Differential Effects of Central Angiotensin II and Substance P on Sympathetic Nerve Activity in Conscious Rats

Implications for Cardiovascular Adaptation to Behavioral Responses

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SUMMARY. The centrally induced effects of angiotensin II and substance P on the cardiovascular system and on neuronal efferent activity of the splanchnic, renal, and adrenal nerves were investigated in chronically instrumented conscious rats. The pressor responses to substance P injected into the lateral brain ventricle were accompanied by marked and short latency increases in heart rate, cardiac output, splanchnic, renal, and adrenal nerve activity, and a rise in plasma noradrenaline and adrenaline. Behaviorally, an arousal-type reaction was observed. In contrast, the pressor responses to intracerebroventricular angiotensin II were associated with initial decreases in heart rate, cardiac output, splanchnic, renal, and adrenal nerve activity, and a fall in plasma noradrenaline at the time of the maximal blood pressure increase. In some but not all animals, a second blood pressure peak associated with increases in heart rate and splanchnic nerve activity was observed after several minutes. Incomplete chronic sinoaortic baroreceptor deafferentiation prevented the angiotensin II-induced fall in heart rate but not the initial fall in splanchnic nerve activity. The decreases in splanchnic nerve activity also occurred in diabetes insipidus rats and persisted in Long Evans rats after vascular vasopressin receptor blockade with $d(CH_2)_5AVP$, despite marked reductions of the pressor responses in both groups. Peripheral α-adrenoceptor blockade with prazosin or ganglion blockade with hexamethonium inhibited the central angiotensin II pressor responses only in combination with vasopressin receptor blockade. On the other hand, either sympatholytic drug, alone, abolished the pressor responses in the diabetes insipidus rats. This indicates that in intact conscious rats the central pressor effects of angiotensin II are initiated by vasopressin release but become dependent on the sympathetic nervous system when vasopressin is absent or not effective. When rats were allowed to drink in response to angiotensin II, a further sharp rise in blood pressure occurred, together with increases in heart rate and splanchnic nerve activity. The results demonstrate fundamental differences in the mechanisms by which central pressor peptides can influence cardiovascular and autonomic function. It is conceivable that the distinct sympathetic response patterns to central angiotensin II and substance P receptor stimulation form part of a specific cardiovascular adjustment to the individual behavioral reactions, such as drinking, as in the case of angiotensin II, or arousal within the central processing of pain, as in the case of substance P. (*Circ Res 56: 563-575, 1985*)

THE octapeptide angiotensin (AII), a circulating vasopressor hormone, increases blood pressure not only by its effects on peripheral target organs but also by a direct action on the brain. The centrally mediated effects of AII include stimulation of vasopressin (AVP), oxytocin, and adrenocorticotropic hormone (ACTH) release from the pituitary gland, and induction of drinking behavior [for review, see Severs and Daniels-Severs (1973), Fitzsimons (1980), and Lang et al. (1983a)]. AII-sensitive sites can be reached from inside and outside the blood-brain barrier; these include the subfornical organ, the AV3V region, and the area postrema [for review, see Ferrario et al. (1972), Buckley and Jandhyala (1977), Ganten and Stock (1978), and Brody and Johnson (1980)].

The possible physiological and pathophysiological significance of the central effects of AII was underlined by the discovery of an active renin angiotensin system in the brain and its increased activity in the hypertensive state (Ganten et al., 1983). However, despite a wealth of experimental data, the hemodynamic consequences of central AII receptor stimulation are still not fully understood. Evidence has been presented that sympathetic stimulation, the release of AVP, and interference with the baroreceptor reflex can contribute to the central pressor actions of this peptide, but there is still uncertainty as to the relative significance and mutual interactions of these mechanisms. Investigations into the role of the sympathetic nervous system have yielded contradictory results. Increased, unchanged, or even decreased

sympathetic activity has been reported, depending on species, site of injection, and location of the sympathetic nerves from which the responses were recorded (Aars and Akre, 1968; Morrison and Pickford, 1969; Ferrario et al., 1972; Fukiyama, 1972; Severs and Daniels-Severs, 1973; Mann et al., 1982; Tobey et al., 1983; Stein et al., 1984). A differential regional involvement of sympathetic nerves in anesthetized dogs and cats has already been implied by Fukiyama (1972), Tobey et al. (1983), and Stein et al. (1984). A major reason for the discrepancies in the literature may be the fact that in none of the previous studies was sympathetic nerve activity assessed directly in conscious animals.

