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Effect of losartan on afferent nerve stimulation

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Abstract

The present study was undertaken to investigate the effects of losartan, a non-peptide angiotensin II subtype 1 (AT_1) receptor antagonist, on both the pressor responses elicited by stimulation of afferent vagal nociceptive fibres and the involvement of the sympathetic nervous system (evaluated by plasma levels of noradrenaline and its co-neurotransmitter neuropeptide Y) in dogs. Electrical stimulation of the afferent fibres of the vagus (1, 5, 10 and 20 Hz) elicited a frequency-dependent increase in blood pressure and heart rate. Plasma noradrenaline levels only increased after stimulation at frequencies of 10 and 20 Hz. Plasma neuropeptide Y levels did not change. Losartan (10 mg/kg i.v.) induced both a decrease in resting blood pressure and an increase in basal plasma levels of noradrenaline and neuropeptide Y. Losartan failed to modify the magnitude of the electrically-evoked pressor and positive chronotropic responses. The angiotensin AT_1 receptor antagonist elicited a fall in plasma noradrenaline values after a 1 Hz stimulation and abolished the increase in plasma noradrenaline levels induced by the 10 (but not 20) Hz stimulation. The data suggest that angiotensin AT_1 receptors are not directly involved in acute pressor responses induced by stimulation of afferent vagal fibres. Moreover, the results show that, besides its sympatho-inhibitory effect, losartan can exert a sympatho-excitatory action as shown by the increase in the plasma levels of both noradrenaline and its coneurotransmitter, neuropeptide Y.

Keywords: Losartan; Afferent nerve stimulation; Arterial hypertension; Noradrenaline; Neuropeptide Y

1. Introduction

Afferent stimulation of sensory nerve fibres induces reflex modifications of arterial blood pressure due to the stimulation of nociceptive and/or visceral fibres. According to the frequency of stimulation, Aα, Aδ or C fibres are stimulated. A pressor response can be observed when C fibres are involved, i.e., for the highest frequencies of stimulation (Laporte and Montastruc, 1957). It was already reported that these cardiovascular responses are related to an increase in sympathetic tone since β-adrenoceptor antagonists are able to suppress the pressor response (Montastruc et al., 1978) and since noradrenaline plasma levels increase for the highest frequencies of stimulation (Montastruc et al., 1992). Previous results also suggest the involvement of endogenous opiate peptides (Montastruc et al., 1981) and neurohypophysal peptides such as vasopressin and oxytocin (Montastruc et al., 1985a) in these cardiovascular reflexes.

The role of the renin angiotensin aldosterone system in the control of blood pressure is well-known. Angiotensin II acts at a number of sites of the central nervous system known to influence cardiovascular regulation (Timmermans et al., 1993). The recent availability of drugs that interact with angiotensin II receptors allows the role of angiotensin II in blood pressure control to be studied. Thus, in order to further explore the role of angiotensin II in the pressor responses to the stimulation of afferent vagal fibres, the present study investigates the effects of losartan, a non-peptide angiotensin II subtype 1 (AT_1) receptor antagonist (Goa and Wagstaff, 1996), on both the pressor responses elicited by the stimulation of afferent vagal fibres and the involvement of the sympathetic nervous system (evaluated by the plasma levels of noradrenaline and its co-neurotransmitter neuropeptide Y).

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2. Materials and methods

2.1. Experimental protocols

2.1.1. Stimulation of afferent sensory fibres

2.1.1.1. Effects on blood pressure and heart rate. Eight beagle dogs of either sex weighing 9 to 17 kg were anaesthetized with urethane (1 g/kg i.v.), curarized by gallamine (2 mg/kg i.v.) and artificially ventilated with an Ideal Palmer pump (insufflated air: 15 ml/kg with frequency of 16/min). As in previous experiments (Laporte and Montastruc, 1957; Baïsset et al., 1959; Baïsset and Montastruc, 1964; Montastruc and Dang Tran, 1984a; Montastruc et al., 1985a, 1992), urethane was chosen because it increased vascular reactions (especially pressor responses to nervous stimulation). Adequate anesthesia was maintained by injection of 0.1 g of urethane every half hour. Body temperature of the animals was maintained at a constant level around 38°C. Systolic and diastolic blood pressures were recorded by means of a catheter introduced into the abdominal aorta via the left femoral artery under local anesthesia (xylocaïne 5%) and connected to a Gould P23 ID transducer or one channel of a Honeywell recorder.

