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Involvement of neurohumoral factors in the pressor mechanism of N^G-nitro-L-arginine

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Abstract

The mechanism of the N^G-nitro-L-arginine (L-NNA)-induced pressor response was examined in pentobarbital-anesthetized dogs. The pressor effect of L-NNA (50 mg/kg, i.v.) was significantly and equally diminished by pretreatment with either hexamethonium (25 mg/kg, i.v.) or phentolamine (5 mg/kg, i.v.). The intracisternal administration of L-NNA (1 mg/kg), which did not cause changes in cardiovascular parameters when administered systemically, produced a significant pressor response and tachycardia. Furthermore, significant suppression of L-NNA-induced pressor responses was observed after treatment of dogs with captopril (5 mg/kg, i.v.) or a non-peptide angiotensin II receptor antagonist, losartan (10 mg/kg, i.v.), or bilateral occlusion of renal veins. The inhibitory effects of hexamethonium and losartan were additive. These results suggest that, in addition to vasoconstriction due to the inhibition of endothelial nitric oxide production, increased activity of the sympathetic nervous and renin-angiotensin systems contributes significantly to the development of pressor responses produced by the intravenous injection of L-NNA in anesthetized dogs.

Keywords: Nitric oxide (NO); N^G-Nitro-L-arginine; Pressor response; Sympathetic nervous system; Renin-angiotensin system; (Dog)

1. Introduction

There is now considerable evidence that the endothelium-derived relaxing factor (EDRF) released from vascular endothelial cells is nitric oxide (NO) (Palmer et al., 1987; Ignarro et al., 1987) or a closely related compound, such as *S*-nitrosocysteine (Myers et al., 1990). NO is formed by the catalytic conversion of L-arginine by the enzyme NO synthase (Palmer et al., 1988a; Sakuma et al., 1988). It has been shown that the activity of NO synthase and endothelium-dependent vasodilator responses are inhibited by L-arginine analogues, such as N^G-monomethyl-L-arginine (L-NMA) (Palmer et al., 1988b; Rees et al., 1989a, 1990) and N^G-nitro-L-arginine (L-NNA) (Ishii et al., 1990).

Since administration of L-NMA (Rees et al., 1989b; Aisaka et al., 1989; Rees et al., 1990; Gardiner et al., 1990) and L-NNA (Wang and Pang, 1990, 1991; Pucci et al., 1992) into animals causes long-lasting pressor responses, it has been considered that the basal production of NO in endothelial cells plays an important role in the regulation of blood pressure (Aisaka et al., 1989; Rees et al., 1989b). However, it is now apparent that NO is formed in and released from various cell types (Ishii et al., 1989; Knowles et al., 1989; Bredt et al., 1990; Ishii et al., 1991; Sheng et al., 1991; Schmidt et al., 1992). Therefore, it is possible that NO produced in non-endothelial cells contributes to the regulation of blood pressure. Indeed, recent reports have demonstrated that administration of NO synthase inhibitors causes an increase in sympathetic neurogenic vasoconstriction (Lacolley et al., 1991), an increase in sympathetic outflow (Sakuma et al., 1992; Togashi et al., 1992) and an impairment of so called 'nitrergic' vasodilator nerve function (Toda et al., 1993), although several observations do not support there being a contribution of neurohumoral systems to L-NNA-induced pressor responses (Wang and Pang, 1991; Elsner et al., 1992; Pucci et al., 1992). Thus, the mechanism of

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pressor effect of NO synthase inhibitors, or in other words, the relative significance of NO produced in endothelial cells and other cell types in regulating blood pressure, seems to vary depending on the experimental conditions and species of experimental animals (Wang et al., 1991; Van Gelderen et al., 1991).

Compared to extensive studies conducted in rodents, investigations on the NO-related regulatory mechanism of the cardiovascular system have not yet been carried out thoroughly in other animal species, such as cats, dogs, sheep, pigs, etc. To obtain more information on this aspect in larger animals, pressor responses to L-NNA were analyzed in the presence of various pharmacological and physical interventions in pentobarbital-anesthetized dogs.

