106±3 mmHg, vs. vehicle 107±5 mmHg), heart rate (323±13 bpm, vs. vehicle 329±9 bpm) and renal, mesenteric and hindquarter vascular resistance. The pre-treatment with prazosin into the 4th ventricle did not affect the hypotension (−37±8 mmHg, $P>0.05$), bradycardia (−34±5 bpm, $P>0.05$) and the reduction in renal (−68±13%, $P>0.05$), mesenteric (−44±13%, $P>0.05$) and hindquarter (−47±11%, $P>0.05$) vascular resistance produced by moxonidine into the 4th ventricle (Fig. 3A–E).

Injection of prazosin (80, 160 and 320 nmol/2 μl) into the lateral ventricle also produced no change in baseline arterial pressure (104±3 mmHg vs. vehicle: 103±2 mmHg), heart rate (321±7 bpm, vs. vehicle: 318±12 bpm) and renal, mesenteric and hindquarter vascular resistance. Prazosin into the lateral ventricle abolished the decrease in renal vascular resistance (−17±4, −6±9 and 2±11%), [$F(11, 77)=259.37$, $P<0.01$] produced by moxonidine into the lateral ventricle (Fig. 3C).

4. Discussion

Previous studies have already shown that moxonidine injected into the 4th ventricle reduces arterial pressure, heart rate and regional vascular resistances, while injections of moxonidine into the lateral ventricle produce no change in arterial pressure and heart rate (Moreira et al., 2003, 2004). The present results show that the pre-treatment with yohimbine into the 4th ventricle reduced the hypotension, bradycardia and vasodilation induced by moxonidine, while prior injection of prazosin into the 4th ventricle had no effect on these responses, which suggests that the cardiovascular effects of moxonidine acting in the brainstem are at least partially mediated by the activation of α_2-adrenergic receptors. Although moxonidine injected into the lateral ventricle (at the same doses used in the 4th ventricle) produces no change on arterial pressure and heart rate and mesenteric and hindquarter vascular resistances, it reduces renal vascular resistance, a response blocked by the pre-treatment with the α_1-adrenoceptor antagonist prazosin, but not by yohimbine. Therefore, moxonidine can induce renal vasodilation acting in different central areas and activating different adrenergic receptors, i.e. renal vasodilation results from the activation of α_1-adrenoceptors in the forebrain, while in the hindbrain it is produced by the activation of α_2-adrenoceptors.

The involvement of α_2-adrenoceptors and/or imidazoline receptors in the anti-hypertensive effects of drugs like clonidine and moxonidine is still controversial. Some studies have suggested that moxonidine reduces sympathetic activity and arterial pressure acting on central imidazoline receptors (Bousquet et al., 1984; Ernsberger et al., 1993, 1994, 1997), while others have suggested the action of moxonidine on central α_2-adrenoceptors (Armah et al., 1988; Schlicker et al., 1990; Allen and Guyenet, 1993; Urban et al. 1995; Guyenet, 1997; Hayar and Guyenet, 2000). Yohimbine intracerebroventricularly (i.c.v.) attenuated the hypotension produced by clonidine i.c.v. in spontaneously hypertensive rats (SHR), but not in normotensive Wistar–Kyoto rats (Tibirica et al., 1988). The action of moxonidine on central α_2-adrenoceptors has also been suggested for the control of sodium and water intake (de Oliveira et al., 2003; Andrade et al., 2004, 2006). The present results show that pre-treatment with yohimbine, a specific α_2-adrenoceptor antagonist that does not bind to imidazoline receptors, injected into the 4th ventricle reduces the hypotension, bradycardia and vasodilation to moxonidine injected into the same place, which suggests the involvement of central α_2-adrenoceptors on these responses. However, renal vasodilation produced by moxonidine injected into the lateral ventricle depends on the activation of central α_1-adrenoceptors. Similar to

the present results suggesting activation of α_1-adrenoceptors by moxonidine centrally, previous studies have already suggested that the contractile response of rat-tail artery or the increase in myocardial contractility by moxonidine depends on the activation of α_1-adrenoceptors (Raasch et al., 2000; George et al., 2004; Kennedy et al., 2006).

