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Angiotensin AT_2 receptors mediate vasodepressor response to footshock in rats
Role of kinins, nitric oxide and prostaglandins

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Abstract

Footshocks increased mean arterial pressure and heart rate. Systemic administration of losartan, a specific angiotensin AT_1 receptor antagonist, not only inhibited the pressor response to footshocks, but also resulted in vasodepression. Administration of 1-[[4-(dimethylamino)3-methylphenyl]methyl]-5 (diphenylacetyl)-4,5,6,7-tetrahydro-1*H* imidazol (4,5-*c*] pyridine-6-carboxilic acid, ditrifluoro acetate-monohydrate (PD 123319), a specific angiotensin AT_2 receptor antagonist, did not alter the hemodynamic response to footshocks. Simultaneous blockade of angiotensin AT_1 and AT_2 receptors by combined administration of losartan and PD 123319, eliminated the vasodepressor response to footshocks unmasked in losartan-pretreated rats. Saralasin, a non-specific angiotensin receptor antagonist, abolished the cardiovascular response to footshocks similarly like the losartan + PD 123319 treatment. Our data suggest that the vasodepressor response to footshocks in the presence of an angiotensin AT_1 receptor antagonist is triggered by activation of angiotensin AT_2 receptors. We studied the role of kinins, nitric oxide and prostaglandins in the vasodepressor response observed after footshocks. The decrease in mean arterial pressure observed after footshocks in losartan-treated rats was blunted by icatibant (HOE 140), N^G-nitro-L-arginine-methyl ester (L-NAME) or indomethacin, indicating that kinins, nitric oxide and prostaglandins appear to be involved in the pressure response to footshocks during angiotensin AT_1 receptor blockade.

Keywords: Angiotensin AT_2 receptor; Losartan; PD 123319; Kinin; Nitric oxide (NO) synthase; Cyclo-oxygenase; Footshock

1. Introduction

Angiotensin II, the primary effector hormone of the renin–angiotensin system, has a wide range of physiological actions directed at target organs in the cardiovascular system. These actions include vasoconstriction of peripheral blood vessels through activation of smooth muscle cell angiotensin AT_1 receptors. In addition to the direct vasoconstrictor action on vascular smooth muscle, angiotensin II influences vascular tone due to its ability to enhance noradrenergic neuroeffector transmission. Findings from several studies indicate that angiotensin AT_1 receptors are involved in the enhancement of sympathetic transmission by angiotensin II (Reit 1972; Wong et al., 1990). The angiotensin AT_1 receptor antagonist, losartan, but not the angiotensin AT_2 receptor antagonist, PD 123177, blocks the enhancement of vasoconstriction responses to renal sympathetic stimulation produced by angiotensin II in the dog (Wong et al., 1991) and in the pithed rat vasculature (Wong et al., 1992), suggesting an action through stimulation of prejunctional angiotensin AT_1 receptors. The concept of a functional role of the angiotensin AT_1 receptor in the regulation of sympathetic activity is supported by our previous findings that central or peripheral administration of losartan causes inhibition of the vasopressor response elicited by footshocks (Cierco and Israel, 1994). The fact that the pressor response to administration of exogenous norepinephrine is not inhibited by losartan indicates that the facilitatory action of endogenous angiotensin II on sympathetic activity resides at the prejunctional angiotensin AT_1 receptors located at

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the sympathetic nerve terminals, where the facilitatory input of endogenous angiotensin II would be blunted by blockade with losartan.