2. Materials and methods

2.1. Experimental procedure

Healthy mongrel dogs of either sex, weighing 7–15 kg, were anesthetized with an initial dose of sodium pentobarbital (30 mg/kg, i.v). Supplemental doses of the anesthetic were applied through the right cephalic vein when necessary. A tracheotomy was performed to

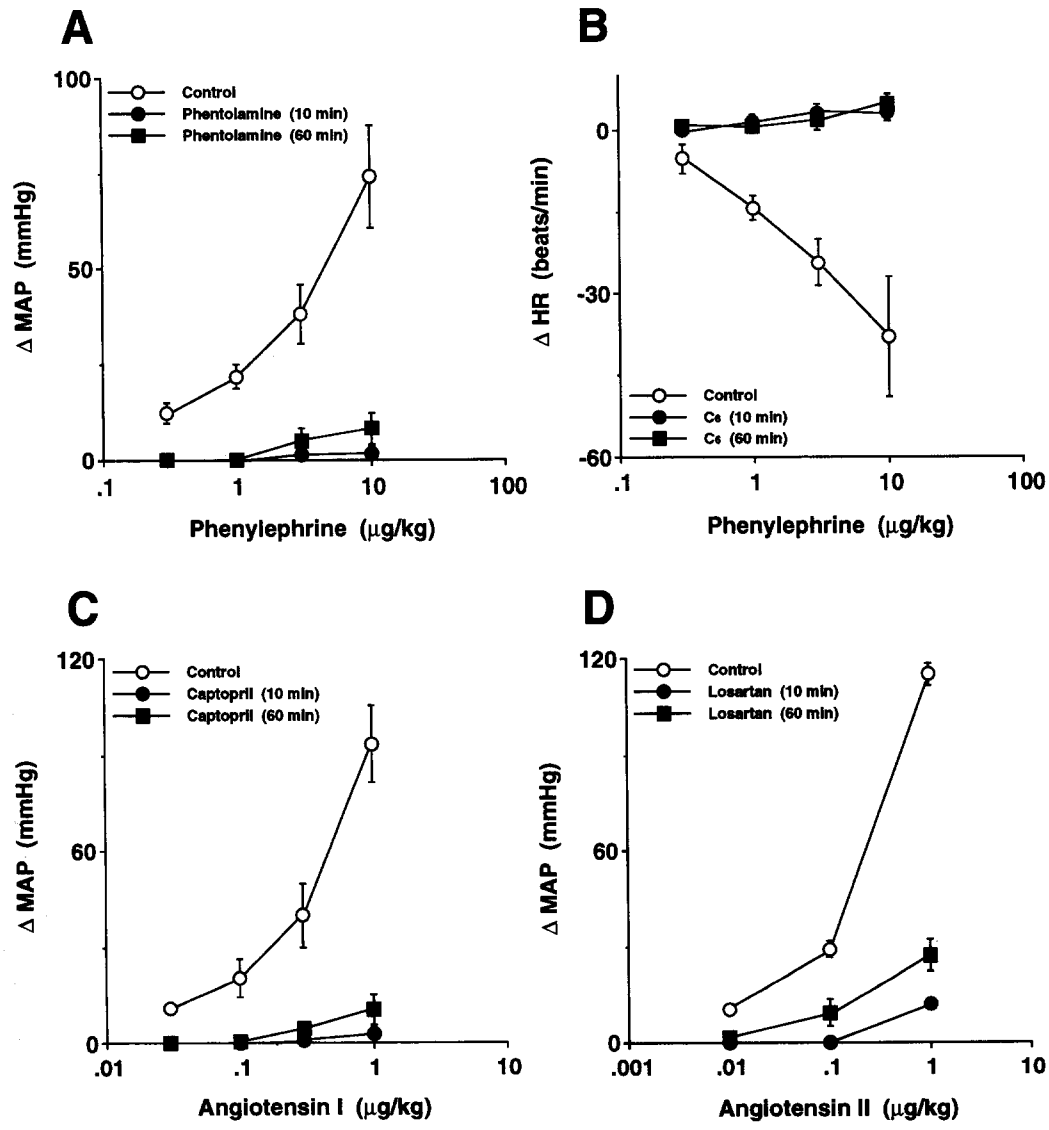

Fig. 1. Effects of phentolamine (5 mg/kg, i.v., A), hexamethonium (C_6, 25 mg/kg, i.v., B), captopril (5 mg/kg, i.v., C) and losartan (10 mg/kg, i.v., D) on blood pressure (mean arterial pressure, MAP) or heart rate (HR) responses to phenylephrine, angiotensin I and angiotensin II. Dose-response relationships for phenylephrine, angiotensin I and angiotensin II were obtained prior to (○) and 10 min (●) and 60 min (■) after the administration of phentolamine, C_6, captopril or losartan. In the case of experiments shown in panels A to C, dogs were not subjected to bilateral vagotomy. Each point with a vertical bar represents the mean ± S.E.M. of three experiments.