Substance P is a neuropeptide that exerts a variety of actions on the central and peripheral nervous system. It has been shown to stimulate neuronal activity and modulate synaptic transmission, and it may be a neurotransmitter involved in the processing of pain [for review, see Pernow (1983)]. Substance P has pressor actions when administered into the brain ventricular system [for review, see Pernow (1983)] and into the anterior and posterior hypothalamus (Unger et al., 1983). In contrast to AII, this peptide does not release AVP (Unger et al., 1981) and is not dipsogenic in the rat. Based on pharmacological evidence, it has been suggested that the central pressor actions of substance P are mediated by sympathetic stimulation (Unger et al., 1981; Petty and Reid, 1982).

In the present investigation, we compared the effects of central AII and substance P receptor stimulation after intracerebroventricular (icv) peptide injection on efferent splanchnic, renal, adrenal, and femoral nerve activity in rats. Particular attention was paid to the following questions: (1) How do the peptide-induced changes in these sympathetic nerves correlate with general changes in sympathetic activity, as evidenced by circulating catecholamines and the effect of pharmacological interference with the sympathetic nervous system? (2) Is the sympathetic response to central AII influenced by the concomitant release of AVP, and do changes in sympathetic activity gain importance for the central AII pressor actions in the absence of AVP? (3) What is the influence of the baroreceptor reflex on the sympathetic response to AII? (4) Is the sympathetic response modified by AII-induced drinking?

Our results provide evidence for distinct cardiovascular and sympathetic response patterns to centrally acting pressor peptides in awake animals. Substance P causes an arousal reaction with generalized sympatho-adrenal stimulation; AII, on the other hand, elicits a more complex reaction with uniform initial decreases in splanchnic, renal, and adrenal nerve activity and subsequent sympathetic stimulation in some animals, the latter being present in all animals if they are allowed to drink following the AII injection.

Methods

Experimental Animals and Procedures

Experiments were performed in conscious male Wistar rats (WI) weighing between 300 and 350 g (Thomae, Biberach, FRG). In experiment 5, male rats of the Brattleboro strain homozygous for hereditary hypothalamic diabetes insipidus (DI), together with Long Evans rats (LE), their genetic controls, were used. Both strains have been bred in Heidelberg since 1972.

Animals were kept under controlled conditions, with respect to temperature, humidity, and light period. For icv injections, chronic cannulas (PP20, Portex Corp.) were implanted into the lateral brain ventricle 1–2 weeks before, and arterial and venous catheters were inserted into the femoral artery and vein 1 or 2 days before the acute experiments. The surgical procedures have been described