Sensory fibres (Aδ and C fibres) of the vagus nerve (in the neck, caudal to the nodose ganglion) were stimulated as previously described (Laporte and Montastruc, 1957; Montastruc and Dang Tran, 1984a; Montastruc et al., 1985a, 1992). Briefly, after dissection, the nerve was sectioned and the central end immersed in a pool of paraffin oil (38°C). The central end of the nerve was stimulated via bipolar stainless steel electrodes. The stimuli consisted in 1 min trains of rectangular pulses (40 V) at supramaximal intensity (duration 0.1 ms). Stimulus frequency was raised stepwise from 1 to 5, 10, 20 and 30 Hz at 1 min intervals during a 4 min stimulus. The experimental conditions permit activation of sensory nociceptive fibres (Aδ and C) as previously described in cats by Laporte and Montastruc (1957). The sensory fibres of the vagus also innervate a variety of visceral receptors: in addition to nociceptive fibres, aortic baroreceptors and chemoreceptors were stimulated (Laporte and Montastruc, 1957). Stimulation of the nerve was repeated twice for periods of 3 min 30 s each separated by 45 min. Losartan (10 mg/kg i.v. during 1 min) was injected 15 min before the beginning of the second stimulation period. The dose of losartan was chosen according to preliminary experiments (not shown) and the data of Bovee et al. (1991) in dogs.

2.1.1.2. Effects on noradrenaline and neuropeptide Y plasma levels. In order to evaluate noradrenaline and neuropeptide Y plasma levels, a second series of experiments was performed using α chloralose for anesthesia since α chloralose does not significantly modify sympathetic activity. Beagle dogs of either sex weighing 9 to 20 kg were anaesthetized with α chloralose (80 mg/kg i.v.). A constant level of anaesthesia was maintained by injection of 15 to 20 mg/kg of α chloralose each hour. The sensory fibres of the vagus were stimulated at 1, 5, 10 and 20 Hz (1 ms trains of rectangular pulses (40 V) at supramaximal intensity (duration: 0.1 ms)). Arterial blood was collected from a catheter in the right femoral artery 3 min before stimulation period and 30 s after the beginning of each stimulation. Six dogs received losartan (10 mg/kg i.v. during 1 min) 15 min before the second period of stimulation whereas in the control group ($n = 4$), NaCl 0.9% was injected under the same experimental conditions instead of losartan.

2.1.2. Effects on conscious dogs

In order to further investigate the effects of losartan on neuropeptide Y, neuropeptide Y plasma levels were assayed before and after injection of losartan (10 mg/kg i.v.) in 6 other conscious dogs. Blood pressure was recorded as mentioned above. Blood samples were collected before, 5, 10, 15 and 30 min after losartan injection.

2.2. Biochemical assays

Plasma catecholamines: fresh arterial blood was collected on lithium heparin with sodium metabisulfite (10 mM), centrifuged at 200 × g for 10 min at 0°C. Plasma was stored at −80°C. As previously described (Damase-Michel et al., 1993), catecholamines were isolated selectively from the sample at 0°C, in darkness, by adsorption on activated alumina, then eluted with 0.1 M acetic acid. Dihydroxybenzylamine was used as internal standard. Catecholamines were assayed by a Waters high-pressure liquid chromatography apparatus using electrochemical (amperometric) detection: the working electrode potential was set at 0.65 V against a Ag/AgCl reference electrode. Catecholamines were separated on a C18 column (3.9 × 150 mm) at a constant flow rate of 1 ml/min. The electrochemical detector response was linear for concentrations ranging from 0.05 pmol/ml to 600 pmol/ml. In these conditions, the detection limit was 0.05 pmol/ml (Poncet et al., 1992).