The reduction of sympathetic activity, vasodilation, hypotension and bradycardia produced by moxonidine and other α_2-adrenoceptor/imidazoline agonists is suggested to depend on the action of these drugs in the rostral ventrolateral medulla and/or nucleus of the solitary tract (Barman and Gebber, 1989; Guyenet et al., 1989; Gomez et al., 1991; Mayorov et al., 1993; Ernsberger et al., 1993, 1994, 1997; Haxhiu et al., 1994; Ernsberger and Haxhiu 1997; Nurminen et al., 1998; Head and Burke, 1998; Tolentino-Silva et al., 2000; Sy et al., 2002). Although reduction in cardiac sympathetic activity by moxonidine acting in the rostral ventrolateral medulla may account for the bradycardia it seems that reduction of heart rate depends more on complex mechanisms involving also vagal facilitation (Badoer et al., 1983). Therefore, besides the rostral ventrolateral medulla, hindbrain sites like the nucleus of the solitary tract, nucleus ambiguus and the dorsal motor nucleus of the vagus may be involved in cardiovascular responses to moxonidine into the 4th ventricle and specially in the bradycardia.

Acting in the forebrain moxonidine strongly inhibits water and sodium intake, increases urinary volume, sodium excretion and salivary gland vascular resistance (Moreira et al., 2003; de Oliveira et al., 2003; Menani et al., 2006) and reduces renal vascular resistance (present results). However, moxonidine in the forebrain produces no effect on arterial pressure, probably as a consequence of the opposite changes in vascular resistance in different vascular beds, like salivary gland and renal vascular resistances or even in other vascular beds not yet tested (Nurminen et al., 1998; Moreira et al., 2003). Although previous studies using sympathetic blockers or renal denervation have suggested that natriuresis and diuresis to central moxonidine depend on change in sympathetic activity, no study has previously shown any renal hemodynamic effect produced by moxonidine acting in the forebrain. The present study is the first to show that moxonidine acting on α_1-adrenoceptors in the forebrain strongly reduces renal vascular resistance. It was already shown that increases of urine and sodium excretion produced by moxonidine into the lateral ventricle were totally blocked by intravenous prazosin, suggesting that changes in peripheral sympathetic and in α_1-adrenoceptor activation are important for the renal responses to moxonidine into the lateral ventricle (Smyth and Penner, 1998). Although it is not possible to exclude the involvement of other mechanisms like atrial natriuretic peptide release (El-Ayoubi et al., 2005), reduction of renal sympathetic activity by moxonidine acting on forebrain α_1-adrenoceptors is probably the main mechanism activated to reduce renal vascular resistance.

The increase in renal blood flow (72 ± 14%) that results from the renal vasodilation produced by moxonidine injected into the lateral ventricle is probably important for the natriuresis and diuresis to moxonidine into the lateral ventricle. Although moxonidine injected into the lateral ventricle and into the 4th ventricle produces similar reduction in renal vascular resistance, the changes in renal blood flow are completely the opposite, i.e., moxonidine into the lateral ventricle increases renal blood flow, while injected into the 4th ventricle moxonidine reduces renal blood flow (−59 ± 9%). Moxonidine injected into the lateral ventricle induces diuresis and natriuresis, while moxonidine into the 4th ventricle produces no effect on urinary excretion (Menani et al., 2006). Therefore, the opposite changes in renal blood flow correlate very well with the different effects of moxonidine on urinary excretion and support the suggestion that the increase in renal blood flow is important for the diuresis and natriuresis produced by moxonidine injected into the lateral ventricle.

In conclusion, the results suggest that the effects of moxonidine acting in the forebrain (renal vasodilation) depend on α_1-adrenoceptor activation, while the cardiovascular effects, including renal vasodilation, produced by moxonidine acting in the brainstem depend at least partially on the activation of α_2-adrenoceptors.

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