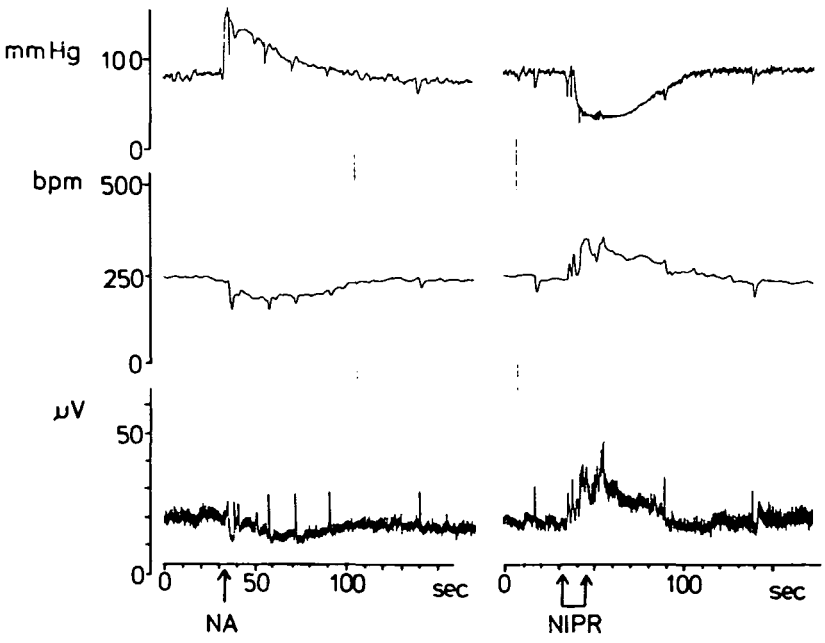

FIGURE 1. *Responses in mean arterial blood pressure (mm Hg), heart rate (beats/min), and mean rectified splanchnic nerve activity (μV) to 1 μg noradrenaline (NA), iv, and 1 μg sodium nitroprusside (NIPR), iv.*

previously (Unger et al., 1981). Measurements of mean arterial blood pressure (MAP) and heart rate were performed via the arterial line with a Statham P23Db pressure transducer, Gould Brush pressure coupler, and Gould Brush 2400 recorder.

Measurements of efferent sympathetic nerve activity were performed with chronic bipolar electrodes implanted 1 or 2 days before recording, using a modification of the method of Ricksten and Thoren (1980), as has been described elsewhere in detail (Unger et al., 1984). Splanchnic, renal, and adrenal nerve activities were recorded from separate groups of animals. The results are expressed in microvolts and represent mean rectified sympathetic nerve activity. The background level was defined as nerve activity measured 30 minutes after the animal was killed. A 24- to 36-hour recovery period was allowed after surgery until nerve recordings were performed in the animals' home cages. The animals were first challenged with intravenous injections of either 1 μg phenylephrine or noradrenaline and 1 μg sodium nitroprusside. Only those preparations showing the appropriate sympathetic responses (Fig. 1) were used in the experiments. At the time of recording, the rats had resumed their regular eating, drinking, and grooming habits, and did not exhibit any signs of stress or pain. In one experiment (experiment 7), nerve recordings were done under α-chloralose anaesthesia (50 mg/kg, iv) 1 day after surgery.

Experiment 1: Effect of icv AII on Blood Pressure, Heart Rate, Splanchnic Nerve Activity (SpNA), Renal Nerve Activity (RNA), and Adrenal Nerve Activity (ANA) in Conscious Rats

Rats (n = 10) were injected icv with 1-10-100 ng AII. Injections commenced after a 1-hour stabilization period. The next dose was given when blood pressure, heart rate, and SpNA had returned to control levels, with a minimum interval of 60 minutes between two injections. The injection volume was 5 μl (1 μl AII solution flushed with 4 μl 0.9% NaCl). An additional group of rats (n = 6) was injected with vehicle alone, to serve as controls. A second group of rats (n = 6) was injected icv with 100 ng AII. Blood pressure, heart rate, and RNA were recorded. A third group of rats (n = 4) was injected icv with 100 ng AII, as described above, and blood pressure, heart rate, and ANA were recorded. Rats were not allowed to drink during this experiment.

Experiment 2: Effect of icv Substance P on Blood Pressure, Heart Rate, and Splanchnic, Renal, and Adrenal Nerve Activity in Conscious Rats

Rats (n = 6) were injected icv with 1 μg substance P. Blood pressure, heart rate, SpNA (n = 6), RNA (n = 6), and ANA (n = 4) were recorded as described above.

Experiment 3: Effect of icv AII and Substance P on Cardiac Output in Conscious Rats

Rats instrumented with chronic brain cannulas and femoral artery catheters were implanted with a Thermistor probe (Mesecke), (external diameter, 0.6 mm) in the aortic arch, and a jugular vein cannula (PP25) with the tip lying at the entrance of the right atrium. The surgical procedures have been described previously in detail (Rascher et al., 1983). Following a recovery period of at least 4 hours after surgery, cardiac output was determined by computed automatic calculation of the dilution curve (HMV BN 7905, Hoyer Co.), after a bolus injection of 0.2 ml 0.9% NaCl at room temperature (20°–22°C) had been administered into the right atrium.

The animals were divided into three groups and injected icv with 100 ng AII (n = 6), 1 μg substance P (n = 6), or vehicle (n = 6). Blood pressure and heart rate were recorded and cardiac output was determined before, and 0.5, 2.5, 5, 10, and 15 minutes after the central injections.