Vascular actions of the angiotensin AT_1 receptor antagonist may not be entirely due to blockade of the angiotensin AT_1 receptor. Angiotensin receptors comprise two major subtypes, AT_1 and AT_2 (Wong et al., 1990). Since the angiotensin AT_2 receptor is not blocked by losartan, it should be expected that the functions mediated via this receptor might be enhanced during angiotensin AT_1 receptor blockade. When the angiotensin AT_1 receptor is blocked, plasma and tissue renin and angiotensins increase markedly (Bunkenburg et al., 1991); angiotensin II may act on angiotensin AT_2 receptors, which could have an opposite effect such as vasodilation. Thus, one could predict that, during footshock stress, increased levels of angiotensin II would bind to unblocked angiotensin AT_2 receptors, leading to a vasodepressor response. In fact, several studies have demonstrated that angiotensin II can also induce endothelium-dependent relaxation in some types of blood vessels. The marked regional differences in ANG-vascular responses depend on the preparation and species studied (Bottari et al., 1993). It has been reported that angiotensin II can elicit a biphasic arterial pressure response in rabbits (Campbell et al., 1990; Chansel et al., 1992) and rats (Scheuer and Perrone, 1993). Furthermore, endothelium-dependent relaxations induced by angiotensin II have been reported for a variety of experimental preparations such as the fowl aorta (Yamaguchi and Nishimura, 1988) and canine renal and cerebral arteries (Toda and Miyazaki, 1981). The heterogeneity of the response to angiotensin II may be related to modulatory effects of the vascular endothelium or stimulation of different angiotensin II receptor subtypes. A few studies in rats suggest that the endothelium-dependent vasorelaxation by angiotensin II is mediated by angiotensin AT_2 receptors thereby counteracting the vasoconstrictor action of angiotensin II at the smooth muscle site. Indeed, in anaesthetized rats, blockade of angiotensin AT_2 receptors enhances the angiotensin-induced pressor response (Scheuer and Perrone, 1993). In addition, it has been shown that angiotensin II degradation products evoked endothelium-dependent relaxation in rat and rabbit cerebral arterioles, presumably through the activation of angiotensin AT_2 receptor subtypes (Harberl et al., 1990, 1991; Brix and Harberl., 1992). Angiotensin II may act on the angiotensin AT_2 receptor subtype, either directly or via the release of autacoids such as kinins and nitric oxide (Seyedi et al., 1995; Siragy and Carey, 1996). In this respect, it has been shown that, in cultured endothelial cells, angiotensin II increases nitric oxide-dependent cyclic GMP production through the stimulation of the angiotensin AT_2 receptor, which in turn leads to an enhanced release of bradykinin (Wiemer et al., 1993).

In the present study, we tested the hypothesis that, in losartan-treated rats, footshocks would result in a vasodepressor response due not only to the blockade of the angiotensin AT_1 receptor, but also to activation of the angiotensin AT_2 sites and through interactions with prostaglandins, nitric oxide or kinins. To this end, we assessed the effect of systemic administration of losartan and/or 1-[[4-(dimethylamino)3-methylphenyl]methyl]-5 (diphenylacetyl)-4,5,6,7-tetrahydro-1*H* imidazol (4,5-*c*] pyridine-6-carboxilic acid, ditrifluoro acetatemonohydrate (PD 123319), on the cardiovascular response to footshocks. This experimental model is known to cause sympathoadrenal and neuroendocrine activation (Lee et al., 1989). In addition, to ascertain the role of kinins, nitric oxide or prostaglandins in the vasodepressor responses to footshocks, experiments were performed in the presence of losartan and/or icatibant (HOE 140), a kinin B_2 receptor antagonist, indomethacin a cyclo-oxygenase inhibitor or N^G-nitro-L-arginine-methyl ester (L-NAME) a nitric oxide synthase inhibitor.

2. Material and methods

2.1. Experimental protocol

Male Sprague–Dawley rats (160–190 g) were housed under controlled conditions of temperature and photoperiod (light on from 0600 to 1800 h) and were provided with free access to laboratory chow and water. To assess the effect of angiotensin II receptor blockers on the cardiovascular response to footshocks, the animals were randomly distributed into the following groups: (1) Control: s.c. or i.p. injected with saline ($N = 8$ each); (2) Pretreated with losartan (2*n*-butyl-4-chloro-5-hydroxymethyl-1[2′-(1*H*-tetrazol-5-yl) biphenyl-4-yl)methyl] imidazole) from Dupont, Wilmington, DE, (1.0 or 10 mg/kg, s.c.) ($N = 8$ each); (3) Pretreated with PD 123319 (*S*) (1-[[4-(dimethylamino)3-methylphenyl]methyl]-5 (diphenylacetyl)-4,5,6,7-tetrahydro-1*H* imidazol (4,5-*c*] pyridine-6-carboxilic acid, ditrifluoro acetatemonohydrate) (Parke Davis, Ann Arbor, MI) (20 mg/kg, s.c.) ($N = 8$); (4) Pretreated with losartan + PD 123319 ($N = 8$); (5) Pretreated with saralasin (250 μg/kg, i.p.) ($N = 8$) (Wong et al., 1990, 1992; Cierco and Israel, 1994; Kraly et al., 1995).

