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Receptor subtypes mediating spinal cardiovascular effects of angiotensin II in rat using losartan and PD 123319

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Abstract

It has previously been shown in this laboratory that intrathecal administration of 10 μg of angiotensin II produces an increase in arterial pressure and heart rate. As two receptor subtypes of angiotensin II, termed AT_1 and AT_2, have been identified in central nervous tissue this study examines the effects of selective antagonists on the pressor and cardioacceleratory responses to intrathecal administration of 10 μg of angiotensin II to the ninth thoracic spinal cord. The two non-peptide antagonists were losartan (2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[(2′-(1*H*)-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole), which is selective for the angiotensin AT_1 receptor, and PD 123319 (1-[[4-(dimethylamino)-3-methylphenyl]methyl]-5-(diphenylacetyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine-6-carboxylic acid, ditrifluoroacetate, dihydrate), which is selective for the angiotensin AT_2 receptor. Intravenous administration of losartan blocked both pressor and cardioacceleratory effects of angiotensin II. Intrathecal administration of losartan blocked only the pressor effects, raising the possibility that block of the heart rate response was in the periphery. Intrathecal administration of PD 123319 blocked the pressor effect of angiotensin II but had no effect on the cardioacceleratory response. However, by itself the antagonist produced a transient increase in arterial pressure and a slower increase in heart rate. The data support the involvement of the angiotensin AT_1 receptor in mediating the effects of exogenously administered angiotensin II but also indicate a possible role of angiotensin AT_2 receptors at the spinal level.

Keywords: Angiotensin; Heart rate; Arterial pressure; Spinal cord; Cardiovascular control; Losartan; PD 123319

1. Introduction

Angiotensin II plays an important role in maintaining fluid and electrolyte homeostasis and cardiovascular function by both peripheral and central actions. Despite some anatomical and morphological evidence that angiotensin II may play a role in regulation of sympathetic output at the spinal level (Galabov, 1992; Fuxe et al., 1976), physiological studies have largely neglected the possibility that angiotensin II can express effects on cardiovascular parameters via actions in the spinal cord (Yashpal et al., 1987, 1989), and in reviews on central effects of angiotensin II this central nervous system site has been largely overlooked (Ferguson and Wall, 1992; Ganten et al., 1978; Bunnemann et al., 1993; Timmermans et al., 1991, 1993; Muscha Steckelings et al., 1992; Smith et al., 1992). Previous experiments done in our laboratory indicated that angiotensin II, when administered intrathecally in the rat, causes increases in arterial pressure and heart rate which are prevented by block of nicotinic transmission in autonomic ganglia, suggesting that angiotensin II activates sympathetic mechanisms by a spinal action (Yashpal et al., 1987, 1989). As well, the data indicated that the effects of angiotensin II may be mediated via two different mechanisms, because a peptide antagonist, [Sar^1,Ile^8]angiotensin II, blocked the pressor but not the cardioacceleratory response (Yashpal et al., 1989). Two distinct types of angiotensin II receptor have been identified, termed AT_1 and AT_2 largely on the basis of studies using selective antagonists (Bunnemann et al., 1993; Timmermans et al., 1991, 1993; Muscha Steckelings et al., 1992; Smith et al., 1992). Therefore, the present study was undertaken to determine, using two non-peptide antagonists of angiotensin II receptors, losartan and PD 123319, whether two types of an-

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giotensin II receptor mediate the respective responses and which type of receptor is involved in expressing effects of angiotensin II on heart rate versus on arterial pressure. In addition, it was important to re-run the experiments with non-peptide antagonists in view of possible non-specific effects of [Sar^1,Ile^8]angiotensin II in the central nervous system (Gruber et al., 1992).

2. Materials and methods

2.1. Surgical preparation

Adult male Sprague-Dawley rats (275–350 g), obtained from Charles River Canada, were anesthetized with urethane (1.5 g/kg, i.p.). An intrathecal catheter (Intramedic PE-10) was passed through a slit in the dura at the atlanto-occipital junction and was positioned so that the inner tip lay at the ninth thoracic (T9) spinal level, corresponding to the principal level of sympathetic neurons to the adrenals (Cummings, 1969; Backman et al., 1990). Spinous processes were used as landmarks. Post mortem examination determined correct positioning of the catheter tip.