make spontaneous ventilation easier. In order to eliminate the influence of parasympathetic nervous activity, dogs were subjected to bilateral vagotomy. Polyethylene catheters were inserted into the right cephalic vein for injection of drugs and into the right femoral artery for measurement of blood pressure, which was recorded on a polygraph system (model RM-6000, Nihon Kohden, Tokyo, Japan) via a pressure transducer (model TDN-R, Gould, Oxnard, CA, USA) and preamplifier (model AP-641G, Nihon Kohden). Heart rate was measured with a heart rate counter (model AT-601G, Nihon Kohden) triggered by the blood pressure pulse. Throughout the experimental period, the body temperature of the dogs was maintained at 37 ± 0.5°C with a thermostat-controlled operation table (model SN-662, Shinano Manufacturing, Tokyo, Japan). At least 40 min were allowed for stabilization before the experiments were begun.

Drugs for the intravenous route were dissolved in and/or diluted with 0.9% NaCl solution. Treatment of dogs with hexamethonium, phentolamine, captopril, and losartan and bilateral occlusion of renal veins were performed 10 min prior to L-NNA administration. In the case of intracisternal (i.c.) administration, L-NNA was dissolved in artificial cerebrospinal fluid of the following composition (mM); NaCl, 125; KCl, 3.0; $MgCl_2$, 1.0; $CaCl_2$, 1.2 and $NaHCO_3$, 25. The fluid was kept at 37°C and bubbled continuously with 5% CO_2 in oxygen. The proper position of the spinal needle was determined at the end of each experiment by injecting trypan blue.

2.2. Drugs

The drugs used were N^G-nitro-L-arginine (Aldrich Chemical Co., Milwaukee, WI), N^G-nitro-D-arginine, angiotensin I (human), angiotensin II (human) (Peptide Institute, Minoh, Japan), phentolamine mesylate (Ciba-Geigy (Japan), Takarazuka, Japan), L-arginine hydrochloride, D-arginine hydrochloride, captopril, L-phenylephrine hydrochloride (Sigma Chemical Co., St. Louis, MO) and hexamethonium chloride (Tokyo Kasei Kogyo Co., Tokyo, Japan). Losartan was a generous gift from Du Pont Merck Pharmaceutical Co., Wilmington, DE, USA.

2.3. Statistical analysis

Results in the text and figures are means ± S.E.M. Statistical differences among mean values were determined by analysis of variance followed by the Fisher's least significant difference test for comparison of different means. In some instances, Student's paired *t*-test was used for comparison. A probability less than 0.05 was considered to be significant in all comparisons.

3. Results

Fig. 1 shows the data obtained from the preliminary experiments carried out to determine the doses of receptor antagonists and enzyme inhibitors. Phentolamine (5 mg/kg, i.v.) blocked the pressor effect of phenylephrine (0.3–10 μg/kg, i.v.) (panel A) and hexamethonium (25 mg/kg, i.v.) abolished the reflex decrease in heart rate produced by phenylephrine (0.3–10 μg/kg, i.v.) (panel B). Captopril (5 mg/kg, i.v.) inhibited the pressor effect of angiotensin I (0.3–1 μg/kg, i.v.) (panel C). Wong et al. (1991) suggested that the action of losartan in dogs is weaker than that obtained in rats, because losartan generates a smaller amount of the active metabolite, EXP3174, in dogs. However, under our experimental conditions, losartan at a dose of 10 mg/kg (i.v.), which was used in the present study, markedly attenuated pressor responses to angiotensin II (0.01–1 μg/kg, i.v.) (panel D).

A bolus i.v. injection of L-NNA (10–50 mg/kg) elicited a slowly developing and long-lasting pressor response. The time course of changes in mean arterial pressure and heart rate after injection of L-NNA (50 mg/kg) is summarized in Fig. 2. The maximum levels