To ascertain the role of kinins, nitric oxide or prostaglandins in the vasodepressor responses to footshocks, a separate group of animals was randomly divided into the following groups: *Icatibant protocol*: (1) Control: saline (s.c.) ($N = 9$); (2) Pretreated with losartan (10 mg/kg, s.c.) ($N = 7$); (3) Pretreated with icatibant (HOE 140) (400 μg/kg, i.p.) ($N = 6$);(4) Pretreated with losartan + icatibant (400 μg/kg, i.p.) ($N = 13$). *Indomethacin protocol*: (1) Control: saline (s.c.) ($N = 9$); (2) Pretreated with losartan (10 mg/kg, s.c.) ($N = 7$); (3) Pretreated with indomethacin (5 mg/kg, i.p.) ($N = 13$); (4) Pretreated

with losartan + indomethacin ($N = 13$). *L-NAME protocol*: (1) Control: saline (s.c.) ($N = 10$); (2) Pretreated with losartan (10 mg/kg, s.c.) ($N = 8$); (3) Pretreated with L-NAME (20 mg/kg, i.p.) ($N = 14$); (4) Pretreated with losarthan + L-NAME ($N = 18$) (Cachofeiro et al., 1995; Paula et al., 1995; Liu et al., 1997). All the control and losartan treated groups were pooled, averaged and expressed as a single figure.

2.2. Measurement of cardiovascular responses to footshocks

Blood pressure was measured by the tail-cuff method. Systolic and diastolic pressure and heart rate were recorded daily using a tail-cuff digital plethysmograph (LE 5000, LETICA Scientific Instruments, Barcelona, Spain). To minimize stress, rats were trained daily with the plethysmograph 1 week prior to the experiment. Moderate warming of the rats was standardized by placing the cage containing the rat into an oven (Memmert, 91126 Schwabach, Western Germany) (60 × 50 × 40 cm, internal dimensions) at 42°C, for 15 min immediately before cardiovascular parameters determination. Cardiovascular parameters were measured daily at the same time of the day during the training and experimental periods. All the plethysmographic readings were reproducible during at least 10 min of consecutive measurements and were similar in magnitude from animal to animal. Plethysmographic pressure values were validated in early experiments with direct measurements with intra-arterial catheter recordings (data not shown).

Forty five minutes after drug treatment, the animals were transferred to a Plexiglas chamber with a copper rod floor where they received mild footshocks (2 Hz, 100 V, 5 ms, for 5 min) delivered by a Grass stimulator (Model S48). The rats were placed into the heating oven and after 10 min of heating, footshock-stimulation was performed inside the oven for a period of 5 min. Immediately after this procedure, measurements of peak cardiovascular responses were taken. Basal mean arterial pressure and heart rate were determined before drug treatment and 5 min before the start of the experiment with footshocks. The mean arterial pressure and heart rate determined immediately before footshocks were considered as basal. The procedures used in these experiments were reviewed and approved by the Animal Care and Use Committee of The Central University of Venezuela, School of Pharmacy, Caracas.

All data are expressed as mean arterial pressure calculated from the sum of diastolic blood pressure and one third the pulse pressure, and are expressed as the means ± S.E.M. Statistical differences between groups were evaluated by one-way analysis of variance (ANOVA) and a value of $P < 0.05$ was considered significant.

3. Results

As shown in Fig. 1, footshocks caused a significant increase in mean arterial pressure and heart rate. Footshock stimulation in the presence of the angiotensin AT_1 receptor blocker, losartan, resulted in a consistent, dose-dependent, vasodepressor response, while the heart rate response was not altered (heart rate response not shown). PD 123319 alone did not alter the hemodynamic response to footshocks. However, when losartan and PD 123319 were used in combination to block both angiotensin AT_1 and AT_2 receptor subtypes, the vasodepressor response was eliminated as compared with the response to losartan alone (Bonferroni P value, for losartan vs. losartan + PD 123319, $P < 0.01$). Therefore, blockade of the vasopressor response to electric stimulation by a selective angiotensin AT_1 receptor antagonist unmasked a vasodepressor response, which was completely abolished by combined blockade of both receptor subtypes. (Mean arterial pressure values in mm Hg: basal: 101.4 ± 2.1; basal + footshocks: 126.6 ± 1.9; losartan$_b$ (1 mg/kg): 99.7 ± 1.9; losartan + footshocks: 90.2 ± 1.7; losartan$_b$ (10 mg/kg): 98.6 ± 1.5; losartan + footshocks: 84.2 ± 2.7; PD 123319$_b$: 100.9 ± 1.76; PD 123319 + footshocks: 125.7 ± 2.6; PD 123319 + losartan$_b$: 99.8 ± 2.3; PD 123319 + losartan + footshocks: 102.9 ± 3.)