A second polyethylene cannula (Intramedic PE-50) was filled with heparinized saline (75 IU/ml in 0.9% NaCl) and inserted into the left common carotid artery with the tip positioned approximately at the level of the aortic arch. This catheter was then connected to a Statham transducer (Gould PE 23 ID) which was attached to a Grass P5 polygraph to monitor arterial pressure and heart rate. Heart rate was determined in beats per min (bpm) by counting the number of beats in a 10 s period and multiplying by 6. In some experiments, a third catheter (Intramedic PE-50) was inserted into the right femoral vein for intravenous (i.v.) injection of various drugs.

After surgical preparation and a period of 30 min to allow the animals to stabilize, five readings of arterial pressure and heart rate were taken over a period of 10 min and averaged to give baseline values. Agents were then administered intrathecally or intravenously with zero time being the end of administration of angiotensin II. Readings of arterial pressure and heart rate were taken each minute for 15 min and then at 20 and 30 min.

Rectal temperature was maintained at approximately 37°C with a heating pad. Each rat was used in only one experiment.

2.2. Intrathecal administration of angiotensin II

Angiotensin II (human) was purchased from Peninsula Laboratories (Lot No. 022661). The peptide was delivered over a period of 30–50 s at a dose of 10 μg, dissolved in 10 μl of artificial cerebrospinal fluid (CSF; an aqueous solution, in mM, of 128.6 NaCl, 2.6 KCl, 1.0 $MgCl_2$ and 1.4 $CaCl_2$; pH adjusted to 7.33). Following delivery of the peptide, the catheter was flushed with 10 μl of CSF (catheter volume was 6–8 μl). In control experiments, 10 μl of CSF replaced the angiotensin II solution.

2.3. Intravenous administration of losartan

The first series of pharmacological experiments with antagonists involved the use of the angiotensin AT_1 receptor antagonist, losartan potassium (DuP 753; MK 954; 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[(2′-(1*H*)-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole). It was provided by DuPont Pharmaceuticals. The antagonist was injected via the i.v. catheter, at a dose of 10 mg/kg, in a volume of 0.3 ml, 5 min prior to intrathecal administration of angiotensin II (10 μg); this dose of angiotensin II was chosen because previous reports have found this dose to be effective (DeGraaf et al., 1993; Brooks et al., 1992). The catheter was then flushed with 0.2 ml of saline (0.9% NaCl). The intravenous route was selected first because losartan has been reported to have access to the central nervous system upon systemic administration (Li et al., 1993; Song et al., 1991; Fregly and Rowland, 1991); this point is covered further in Section 4.

2.4. Intrathecal administration of losartan

In an attempt to determine whether effects of losartan were expressed at the spinal level, a further series of experiments was done giving the compound intrathecally. Thus, the angiotensin AT_1 receptor antagonist was given 2 min prior to injection of 10 μl of either CSF or angiotensin II (10 μg). The procedures were otherwise the same as above.

2.5. Intrathecal administration of PD 123319

In the final series of experiments the angiotensin AT_2 receptor antagonist, PD 123319-0121K, 1-[[4-(dimethylamino)-3-methylphenyl]methyl]-5-(diphenylacetyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine-6-carboxylic acid, ditrifluoroacetate, dihydrate, was given intrathecally. This compound was provided by Parke-Davis Pharmaceutical Research Divisions, Warner-Lambert. This AT_2 receptor antagonist was given 2 min prior to injection of 10 μl of either CSF or angiotensin II as above.

2.6. Statistical analysis

Results from each rat were tabulated as the change in systolic and diastolic arterial pressures and heart rate. Data were calculated as the change from the mean baseline values. Data for the figures were summarized by taking the mean ± S.E.M. of the values from each group of rats at each sample time following administration. These changes were analyzed by a *t*-test analysis (non-pairwise) compari-

son using SigmaStat. The level of statistical significance adopted was $P < 0.05$ and the confidence level was 90%.

3. Results

Intrathecal administration of angiotensin II had no effect on respiratory frequency, which remained at a mean value of approximately 100 breaths per min.