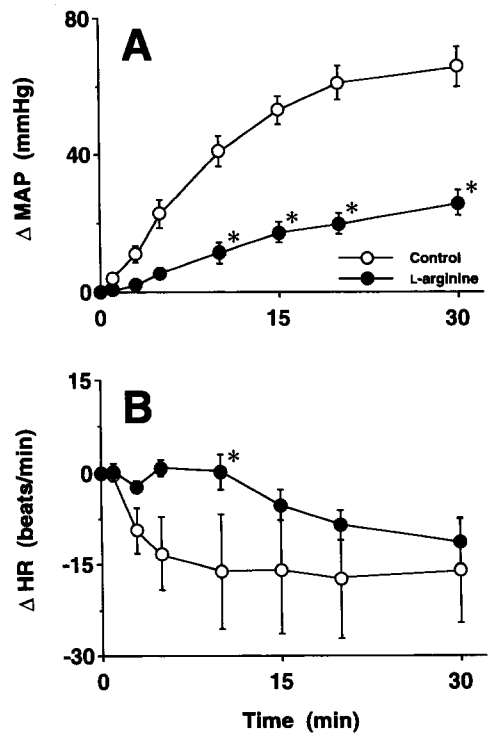

Fig. 2. Time course of the effect of N^G-nitro-L-arginine (L-NNA, 50 mg/kg, i.v.) on mean arterial pressure (MAP, A) and heart rate (HR, B) in control (○) and L-arginine (500 mg/kg, i.v., ●)-treated dogs. L-NNA was administered at time 0. Each point with a vertical bar represents the mean ± S.E.M. of six to seven experiments. * Significantly different ($P < 0.05$) from controls.

of both parameters were attained within 20–30 min and these levels were maintained for at least 90 min. The increase in mean arterial pressure and decrease in heart rate observed 30 min after administration of L-NNA (50 mg/kg, i.v.) were 66 ± 6 mmHg and 16 ± 9 beats/min, respectively ($n = 7$). Pretreatment of dogs with L-arginine (500 mg/kg, i.v.), but not D-arginine (500 mg/kg, i.v., data not shown), significantly ($P < 0.05$) attenuated pressor responses to L-NNA. N^G-nitro-D-arginine (50 mg/kg, i.v.) did not cause any changes in mean arterial pressure and heart rate (data not shown). These data indicate that the pressor effect of L-NNA observed in these experiments is associated with inhibition of NO synthase.

Pretreatment of dogs with hexamethonium (25 mg/kg, i.v.) or phentolamine (5 mg/kg, i.v.) significantly lowered the basal mean arterial pressure by about 25–30 mmHg (Table 1). Moreover, as shown in Fig. 3A, each treatment significantly ($P < 0.05$) attenuated the pressor response to L-NNA (50 mg/kg, i.v.). The increases in mean arterial pressure in hexamethonium- or phentolamine-treated dogs were 40 ± 5 mmHg ($n = 6$) and 46 ± 3 mmHg ($n = 5$), respectively, at 30 min after injection of L-NNA. In contrast, hexamethonium significantly ($P < 0.05$) enhanced pressor responses to angiotensin II (0.03–0.3 μg/kg). The increases in mean arterial pressure induced by angiotensin II at doses of 0.03, 0.1 and 0.3 μg/kg observed under the control conditions were 17 ± 2, 31 ± 4 and 66 ± 11 mmHg, whereas those after hexamethonium administration were 28 ± 4, 58 ± 4 and 112 ± 15 mmHg, respectively ($n = 5$). Similar results were obtained when phenylephrine was used as a pressor agent (data not shown). Hexamethonium decreased basal heart rate (Table 1) and abolished bradycardia induced by L-NNA (Fig. 3B), suggesting that the cardiac sympathetic nervous system contributes to maintain heart rate at a certain level under basal conditions and that L-NNA-induced bradycardia results from decreased sympathetic activity as a reflex to pressor responses caused by the drug. The amount of catecholamines released from the sympathetic nervous system and the adrenal medullae may increase after treatment of dogs with phentolamine due to lowered blood pressure and blockade of α_2-adrenoceptors at the nerve endings, suggesting that phentolamine makes heart rate more dependent on the sympathetic activity compared to the control conditions. Thus, L-NNA-induced bradycardia is potentiated after treatment with phentolamine. Similar results were also obtained with L-NNA at a submaximal dose of 10 mg/kg, i.v. (data not shown).