Plasma concentrations of neuropeptide Y were determined by radioimmunoassay using a specific antiserum as previously described (Damase-Michel et al., 1993). Duplicate 100 μl aliquots of plasma were obtained from the abdominal aorta as indicated above. Plasma samples were incubated with [^{125}I]neuropeptide Y and a specific rabbit antiserum (Peninsula Laboratories Europe, UK). Bound antigen was separated by a second antibody method, and its radioactivity was measured in a gamma counter. The antiserum shows no cross-reactivity to structurally related peptides, such as peptide YY or pancreatic polypeptide (respectively less than 0.003% and 0.002%) or with losartan. Losartan was added to 8 samples of plasma in order to obtain concentrations ranging from 2.5 to 20 μg/ml and

the values of neuropeptide Y were compared to those obtained with the same plasma sample without losartan. The response was linear for concentrations ranging from 10 fmol/ml to 3 pmol/ml The detection limit was 10 fmol/ml. Day-to-day variability was 4% and within-run one 3% (Poncet et al., 1992).

2.3. Drugs

Losartan was a gift from the DuPont Merck Pharmaceutical and dissolved in 0.9% w/v NaCl solution.

2.4. Statistical analysis

All data are presented as mean values ± standard error of the mean (S.E.M.). Statistical analysis was performed by the use of the Friedman two way analysis of variance, a non parametric test equivalent of a 2-way ANOVA for repeated measures designed with a single group. Using a non-parametric test for paired comparisons (Wilcoxon test), values after each frequency of stimulation were compared to basal (pre-stimulation) or pre-treatment (before losartan) values. The level of significance was $P < 0.05$.