3.1. Effects of intrathecal administration of angiotensin II

Angiotensin II delivered at a dose of 10 μg to the ninth thoracic (T9) spinal level 2 min after intrathecal administration of CSF ($n = 10$) produced an increase in both arterial pressure and heart rate. Systolic and diastolic arterial pressures both increased rapidly, to peak at 2–3 min after administration (at 26.5 ± 5.2 and 26.2 ± 6.2 mmHg, respectively). By 15 min, the pressures had returned to preadministration levels (Fig. 1). Heart rate also increased rapidly following administration, but in this case the effect peaked at about 5 min. In addition, the response persisted throughout the experiment (Fig. 2). In rats given only CSF ($n = 6$), there was no significant change in systolic or diastolic pressure or in heart rate. The *t*-test analysis revealed that the data from the two groups of rats were significantly different: systolic pressure at 1–15 min (8–11, 14 and 15 min, $P < 0.05$, 1–7 min, $P < 0.01$), diastolic pressure at 1–10 min (9 and 10 min, $P < 0.05$, 1–8 min, $P < 0.01$). Heart rate was different between the two groups at 2–30 min (2 and 6–15 min, $P < 0.05$, 3–5, 20 and 30 min, $P < 0.01$). These effects are the same as those found in our earlier experiments (Yashpal et al., 1987, 1989) and thus confirm the reliability of angiotensin II administration for the following experiments.

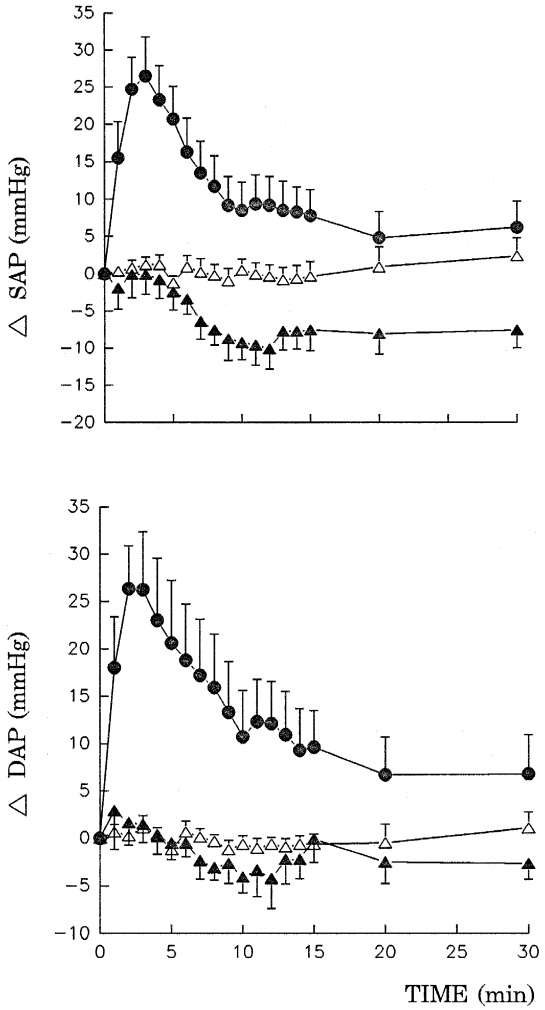

Fig. 1. Time–effect curve for the effects of intravenous administration of losartan on the systolic and diastolic arterial pressure responses to intrathecal administration of angiotensin II (10 μg) or CSF at T9. Losartan was given at a dose of 10 mg/kg. (●) CSF followed by angiotensin II ($n = 10$); (△) losartan followed by CSF ($n = 6$); (▲) losartan followed by angiotensin II ($n = 6$). Each ordinate represents the mean (±S.E.M.) change from the preadministration values of systolic arterial pressure (SAP) and diastolic arterial pressure (DAP). Zero time was the end of the second administration.