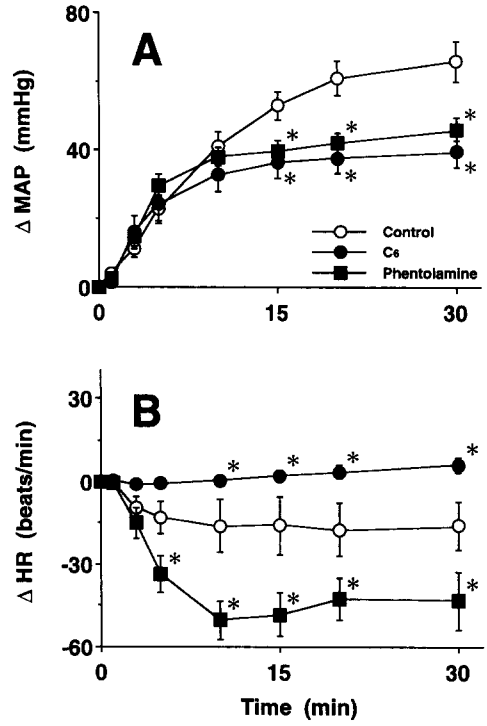

Fig. 3. Time course of the effect of N^G-nitro-L-arginine (L-NNA, 50 mg/kg, i.v.) on mean arterial pressure (MAP, A) and heart rate (HR, B) in control (○), hexamethonium (C_6, 25 mg/kg, i.v., ●)- and phentolamine (5 mg/kg, i.v., ■)-treated dogs. L-NNA was administered at time 0. Each point with a vertical bar represents the mean ± S.E.M. of five to seven experiments. * Significantly different ($P < 0.05$) from controls.

Table 1
Baseline values (means ± S.E.M.) of mean arterial pressure (MAP) and heart rate (HR) in anesthetized dogs prior to and 10 min after hexamethonium (C_6, 25 mg/kg, i.v.), phentolamine (5 mg/kg, i.v.), captopril (5 mg/kg, i.v.), losartan (10 mg/kg, i.v.), bilateral occlusion of renal veins (O.R.V.) and C_6 (5 mg/kg, i.v.) + losartan (10 mg/kg, i.v.).

	MAP (mmHg)		HR (beats/min)	
	Before	After	Before	After
Control	110 ± 5		183 ± 6 [a]	
C_6	120 ± 8	95 ± 11 [a]	173 ± 8	124 ± 6 [a]
Phentolamine	133 ± 7	101 ± 10 [a]	189 ± 14	222 ± 18 [a]
Captopril	134 ± 8	119 ± 10 [a]	179 ± 15	190 ± 14 [a]
Losartan	113 ± 11	99 ± 13 [a]	191 ± 17	193 ± 17
O.R.V.	127 ± 6	92 ± 13 [a]	168 ± 5	150 ± 9
C_6 + Losartan	129 ± 7	106 ± 3 [a]	187 ± 16	133 ± 9 [a]

[a] Significantly different ($P < 0.05$) from corresponding control values within the same group. Numbers of experiments were four to seven per group.

The amount of EDRF/NO released from endothelial cells has been suggested to vary depending on vascular tone (Vargas et al., 1990). To assess whether the blockade of the pressor response to L-NNA by hexamethonium and phentolamine was simply due to the initial decrease in basal blood pressure caused by these two agents, we examined the relationship between basal blood pressure and L-NNA-induced pressor responses. The L-NNA-induced increases in mean arterial pressure obtained 30 min after administration

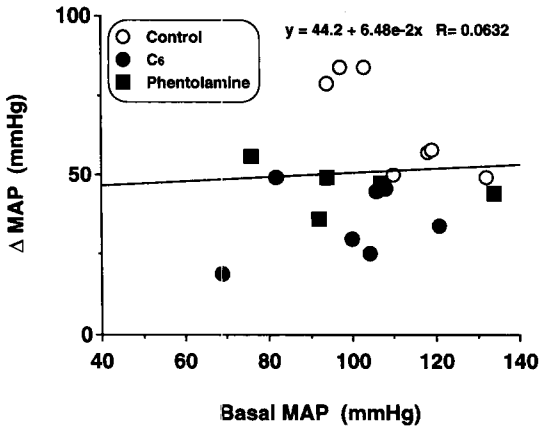

Fig. 4. Relationship between increases in mean arterial pressure (MAP) obtained 30 min after N^G-nitro-L-arginine (L-NNA, 50 mg/kg, i.v.) and basal MAP levels measured just before L-NNA in control (○), hexamethonium (C_6, 25 mg/kg, i.v., ●)- and phentolamine (5 mg/kg, i.v., ■)-treated dogs.

in control, hexamethonium- or phentolamine-treated dogs were plotted against the basal mean arterial pressure measured just before L-NNA (Fig. 4). As shown in the figure, there was no significant correlation between the two parameters.