The effects of the vehicle or saralasin (250 μg/kg, i.p.), on mean arterial pressure response to footshocks are shown in Fig. 1. Saralasin administration did not alter basal MAP, however, it reduced by 86% the vasopressor response and inhibited the vasodepressor response to footshocks. These actions were similar to the ones observed with losartan + PD 123319 treatment. (Mean arterial pres-

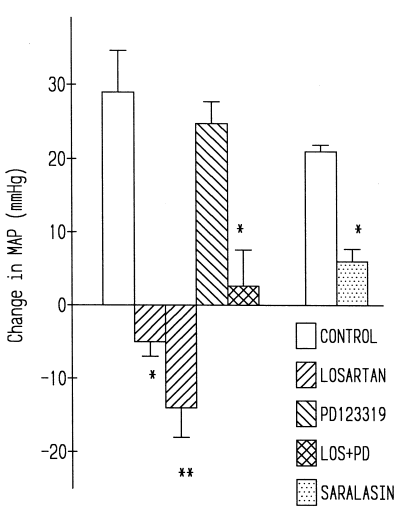

Fig. 1. Mean arterial pressure responses to footshocks. Vehicle (saline). Losartan (*1.0 and **10 mg/kg, s.c.); PD 123319 (20 mg/kg, s.c.); saralasin (250 μg/kg, i.p.). Values represent means ± S.E.M.; $N = 8$ per group; $^{*}P < 0.05$ and $^{**}P < 0.01$ compared with vehicle control (Bonferroni P values, ANOVA).

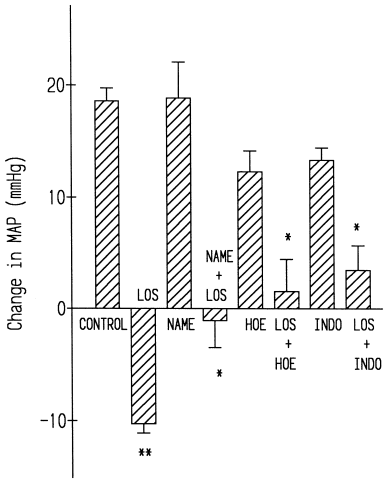

Fig. 2. Effect of icatibant (HOE-140), L-NAME and indomethacin on the pressor response to footshocks. Vehicle ($N = 28$); losartan (10 mg/kg, s.c.) ($N = 22$) $P < 0.01$ (Bonferroni P values, ANOVA); icatibant (400 μg/kg, i.p.) ($N = 6$); losartan + icatibant ($N = 13$), $^{*}P < 0.03$ compared with icatibant; L-NAME (20 mg/kg, i.p.) ($N = 14$); losartan + L-NAME ($N = 18$), $^{*}P < 0.05$ compared with L-NAME; indomethacin (5 mg/kg, i.p.) ($N = 13$); losartan + indomethacin ($N = 13$), $^{*}P < 0.05$ compared with indomethacin. Values represent means ± S.E.M.

sure values in mm Hg: saralasin$_b$: 96.93 ± 1.36; saralasin + footshocks: 109.31 ± 1.21.)