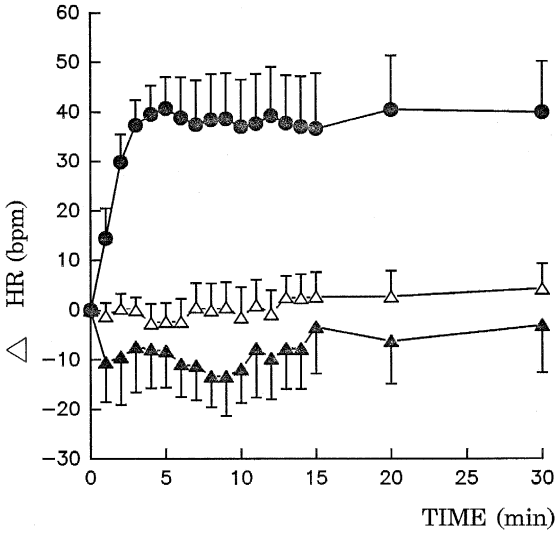

Fig. 2. Time–effect curve for the effects of intravenous administration of losartan on the heart rate response to intrathecal administration of angiotensin II (10 μg) or CSF at T9. Losartan was given at a dose of 10 mg/kg. (●) CSF followed by angiotensin II ($n = 10$); (△) losartan followed by CSF ($n = 6$); (▲) losartan followed by angiotensin II ($n = 6$). Each ordinate represents the mean (±S.E.M.) change from the preadministration values of heart rate (HR). Zero time was the end of the second administration.

3.2. Effects of intravenous administration of losartan on responses to angiotensin II

As losartan has been reported to have access to central nervous system tissue from the circulation, experiments were begun with a study to determine the effects of systemic administration of the antagonist on the effects of

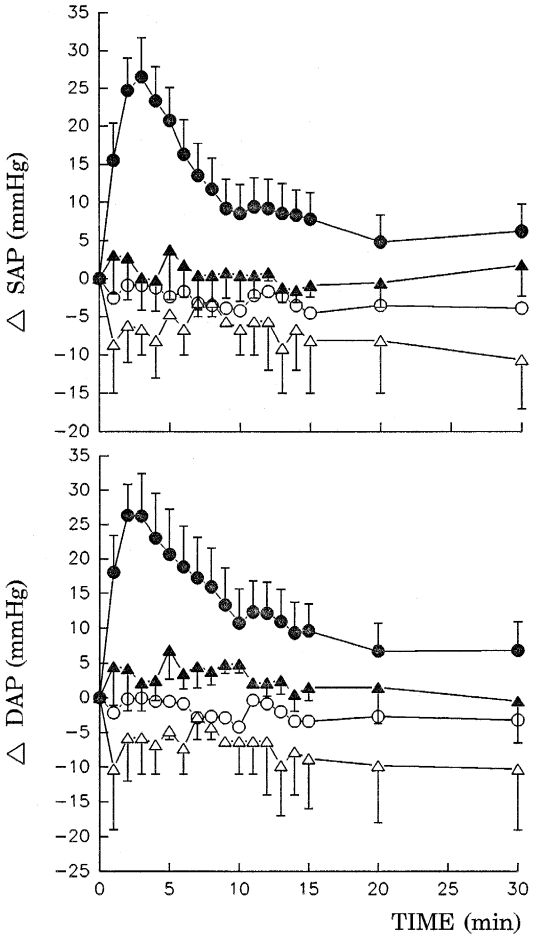

Fig. 3. Effects of pretreatment with CSF or with losartan, given intrathecally at a dose of 10 μg, on the change in arterial pressure in response to intrathecal administration of angiotensin II (10 μg) or CSF at T9. (○) CSF (two doses; $n = 6$); (●) CSF followed by angiotensin II ($n = 10$); (△) losartan followed by CSF ($n = 3$); (▲) losartan followed by angiotensin II ($n = 2$). Details are otherwise the same as in Fig. 1.

intrathecal administration of angiotensin II on systolic pressure, diastolic pressure and heart rate. Figs. 1 and 2 illustrate the effects of angiotensin II given 5 min after i.v. administration of 10 mg/kg of losartan ($n = 6$). In this case, the responses to angiotensin II administration were blocked by intravenous administration of losartan. The *t*-test analyses between the control angiotensin II group and the group pretreated with losartan were significantly different: systolic pressure was different at 1–30 min (14–30 min, $P < 0.05$, 1–13 min ($P < 0.01$), diastolic pressure was different at 1–13 min (1 and 9–13 min, $P < 0.05$, 2–8 min, $P < 0.01$) and heart rate was different at 1–30 min (1 min, $P < 0.05$, 2–30 min, $P < 0.01$).

In a control group in which losartan was given i.v. followed 5 min later by intrathecal administration of CSF ($n = 6$), there was no significant change in arterial pressure or heart rate from preadministration values (Figs. 1 and 2).