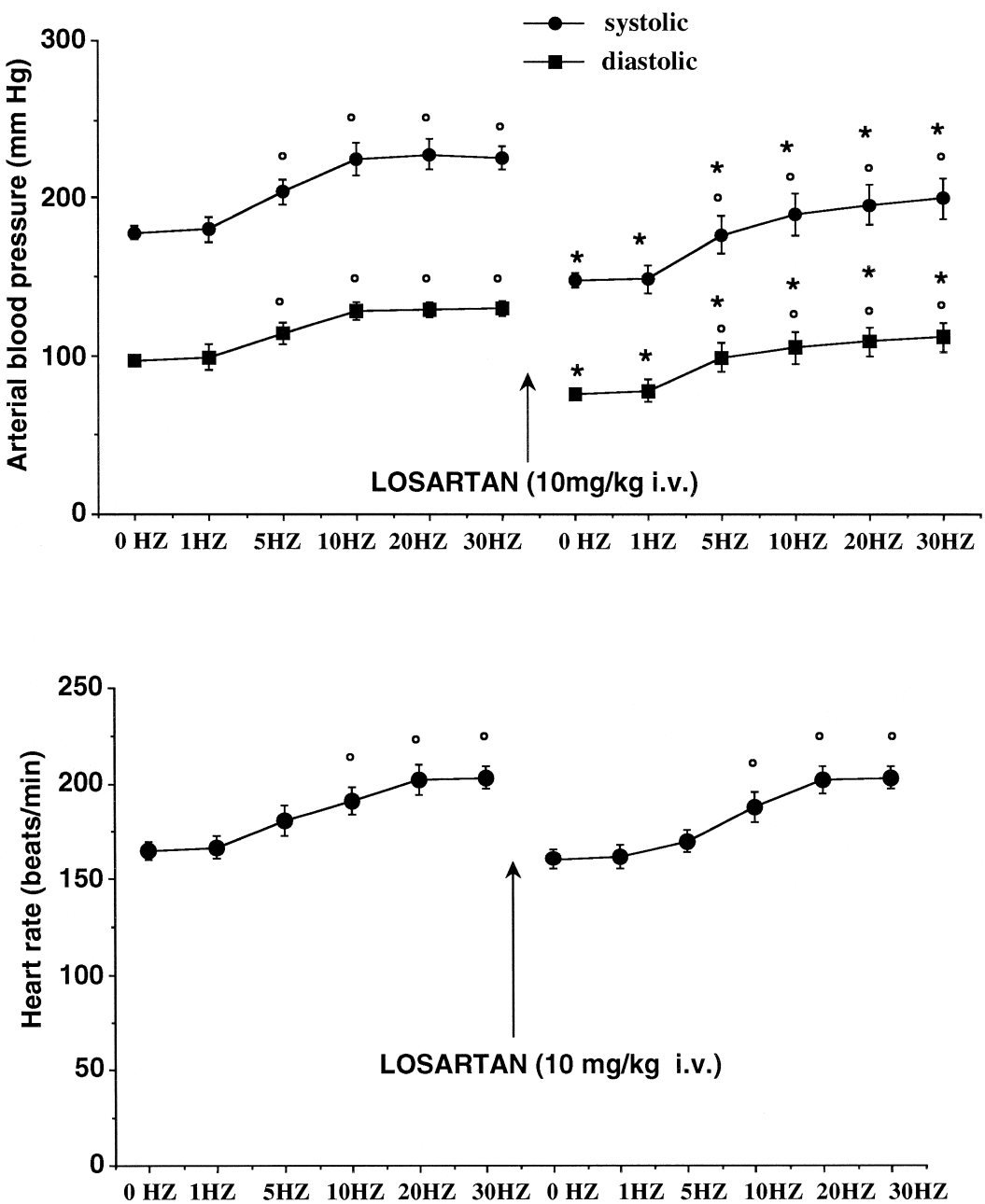

Fig. 1. Effect of afferent vagal stimulation on systolic and diastolic blood pressures (upper panel) and heart rate (lower panel) before and after losartan injection in urethane-anaesthetized dogs ($n = 8$). According to Friedman's two-way analysis of variance, there is a significant difference between the values obtained for each frequency of stimulation ($P < 0.0001$). The changes were compared to pre-stimulation ($^{\circ}P < 0.05$) or pre-treatment ($* P < 0.05$) values using Wilcoxon's test. Mean values ± S.E.M. are shown.

3. Results

3.1. Stimulation of afferent sensory fibres in anaesthetized dogs

3.1.1. Effects on blood pressure and heart rate

In anaesthetized dogs, resting values (before nerve stimulation) of systolic and diastolic blood pressures were 178 ± 4 mmHg and 97 ± 4 mmHg respectively (Fig. 1). This relatively high level of blood pressure is due to the type of anaesthesia (Montastruc et al., 1985a). Resting heart rate values were 160 ± 6 beats per min.

Electrical stimulation of the central end of the vagus nerve elicited a frequency-dependent increase in blood pressure as well as an increase in heart rate.

Using Friedman analysis, there is a significant difference between the values of systolic, diastolic blood pressures and heart rate obtained for each frequency of stimulation ($P < 0.0001$). The increase was significant from the 5 Hz frequency for blood pressure and from the 10 Hz frequency for heart rate.

Fifteen minutes after the injection of losartan (10 mg/kg i.v.), systolic and diastolic blood pressures were signifi-