The administration of icatibant (HOE 140), L-NAME or indomethacin had no significant effect on the mean arterial pressure response to footshocks. However, icatibant, L-NAME or indomethacin blunted the vasodepressor response to footshocks unmasked in losartan-treated rats (Fig. 2) (Bonferroni P value, for losartan vs. losartan + L-NAME, $P < 0.05$; vs. losartan + icatibant and losartan + indomethacin, $P < 0.01$). Therefore, the vasopressor and the vasodepressor response to footshocks was completely abolished by combined blockade of angiotensin AT_1 receptor and kinin B_2 receptor, nitric oxide synthase or cyclooxygenase inhibition. (Mean arterial pressure values in mm Hg: basal: 101.8 ± 1.6; basal + footshocks: 121.8 ± 2.8; losartan$_b$: 96.91 ± 1.58; losartan + footshocks: 86.12 ± 1.29; L-NAME$_b$:113.76 ± 2.42; L-NAME + footshocks: 130.44 ± 2.68; L-NAME + losartan$_b$: 109.12 ± 2.07; L-NAME + losartan + footshocks: 109.2 1 ± 2.55; icatibant$_b$: 98.6 ± 2.1; icatibant + footshocks: 112.6 ± 3.1; icatibant + losartan$_b$: 98.66 ± 2.7; icatibant + losartan + footshocks: 99.76 ± 3; indomethacin$_b$: 102.5 ± 1.5; indomethacin + footshocks: 116.2 ± 2.2; indomethacin + losartan$_b$: 97.5 ± 1.46; indomethacin + losartan + footshocks: 101.5 ± 3.21.)

4. Discussion

Acute stress induced by footshocks causes sympathoadrenal activation with increases in arterial pressure and heart rate (Lee et al., 1989). In our early study, we have shown that central or peripheral blockade of angiotensin AT_1 receptors with losartan produces a dose-dependent inhibition of the vasopressor responses to sympathetic stimulation, probably due to a reduced rise in peripheral resistance because the heart rate response to footshocks was not affected by losartan (Cierco and Israel, 1994). Because the increase in mean arterial pressure induced by injection of exogenous norepinephrine was unchanged by systemic administration of losartan, a prejunctional rather than postjunctional inhibition of angiotensin AT_1 receptor may account for the observed reduction of the facilitation of noradrenergic transmission induced by footshocks (Cierco and Israel, 1994). This is in agreement with the results of Wong et al. (1991, 1992) who demonstrated that prejunctional angiotensin AT_1 receptors in the pithed rat vasculature and renal angiotensin AT_1 prejunctional receptors in anesthetized dogs mediate endogenous angiotensin-induced adrenergic facilitation.

In the present study, we demonstrated that, in addition to its inhibitory action on the vasopressor response to footshocks, peripheral angiotensin AT_1 receptor blockade with losartan caused, in a dose-dependent manner, a vasodepressor response to footshocks. The vasodepressor response unmasked in the presence of losartan was blocked by PD 123319, which is known to be a specific angiotensin AT_2 receptor antagonist (Wong et al., 1990), thus, supporting the hypothesis that the vasodepressor response is mediated in part by activation of the angiotensin AT_2 receptor. The angiotensin AT_2 receptor antagonist by itself did not have any effect on the cardiovascular response to footshocks compared with that of vehicle group, suggesting that the angiotensin AT_2 receptor may exert a vasodepressor response only when the angiotensin AT_1 receptor is blocked. Therefore, the combined blockade of angiotensin AT_1 and AT_2 receptors specifically and completely eliminates both the vasopressor and vasodepressor responses to endogenous angiotensin II, suggesting a role for the angiotensin AT_2 receptor in the regulation of the hemodynamic response to footshocks. To support this hypothesis and to better define the involvement of angiotensin AT_1 and AT_2 receptors in the cardiovascular response to footshocks, saralasin, a peptidic non-selective antagonist was employed. Indeed, intraperitoneal administration of saralasin markedly inhibited the vasopressor (86% reduction) and vasodepressor responses to footshocks in the same way as did losartan + PD 123319 administration. Since saralasin did not alter the basal mean arterial pressure, a possible agonistic effect of the peptide can be eliminated.

These results are not surprising in view of the fact that the effects of selective stimulation of either angiotensin AT_1 or AT_2 receptors have been shown to oppose each other in various biological systems. Most known effects of angiotensin II, such as increasing blood pressure, stimulation of myocyte hypertrophy, vasopressin release and drinking are attributed to the stimulation of the angiotensin