To obtain more information on the mechanisms by which hexamethonium and phentolamine prevented

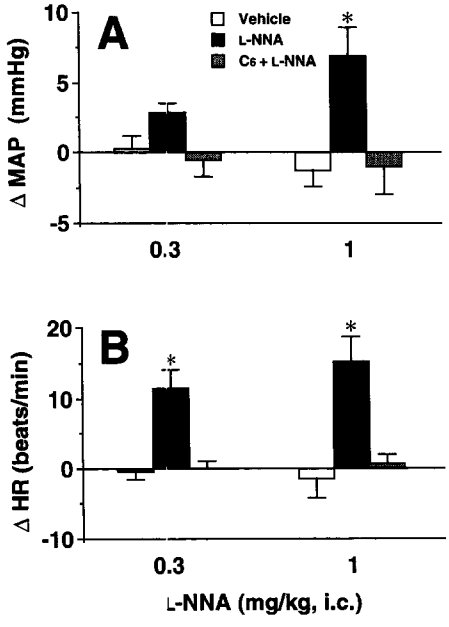

Fig. 5. Maximum changes in mean arterial pressure (MAP, A) and heart rate (HR, B) induced by injections of N^G-nitro-L-arginine (L-NNA) into the cisterna magna in anesthetized dogs. Open, closed and hatched columns represent data obtained from dogs injected with vehicle, L-NNA and L-NNA under treatment with hexamethonium (C_6, 25 mg/kg, i.v.), respectively. Each column with a vertical bar represents the mean ± S.E.M. of four to six experiments. * Significantly different ($P < 0.05$) from vehicle controls.

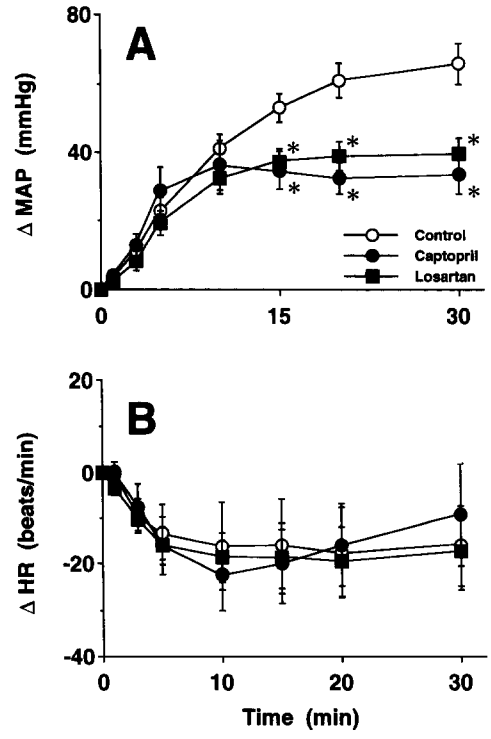

Fig. 6. Time course of the effect of N^G-nitro-L-arginine (L-NNA, 50 mg/kg, i.v.) on mean arterial pressure (MAP, A) and heart rate (HR, B) in control (○), captopril (5 mg/kg, i.v., ●)- and losartan (10 mg/kg, i.v., ■)-treated dogs. L-NNA was administered at time 0. Each point with a vertical bar represents the mean ± S.E.M. of five to seven experiments. * Significantly different ($P < 0.05$) from controls.

L-NNA-induced pressor responses, we examined whether the central action of L-NNA participates in the increase in blood pressure elicited by the intracisternal injection of small doses. L-NNA (0.3 and 1 mg/kg, i.c.) significantly increased blood pressure and heart rate, and these responses were abolished by pretreatment of dogs with hexamethonium (25 mg/kg, i.v.) (Fig. 5). Peak changes in mean arterial pressure and heart rate obtained after the intravenous injection of L-NNA at 1 mg/kg were 3 ± 1 mmHg and -3 ± 2 beats/min, respectively ($n = 4$), which were not different from the pre-injection levels.

We next examined the possibility that the renin-angiotensin system might contribute to the pressor responses to L-NNA. The dogs were treated with captopril (5 mg/kg, i.v.) or a non-peptide angiotensin II receptor antagonist, losartan (10 mg/kg, i.v.), prior to the administration of L-NNA. Although captopril did not attenuate the pressor responses to intravenous angiotensin II (0.3 μg/kg, 55 ± 9 mmHg vs. 66 ± 11 mmHg, $n = 5$), intravenous phenylephrine (10 μg/kg, 40 ± 3 mmHg vs. 50 ± 6 mmHg, $n = 5$) and intracisternal L-NNA (1 mg/kg, 7 ± 2 mmHg vs. 8 ± 3 mmHg, $n = 4$), treatment with captopril or losartan inhibited the pressor effects of intravenous L-NNA at doses of