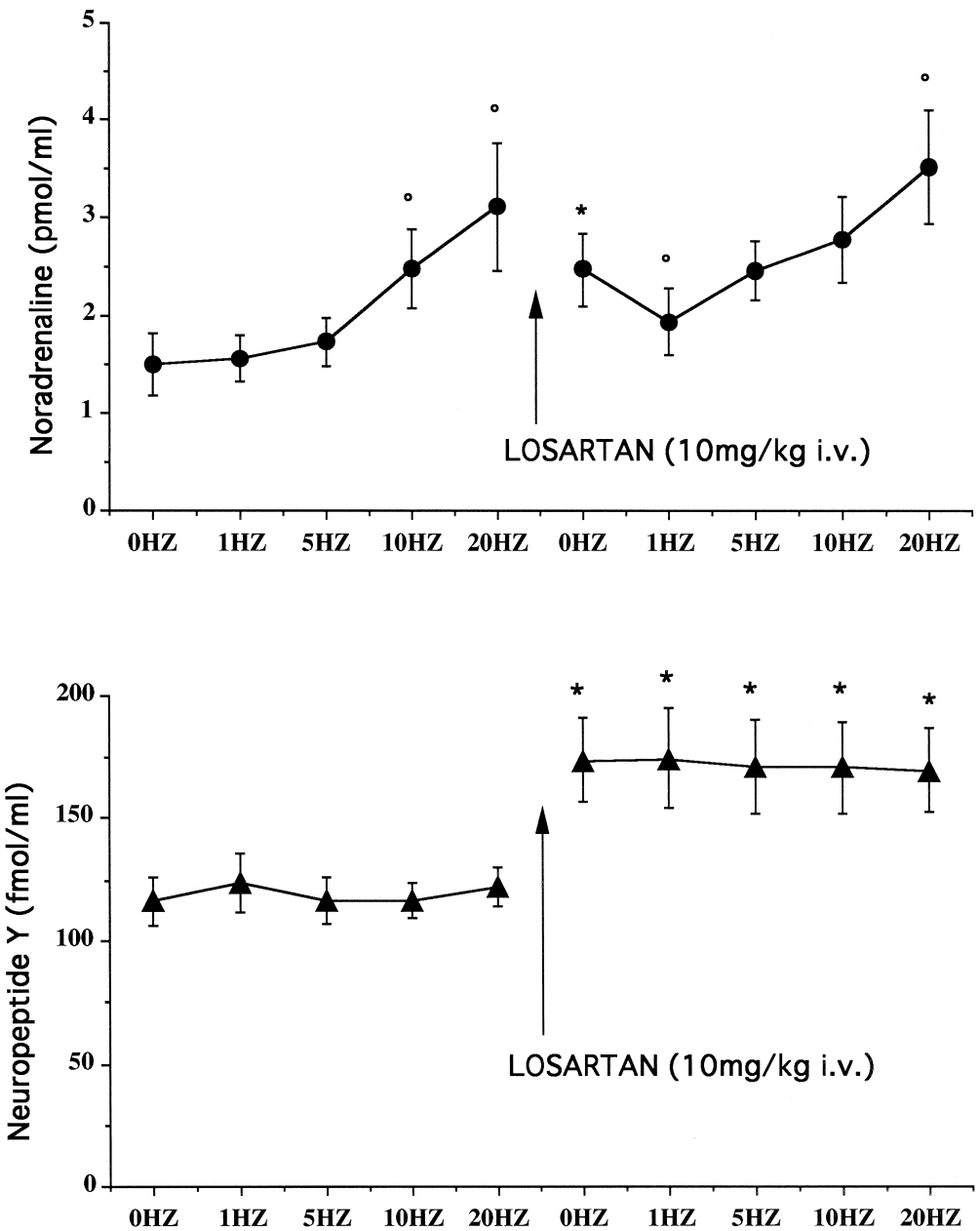

Fig. 2. Effect of afferent vagal stimulation on plasma noradrenaline (upper panel) and neuropeptide Y (lower panel) levels before and after losartan injection in chloralose-anaesthetized dogs ($n = 6$). According to Friedman's two-way analysis of variance, there is a significant difference between the values obtained for each frequency of stimulation ($P < 0.0001$). The changes were compared to pre-stimulation ($^{\circ}P < 0.05$) or pre-treatment ($* P < 0.05$) values using Wilcoxon's test. Mean values ± S.E.M. are shown.

cantly decreased (-30 ± 5 mmHg and -21 ± 3 mmHg respectively) without any significant change in heart rate when compared to pre-treatment values (165 ± 5 beats per min).

Losartan did not modify the magnitude of the pressor and positive chronotropic responses observed after afferent fibre stimulation.

3.1.2. Effects on catecholamine and neuropeptide Y plasma levels

In α chloralose anaesthetized dogs, electrical stimulation of the central end of the vagus nerve elicited a frequency-dependent increase in noradrenaline (from 1.49 ± 0.31 pmol/ml for basal values to 3.12 ± 0.65 pmol/ml for the 20 Hz stimulation) and adrenaline (from 1.20 ± 0.39