3.3. Effects of intrathecal administration of losartan on responses to angiotensin II

As systemically administered losartan could have expressed its effects via peripheral or spinal actions, an additional series of experiments was run, giving the antagonist intrathecally rather than i.v. Figs. 3 and 4 illustrate the effects of intrathecal administration of losartan on the cardiovascular responses to intrathecal administration of angiotensin II. Administration of 10 μg of losartan 2 min before angiotensin II was given ($n = 2$) blocked the pressor responses to angiotensin II; there was no significant difference between this group and the group given CSF alone. In pilot experiments this dose of losartan was found to optimally block pressor responses to intrathecal administration of angiotensin II.

However, the cardioacceleration induced by angiotensin II was not as obviously blocked; the increase in heart rate was delayed in onset compared to the response to angiotensin II following CSF administration. In this case, though, while the maximum change in heart rate was similar to that in the group given angiotensin II following CSF administration, the *t*-test revealed that administration of angiotensin II in the group pretreated with losartan did not differ from the group given CSF alone.

To determine whether the increase in heart rate in this case was due to angiotensin II or to losartan, a fourth group of rats was run in which losartan was given followed by CSF ($n = 3$). This group was not different from the group given CSF alone.

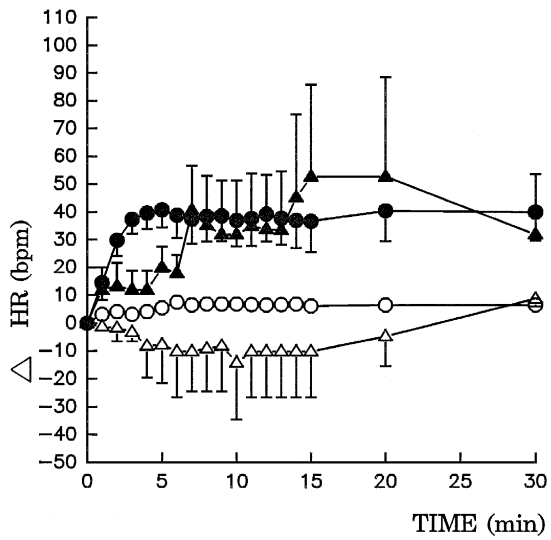

Fig. 4. Effects of pretreatment with CSF or with losartan, given intrathecally at a dose of 10 μg, on the change in heart rate in response to intrathecal administration of angiotensin II (10 μg) or CSF at T9. (○) CSF (two doses; $n = 6$); (●) CSF followed by angiotensin II ($n = 10$); (△) losartan followed by CSF ($n = 3$); (▲) losartan followed by angiotensin II ($n = 2$). Details are otherwise the same as in Fig. 2.

3.4. Effects of intrathecal administration of PD 123319 on responses to angiotensin II

Intrathecal administration of 10 μg of PD 123319 produced a rapid and transient increase in arterial pressure, as shown with the group given PD 123319 followed by intrathecal administration of CSF ($n = 8$; Fig. 5); this dose of PD 123319 was chosen from pilot studies in which lower doses were without any effect. In the group given angiotensin II 2 min after PD 123319 was given ($n = 7$), the pressure change was identical to the previous group. Thus, the *t*-test analysis showed that there was no difference between the two groups. However, there was also no difference between both groups given PD 123319 and the group described above which was given two intrathecal injections of CSF.