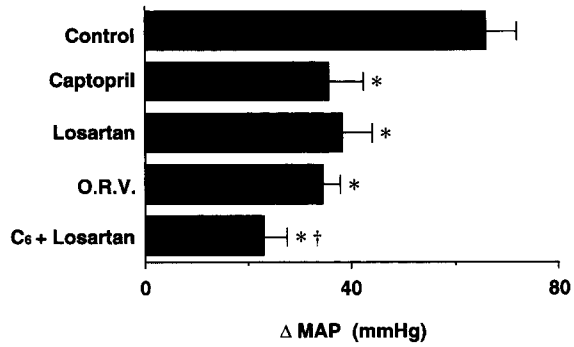

Fig. 7. Suppression by pharmacological interventions and bilateral occlusion of renal veins (O.R.V.) of N^G-nitro-L-arginine (L-NNA)-induced pressor responses in anesthetized dogs. Treatment with captopril (5 mg/kg, i.v.), losartan (10 mg/kg, i.v.), hexamethonium (C_6, 25 mg/kg, i.v.) plus losartan and O.R.V. was given 10 min prior to L-NNA (50 mg/kg, i.v.). Each column with a vertical bar represents the mean ± S.E.M. increase in mean arterial pressure (MAP) observed 30 min after L-NNA administration. Numbers of experiments were four to seven. *Significantly different ($P < 0.05$) from controls. †Significantly different ($P < 0.05$) from the losartan-treated group.

50 mg/kg (Fig. 6A) and 10 mg/kg (data not shown). In addition, bilateral occlusion of the renal veins also suppressed the pressor responses to L-NNA (Fig. 7). Although both of these interventions significantly ($P < 0.05$) reduced the basal mean arterial pressure (Table 1), no significant correlation was observed between the basal mean arterial pressure and the L-NNA-induced increase in mean arterial pressure (data not shown). Furthermore, Fig. 7 demonstrates that the inhibitory effects of hexamethonium and losartan on the pressor responses to L-NNA were additive.

4. Discussion

Pressor responses to NO synthase inhibitors in rodents, such as rats, rabbits and guinea-pigs, have been attributed to a decreased production of NO in vascular endothelial cells (Aisaka et al., 1989; Rees et al., 1989b, 1990; Gardiner et al., 1990). In the present study, we showed that an intravenous injection of L-NNA induces a slowly developing and long-lasting pressor response also in anesthetized dogs, the time course of which is very similar to that observed in rodents. However, it is now apparent that NO is synthesized in a wide variety of cell types and is involved in many physiological functions (Ishii et al., 1989; Knowles et al., 1989; Bredt et al., 1990; Ishii et al., 1991; Sheng et al., 1991; Schmidt et al., 1992). Therefore, we should be cautious when we consider the pressor mechanism of NO synthase inhibitors especially in animal species other than the well-studied rat. Based on the data presented in this paper, we would like to propose that the mechanism of L-NNA-induced pressor responses in anesthetized dogs involves activation of both the sympathetic nervous and renin-angiotensin systems, in addition to the inhibition of basal NO production in vascular endothelial cells.

Previous reports demonstrated that pretreatment of rats with ganglion-blocking agents significantly reduces the pressor effect of NO synthase inhibitors. The authors suggested that the sympathetic nervous system modulates the formation of NO in vascular endothelial cells by normal sympathetic discharge, humoral activation of α-adrenergic receptors, and vascular tone per se (Vargas et al., 1990; Lacolley et al., 1991). However, several papers have presented conflicting data that L-NNA-induced pressor responses in rats are potentiated after ganglion blockade (Wang and Pang, 1991; Pucci et al., 1992). This potentiation is considered to be due to decreased inhibitory baroreceptor reflexes. In addition, it has been shown that intravenous and intracisternal injections of L-NMA increase renal sympathetic nerve activity (Sakuma et al., 1992; Togashi et al., 1992). However, the authors of these papers concluded that the pressor effect of intravenous L-NMA in rats could be attributed mostly to its peripheral actions. Thus, the contribution of the sympathetic nervous system to the pressor responses to NO synthase inhibitors in rats is still equivocal.

In the case of dogs, the mechanism by which L-NNA elevates blood pressure has been described in some detail in a recent paper by Toda et al. (1993). They demonstrated that hexamethonium abolished the L-NNA-induced pressor responses, whereas phentolamine failed to affect them. Based on these data, they proposed an attractive hypothesis that the pressor response to L-NNA is due to a decreased activity of inhibitory nitrergic neurons innervating vascular smooth muscle cells.