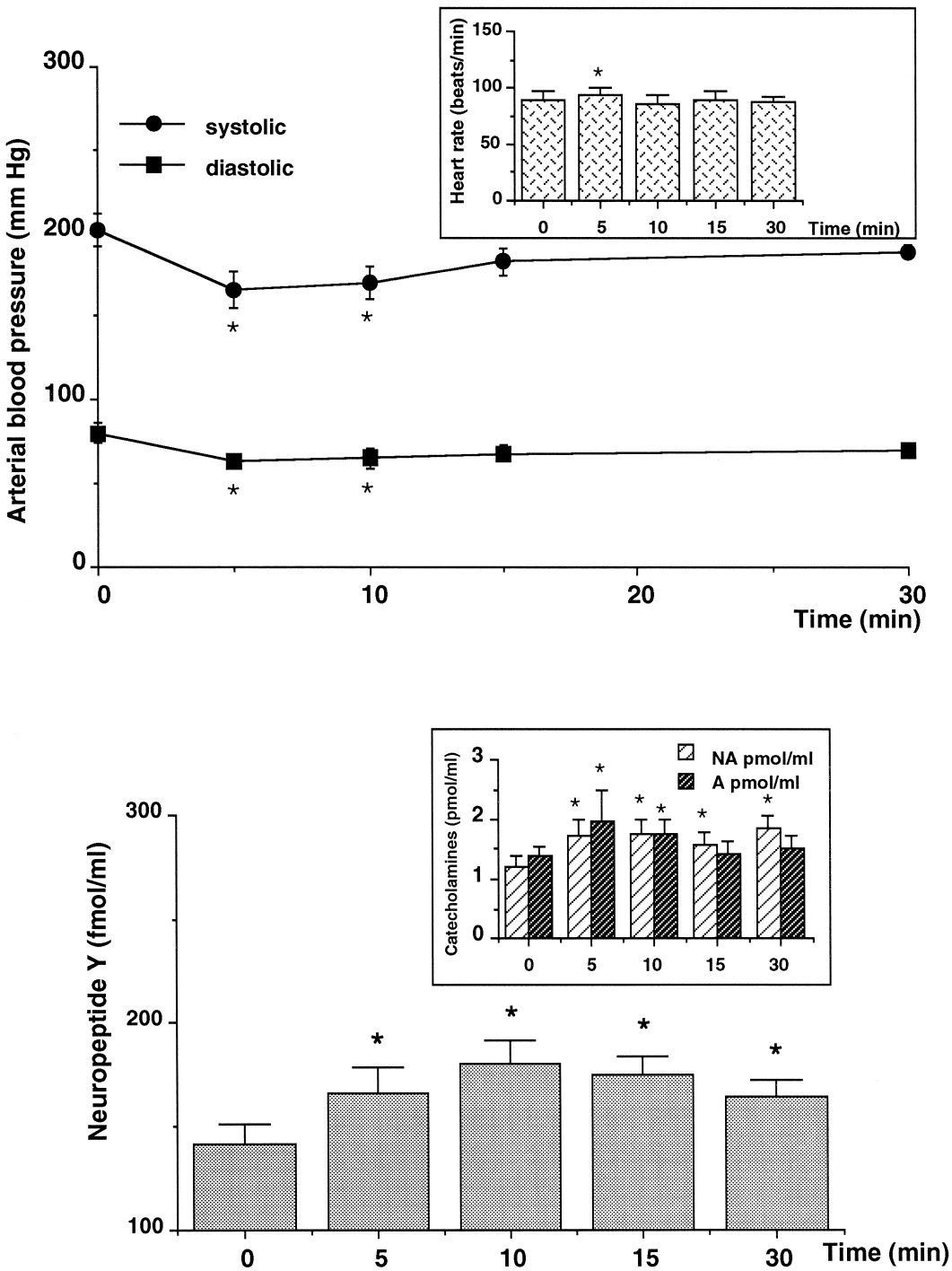

Fig. 3. Effect of losartan (10 mg/kg i.v.) on systolic and diastolic blood pressures (upper panel), heart rate (upper insert), neuropeptide Y (lower panel) and catecholamines (lower insert) plasma levels in conscious dogs ($n = 6$). The changes were compared to pre-treatment ($* P < 0.05$) values using Wilcoxon's test. Mean values ± S.E.M. are shown.

pmol/ml for basal values to 2.35 ± 0.50 pmol/ml for a 20 Hz stimulation) plasma levels without any change in neuropeptide Y plasma levels (from 117 ± 10 fmol/ml to 123 ± 8 fmol/ml for the 20 Hz stimulation) (Fig. 2).