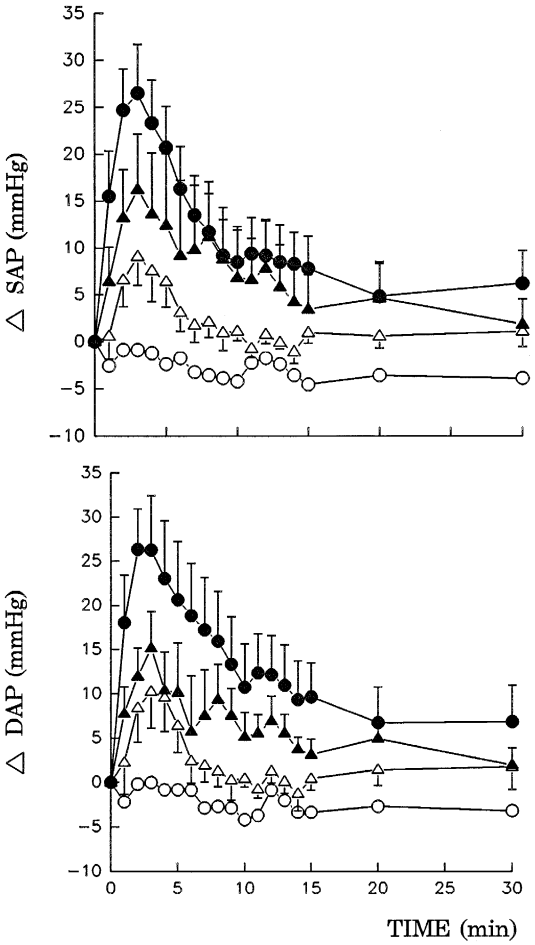

Fig. 5. Effects of intrathecal administration of PD 123319 on the systolic and diastolic arterial pressure responses to intrathecal administration of angiotensin II (10 μg) or CSF at T9. PD 123319 was given intrathecally at a dose of 10 μg. (○) CSF (two doses; $n = 6$); (●) CSF followed by angiotensin II ($n = 10$); (△) PD 123319 followed by CSF ($n = 8$); (▲) PD 123319 followed by angiotensin II ($n = 7$). For comparative purposes, the data from Fig. 1 representing the group given CSF followed by angiotensin II are included. Details are otherwise the same as in Fig. 1.

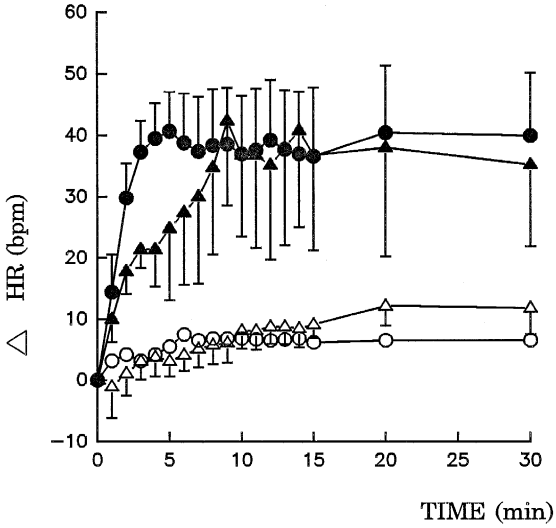

Fig. 6. Effects of intrathecal administration of PD 123319 on the heart rate response to intrathecal administration of angiotensin II (10 μg) or CSF at T9. PD 123319 was given at a dose of 10 μg. (○) CSF (two doses; $n = 6$); (●) CSF followed by angiotensin II ($n = 10$); (△) PD 123319 followed by CSF ($n = 8$); (▲) PD 123319 followed by angiotensin II ($n = 7$). Details are otherwise the same as in Fig. 2.

Heart rate was affected differently from arterial pressure (Fig. 6). The group given PD 123319 and then CSF showed a gradual increase in heart rate. However, the antagonist did not block the increase in heart rate produced by angiotensin II administration.

4. Discussion

The present data confirm excitatory effects of angiotensin II at the spinal level on sympathetic output to the vessels and to the heart. However, they also indicate a rather complex control of sympathetic output involving both angiotensin AT_1 and AT_2 receptors in the spinal cord. Thus, while systemic administration of the angiotensin AT_1 receptor antagonist, losartan, blocked the pressor and cardioacceleratory responses to intrathecal administration of angiotensin II, it blocked only the pressure effects when it was given intrathecally. Therefore, the block of the heart rate response by systemic administration could be due to a peripheral effect. A central site of action in the antagonism of the pressor response is consistent with the observation that losartan does not inhibit pressor responses to sympathetic nerve stimulation in the pithed rat (Ohlstein et al., 1992).