AT_1 receptor (Ganz et al., 1990; Everett et al., 1994). There is evidence that these actions are under inhibitory control by angiotensin AT_2 receptors (Höhle et al., 1995). Indeed, angiotensin AT_2 receptors antagonize both pressor and growth effects of the angiotensin AT_1 receptor (Ichiki et al., 1995; Nakajima et al., 1995) and the centrally mediated angiotensin-induced release of vasopressin and drinking (Höhle et al., 1995). In relation to the cardiovascular system, it has been demonstrated that angiotensin II and angiotensin III can produce a biphasic arterial blood pressure response. The vasopressor response is mediated by angiotensin AT_1 while the vasodepressor response is related to angiotensin AT_2 receptors (Scheuer and Perrone, 1993). Furthermore, it has been shown that targeted deletion, to eliminate the gene encoding the angiotensin AT_2 receptor, results in angiotensin AT_2 receptor null mice, which exhibited elevated pressor sensitivity to intravenous infusion of angiotensin II and an increased basal blood pressure (Ichiki et al., 1995). Thus, the existence of an equilibrium between vasoconstrictor angiotensin AT_1 and vasodilator AT_2 receptor could be proposed. This balance could play an important role in the mechanism of action of angiotensin AT_1 receptor antagonists. Consequently, when angiotensin II action is eliminated by losartan, the effects of angiotensin AT_2 receptor stimulation should be overexpressed. In this way, the angiotensin AT_2 receptor may contribute to the impairment of the direct vasoconstriction caused by angiotensin II that, in turn, may favor blood flow when plasma levels of angiotensin II are elevated, as in the case of footshock-stress and angiotensin AT_1 receptor blockade.

The mechanism whereby the angiotensin AT_2 receptor mediates the vasodepressor response to footshocks may be explained through a decrease in peripheral vascular resistance. Vasodilator responses to angiotensin II have been demonstrated in several ''in vitro'' studies in the arterial mesenteric vascular bed, dog renal artery strips, and rat skeletal muscle vascular bed and ''in vivo'' in rat and rabbit cerebral arterioles (Harberl et al., 1990, 1991), in anesthetized rats with a bolus injection of angiotensin II and angiotensin III and in the present study. The exact mechanism of angiotensin II vasorelaxation or the second messenger of this receptor is not well established. The vasorelaxation in response to angiotensin II may be due to the release of dilator substances from the endothelium, induced by angiotensin AT_2 receptor stimulation (Brix and Harberl, 1992). Indeed, it has been shown that vasorelaxation in several experimental preparations is blocked by inhibitors of prostaglandin synthesis (Fleming and Joshua, 1984) or by methylene blue, a soluble guanylyl cyclase inhibitor, suggesting a role for the nitric oxide-guanylyl cyclase system (Martin et al., 1985; Marshall et al., 1988; Harberl et al., 1990). It could be that the angiotensin AT_2 receptor exerts its hemodynamic effects by stimulating the local release of nitric oxide either directly or via kinins (Hecker et al., 1994; Seyedi et al., 1995; Siragy and Carey, 1996), which together with blockade of the angiotensin AT_1 receptor may have a vasodilator effect. It has been reported that, in cultured bovine aortic endothelial cells, angiotensin II induces a six- to sevenfold increase in the release of cGMP. This effect was abolished by a kinin antagonist and a nitric oxide synthesis inhibitor and markedly inhibited by an angiotensin AT_2 receptor antagonist, but only marginally inhibited by an angiotensin AT_1 receptor antagonist (Seyedi et al., 1995), suggesting that the angiotensin-stimulated release of nitric oxide is predominantly due to stimulation of the angiotensin AT_2 receptor and may lead to an increase in the effect of kinins, stimulation of nitric oxide and increased cGMP formation. Also, it has been shown that, in microvessels of the dog heart angiotensins stimulate cGMP via either the angiotensin AT_2 receptor and/or a non-angiotensin AT_1 or AT_2 receptor (AT_n), kinins, and nitric oxide (Seyedi et al., 1995). Our data for blockade of the vasodepressor response to footshocks with the kinin B_2 receptor antagonist, or with nitric oxide synthase or cyclo-oxygenase inhibition suggest that, during blockade of the angiotensin AT_1 receptor, activation of angiotensin AT_2 or AT_n receptors may lead to an increase in either tissue kinin concentration or the effect of kinins, and the subsequent release of nitric oxide/prostaglandins (Brosnihan et al., 1996).

In summary, this study demonstrated a role of angiotensin AT_2 receptors and kinins in the vasodepressor response unmasked after footshocks in losartan-treated rats. We speculate that footshocks and blockade of angiotensin AT_1 receptors increases both renin and angiotensins, these angiotensins stimulate the angiotensin AT_2 receptor, which in turn may induce vasodepression via kinins and other autacoids.

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