The experiments performed in the control group allowed to verify that the values of catecholamines and neuropeptide Y plasma levels obtained before and during the second period of stimulation were not significantly different from the values obtained before and during the first period of stimulation (data not shown).

Using Friedman analysis, there is a significant difference between the values of catecholamine and neuropeptide Y plasma levels obtained for each frequency of stimulation ($P < 0.0001$). When compared to basal resting values, losartan induced a significant ($P < 0.05$) increase in noradrenaline, adrenaline as well as in neuropeptide Y plasma levels (+0.98 ± 0.21 pmol/ml, +0.50 ± 0.13 pmol/ml and +57 ± 13 fmol/ml respectively) before afferent vagal fibres stimulation.

Losartan elicited a fall in noradrenaline values after a 1 Hz stimulation and abolished the increase in noradrenaline elicited by the 10 (but not the 20) Hz stimulation.

3.2. Effects on conscious dogs

In conscious dogs, losartan (10 mg/kg i.v.) significantly ($P < 0.05$) decreased blood pressure and increased heart rate (Fig. 3). The fall in blood pressure persisted during 30 min after injection whereas heart rate returned to basal values 10 min after the injection.

Under these experimental conditions, noradrenaline, adrenaline and neuropeptide Y plasma levels increased.

4. Discussion

Afferent stimulation of the vagus nerve permits the stimulation of Aδ and C fibres which induces pressor responses (Laporte and Montastruc, 1957; Montastruc et al., 1985a; Montastruc et al., 1992) and an increase in noradrenaline release (Montastruc et al., 1992) for the highest frequencies (10 and 20 Hz) of stimulation. The activation of afferent fibres of the nerves is a rather complex phenomenon involving several mechanisms such as an axon reflex and the release of neuropeptides, particularly substance P, neurokinin A and calcitonin gene-related peptide (Dray et al., 1994). These peptides can modify the excitability of sensory nerves and nearby postganglionic sympathetic fibres. The sensory fibres of the vagus also innervate a variety of visceral receptors such as aortic baroreceptors and chemoreceptors (Korner, 1971; Paintal, 1973; Sato and Schmidt, 1973). The electrically-evoked pressor response involves the activation of bulbar cardiovascular centres, especially the dorsal vagal nucleus, the nucleus of the solitary tract and the vasomotor centers. Previous studies have shown the involvement of central noradrenergic mechanisms in these reflexes since sympatholytic drugs (Stone et al., 1962) or centrally injected adrenoceptor antagonists were able to reduce these pressor effects (Montastruc et al., 1978).

The present study shows that the non-peptide angiotensin AT_1 receptor antagonist, losartan, does not modify the blood pressure response to afferent vagal stimulation but has an inhibitory effect on its sympatho-excitatory response: the angiotensin AT_1 receptor antagonist induced a fall in noradrenaline values when Aα or Aδ fibres were stimulated (lower frequencies) and abolished the increase in noradrenaline plasma levels elicited by the stimulation of the C fibres (frequency 10 Hz). These data agree with the hypothesis that endogenous angiotensin II augments the sympathetic response to physiological (exercise, standing) and pharmacological (sodium nitroprussiate and phenylephrine infusion, diuretic administration) stimuli (Noshiro et al., 1994; Clemson et al., 1994). This inhibitory effect of losartan on the sympathetic nervous system has been described as resulting, first from a presynaptic inhibition of noradrenaline release (Moreau et al., 1993) and secondly, from losartan binding at central angiotensin AT_1 receptors (Gaudet et al., 1997).

By contrast, intravenous losartan elicited an increase in noradrenaline plasma levels in anaesthetized dogs under resting conditions, i.e., when the nerve was not stimulated. The same increase in noradrenaline plasma levels was observed in conscious dogs. Unlike reports showing that plasma noradrenaline has a tendency to decrease with angiotensin AT_1 receptor inhibition (Niederberger et al., 1995; Messerli et al., 1996), such a result agrees with several clinical data describing a rise in noradrenaline after angiotensin AT_1 receptor antagonist administration (Goldberg et al., 1995; Van den Meiracker et al., 1995). One can hypothesize that a reflex sympathetic activation could be elicited by changes in baroreflex activity due to the fall in arterial blood pressure.