A central site for the block of the pressor response is supported by evidence which suggests that peripherally administered losartan has access to central neurons. It has been claimed that losartan does not cross the blood-brain barrier because dipsogenic and pressor responses to chronic i.c.v. administration of angiotensin II are not blocked by

systemic administration of losartan (Bui et al., 1992). However, this contradicts other evidence that systemic administration of losartan does block the dipsogenic effects of angiotensin II given i.c.v. (Fregly and Rowland, 1991). Further supporting the ability of losartan to cross the blood-brain barrier is evidence that systemic administration of losartan inhibits the responses of paraventricular nucleus neurons to local application of angiotensin II and to electrical stimulation of the subfornical organ in the rat (Li et al., 1993). Finally, i.v. administration of losartan inhibits subsequent binding of [Sar^1,Ile^8]angiotensin II in circumventricular organs, paraventricular hypothalamus, median preoptic nucleus and nucleus of the tractus solitarius (Song et al., 1991). Thus, multidisciplinary evidence supports the possibility that systemically administered losartan in the present study blocked the pressor effect of angiotensin II by an action in the spinal cord, although a peripheral action may also have occurred.

The effects of losartan are similar to those reported earlier from experiments using the peptide antagonist [Sar^1,Ile^8]angiotensin II (Yashpal et al., 1989). This antagonist, when given intrathecally, also blocked the pressor but not the cardioacceleratory effects of angiotensin. However, it caused a gradual increase in heart rate without altering baseline arterial pressure when it was administered alone intrathecally. In addition, the peptide antagonist did not block the cardioacceleratory response to angiotensin II administration (Yashpal et al., 1989). Therefore, the present data show that losartan and [Sar^1,Ile^8]angiotensin II differ somewhat in their properties; this is significant in view of the claim that in supraspinal structures the peptide antagonist occupies angiotensin AT_1 receptors (Rowe et al., 1992).

Our data from experiments with the angiotensin AT_2 receptor antagonist, PD 123319, indicate that it blocks the pressor response, because there was no difference between the groups administered the antagonist followed by either CSF or angiotensin II. On the other hand, the cardioacceleration resulting from intrathecal administration of angiotensin II was not blocked. This suggests a possible role of angiotensin AT_2 receptors in pathways to the vessels but not in those to the heart. In addition, the antagonist had effects similar to angiotensin II, in that given alone (in the group given the antagonist followed by CSF) a transient increase in systolic and diastolic pressures was observed along with a slowly developing but sustained increase in heart rate.

In peripheral tissues, AT_1 and AT_2 receptor subtypes seem to mediate the biological actions of angiotensin II via different signal transduction pathways. The angiotensin AT_1 receptor has been shown to interact with G proteins causing a decrease in cellular cAMP and a stimulation of inositol 1,4,5-trisphosphate (IP_3) (Tsutsumi et al., 1992; Tang et al., 1995; Chang et al., 1992; Raizada et al., 1993). The angiotensin AT_2 receptor, on the other hand, may interact with an inhibitory G protein and possibly stimulate protein phosphorylase 2A (Kang et al., 1994; Nahmias and Strosberg, 1995).

The rapid effects of angiotensin II in eliciting pressor and cardioacceleratory effects in the present study are consistent with earlier evidence of a role as a chemical mediator of synaptic transmission in spinal sympathetic pathways. Angiotensin II-like immunoreactive material is found in the thoracic lateral horn (Fuxe et al., 1976), specifically in nerve terminals making synaptic contact with neurons (Galabov, 1992). Angiotensin II-like immunoreactivity is absent in the lateral horn of rats transected spinally one week previously (Ganten et al., 1978) and this is consistent with the suggestion that the source of angiotensin II is descending fibers from magnocellular cells in diencephalic nuclei (Brownfield et al., 1982; Bains and Ferguson, 1995). Angiotensin II binding is observed in the spinal cord (Oldfield et al., 1994), as is angiotensinogen (Sood et al., 1990). Intrathecal administration of angiotensin II to the upper thoracic spinal cord elicits an increase in arterial pressure which is attenuated by intrathecal administration of peptide (Yashpal et al., 1989) and non-peptide (this study) antagonists. Thus, it appears that angiotensin II may be a chemical mediator of synaptic transmission onto spinal sympathetic neurons in pathways to the vessels and that both angiotensin AT_1 and AT_2 receptors mediate the effects of angiotensin II on arterial pressure. Finally, in view of the suggestion that losartan may be useful in the treatment of hypertension (DePasquale et al., 1992; Jablonskis et al., 1992; Mizuno et al., 1992; Toney and Porter, 1993), one of the sites at which it acts may be on spinal neurons.

Acknowledgements

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