One of conclusions drawn from the present study is different from either of those obtained in the previous investigations discussed above: that is, hexamethonium and phentolamine suppress L-NNA-induced pressor responses by eliminating augmented sympathetic influences as a result of the central action of L-NNA. It seems hard to ascribe the inhibitory effects of hexamethonium and phentolamine to lowered blood pressure and/or inhibition of putative nitrergic nervous functions, because of the observations made in the present study as follows. (1) We could not detect any positive correlation between the levels of blood pressure just before L-NNA and the magnitude of the pressor responses induced with L-NNA. (2) A ganglion blocker, hexamethonium, and an α-adrenoceptor antagonist, phentolamine, inhibited the L-NNA-induced pressor response to the same extent. These findings are strikingly different from the data presented by Toda et

al. (1993). The difference in the results is not due to differences in the doses of L-NNA and other agents, since we could not reproduce the results that appeared in their paper even when we used the same doses of drugs as they adopted. Thus, the reason for the difference is presently unknown.

Pressor responses to L-NNA were also suppressed significantly ($P < 0.05$) by captopril and losartan. Furthermore, they were attenuated to the similar extent after bilateral occlusion of renal veins. These data suggest that activation of the renin-angiotensin system contributes considerably to the pressor effect of L-NNA.

Atrial natriuretic peptide and sodium nitroprusside elevates cyclic GMP levels in juxtaglomerular cells and simultaneously inhibits renin release (Kurtz et al., 1986). Studies on renal cortical slices and isolated juxtaglomerular cells revealed that EDRF/NO decreases renin secretion (Vidal et al., 1988; Beierwaltes et al., 1992). Since EDRF/NO stimulates soluble guanylate cyclase in various tissues (Ishii et al., 1989; Knowles et al., 1989; Bredt et al., 1990; Ishii et al., 1991; Sheng et al., 1991; Schmidt et al., 1992), cyclic GMP seems to act as a second messenger to inhibit renin release. However, the data obtained from in vivo experiments and from experiments with perfused kidneys are not consistent with respect to the effect of NO synthase inhibitors on renin secretion (Gardes et al., 1992; Sigmon et al., 1992; Persson et al., 1993; Scholz and Kurtz, 1993). Although plasma renin activity was not measured in the present study, our data strongly suggest that NO contributes to the regulatory mechanism of the renin-angiotensin system in vivo and that the increased activity of this system is responsible at least in part for the pressor responses caused by L-NNA.

It is well established that the renal sympathetic nerves influence renin secretion, via stimulation of β-adrenoceptors. As mentioned above, our data suggest that L-NNA activates the sympathetic nervous system. Therefore, it seems possible that activation of the renin-angiotensin system is mediated by an indirect mechanism through the augmented sympathetic nervous activity. However, the inhibitory effects of hexamethonium and losartan on the pressor response to L-NNA were additive and captopril failed to prevent pressor responses induced by injections of L-NNA into the cisterna magna, suggesting that L-NNA activates the sympathetic nervous and renin-angiotensin systems independently. Another possibility is that the effect of L-NNA is mediated via an action on the macula densa, which controls renin secretion from juxtaglomerular cells. However, further studies are required to test this possibility.

Of additional interest is the observation that, in the presence of hexamethonium and losartan, the increases in mean arterial pressure elicited by L-NNA were about 20 mmHg. Since it is still possible that some unknown mechanisms participate in developing the pressor responses observed after injection of L-NNA, the significance of the basal NO production in the vascular endothelium in dogs seems to be less important than that in rodents for regulating blood pressure.

In conclusion, our results strongly suggest that, in addition to inhibition of the basal production of NO in vascular endothelial cells, intravenous administration of L-NNA activates both the sympathetic nervous and renin-angiotensin systems, and that all of these three pathways contribute significantly to the development of pressor responses induced by L-NNA in anesthetized dogs. Since the data presented here were obtained from experiments with pentobarbital-anesthetized dogs, the relative significance of each component under normal physiological conditions must be evaluated in careful investigations using conscious dogs. Furthermore, it is not clear whether other NO synthase inhibitors, such as L-NMA and N^G-nitro-L-arginine methyl ester, also cause pressor responses via the same mechanism. Nevertheless, we would like to stress here that this is the first report which demonstrates the involvement of augmented activities of the sympathetic nervous and renin-angiotensin systems in the pressor mechanism of L-NNA in dogs.

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