Moreover, the apparent discrepancy in the modulation of noradrenaline release after blockade of angiotensin AT_1 receptors can be explained by the dual sympatho-inhibitory and sympatho-excitatory effects of angiotensin II in the brainstem. Head (1996) has suggested that angiotensin II receptors in the brainstem can modulate sympathetic responses to specific afferent inputs: (1) the sympatho-inhibitory angiotensin II pathways possibly include the caudal ventrolateral medulla and the nucleus of the solitary tract (which is involved in the response to the stimulation of the sensory fibres of the vagus) and (2), the sympatho-excitatory angiotensin AT_1 receptors are located in the rostral ventrolateral medulla and their stimulation by angiotensin II results in a marked sympatho-excitation by activating specific vasomotor cells. Thus, one can suggest that an increase or a decrease of noradrenaline release can be observed after losartan depending on which the angiotensin II pathway is activated by the different frequen-

cies of stimulation. The access of losartan to a brain site was suggested by Song et al. (1991).

Another point of this study concerns the release of neuropeptide Y after losartan administration in anaesthetized dogs. As far as we know, such an increase in neuropeptide Y plasma levels after blockade of angiotensin AT_1 receptors has never been reported. This rise in neuropeptide Y plasma levels was observed independently of the stimulation of the nerve since afferent stimulation does not potentiate the increase in neuropeptide Y plasma levels. This rise in neuropeptide Y plasma levels was not associated with a dramatic increase in noradrenaline. This result confirms a previous study showing that neuropeptide Y release is not involved in the pressor effect elicited by the stimulation of nociceptive sensitive fibres and that neuropeptide Y and noradrenaline release are not necessarily linked (Allen et al., 1984; Lundberg et al., 1990; Montastruc et al., 1992; Poncet et al., 1992). The moderate but constant increase in neuropeptide Y plasma levels elicited by losartan was confirmed in conscious dogs. This unexpected result could suggest that angiotensin AT_1 receptors exert inhibitory control on neuropeptide Y release by sympathetic nerve endings.

The losartan induced-changes in noradrenaline and neuropeptide Y plasma levels were accompanied by a fall in arterial blood pressure without any significant change in heart rate. The blood pressure reduction is explained by the blockade of angiotensin AT_1 receptors which are located primarily on vascular and cardiac tissue, kidney, brain and adrenal gland (Goa and Wagstaff, 1996). However, losartan does not modify the magnitude of the pressor response induced by the stimulation of nociceptive cutaneous and visceral fibres suggesting that angiotensin AT_1 receptors are not directly involved in the acute hypertensive response. These results contrast with those obtained with angiotensin converting enzyme inhibitors such as captopril (Montastruc et al., 1984b) and enalapril (Montastruc et al., 1985b) which induce a decrease in the pressor responses to vagal stimulation. After losartan, the magnitude of the pressor response to afferent nerve stimulation remained unchanged whereas a decrease in sympathetic tone is observed. These data confirm that the increase in sympathetic tone is not the sole mechanism involved in the pressor effect induced by afferent stimulation of the vagal nerves. Previous studies have suggested the involvement of opioids (Montastruc et al., 1981) and neurohypophyseal peptides (Montastruc et al., 1985a) in these responses.

Finally, the present data show that the angiotensin II receptor antagonist, losartan, decreases blood pressure whereas it induces an increase in noradrenaline and neuropeptide Y plasma levels. Depending on the frequency of stimulation, the blockade of angiotensin AT_1 receptors can increase or decrease the noradrenaline release elicited by the stimulation of afferent vagal fibres but does not modify the magnitude of the pressor response suggesting that angiotensin AT_1 receptors are not directly involved in the pressor response induced by afferent fibre stimulation. These results show that besides its sympatho-inhibitory effect, losartan can exert a sympatho-excitatory action as shown by the increase in the plasma levels of both noradrenaline and its coneurotransmitter, neuropeptide Y.

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