Experiment 4: Effects of icv AII and Substance P on Plasma Catecholamines in Conscious Rats

Rats were prepared with chronic brain cannulas and arterial and venous catheters, and were injected icv with 100 ng AII (n = 8) or 10 μg substance P (n = 8), respectively. Control groups (n = 8 each) received icv injections of the vehicle. The 10-μg dose of substance P was found to produce slightly greater pressor responses than the 1-μg dose used in the previous experiments, but otherwise produced similar reactions (Unger et al., 1981). Blood (400 μl) was sampled through an extension of the arterial catheter from outside the cage 1 minute after AII, icv, and 5 minutes after substance P, icv. Sampling procedures and sample processing have been described previously in detail (Unger et al., 1984). Plasma noradrenaline and adrenaline concentrations were assayed by a modified radioenzymatic method (Da Prada and Zürcher, 1976).

Experiment 5: Blood Pressure, Heart Rate, and Splanchnic Nerve Activity after AII, icv, in LE and DI rats—Effect of Pharmacological Interference with Peripheral AVP Receptors and the Sympathetic Nervous System

LE rats (n = 6) were prepared for SpNA recording, and AII (100 ng) was injected icv, as described above. In a second group (n = 6), the experiment commenced with an intravenous (iv) bolus injection of 100 ng AVP. After blood pressure had returned to control levels, 10 μg/kg of the vascular AVP receptor antagonist $d(CH_2)_5AVP$ was injected iv, and the iv AVP injection was repeated to test for peripheral AVP receptor blockade. Five minutes later, AII (100 ng) was injected icv. In some animals, the peripheral AVP injection was repeated once again when the AII pressor response had subsided, to ensure continuous peripheral AVP receptor blockade during the experiment. DI rats (n = 11) were prepared for SpNA recording, as described above. AII (100 ng) was injected icv, and blood pressure, heart rate, and SpNA were recorded. Before the AII injection, rats were allowed to drink ad libitum to ensure adequate hydration.

The second part of this experiment was designed to investigate the role of the sympathetic nervous system for the central pressor responses to AII in the absence of AVP-mediated vasoconstriction.

Groups of DI (n = 10) and LE (n = 8) rats were prepared for blood pressure recording only. In the DI rats, experiments were performed on two consecutive days. On day 1, the animals were injected icv with 100 ng AII. After return of blood pressure to control levels, an infusion of prazosin (100 μg/kg per min) was started. Ten minutes later, the rats received an iv injection of 1 μg phenylephrine to test the degree of peripheral α_1-adrenoceptor blockade, and the icv injection of AII was repeated. On the second day, the animals were pretreated iv with hexamethonium (9 mg/kg bolus injection, followed by an infusion of 600 μg/kg per min), and were injected icv with 100 μg AII 10 minutes after the infusion was begun. Rats were allowed to drink during the stabilization period before AII

injections. In the LE rats, as in DI rats, experiments were performed on days 1 and 2. On day 3, the animals were injected iv with 10 μg/kg of the vascular AVP receptor antagonist $d(CH_2)_5AVP$ after an initial control injection with 100 ng AII, icv. Blockade of the peripheral vascular AVP receptors was tested with 100 ng AVP, iv, and 5 minutes later, the icv injection of AII was repeated. When blood pressure had returned to control levels, a prazosin infusion was started as on the first day, and the icv AII injection was repeated under combined AVP and α_1-adrenoceptor blockade.

Experiment 6: Effect of icv AII on Blood Pressure, Heart Rate, and Splanchnic Nerve Activity in Conscious Chronically Baroreceptor-Denervated Rats

To investigate the possibility that the AII-induced changes in sympathetic discharge were due to baroreceptor reflex activation, we performed baroreceptor denervation (n = 6) by bilateral sinoaortic deafferentiation (SAD) according to the method of Krieger (1964) 4 weeks before the experiment, as described previously (Rascher et al., 1983). The area of carotid bifurcation was exposed in sham-operated controls (n = 6). The animals were prepared for SpNA recordings as described above. The experiment was started with iv injections of 1 μg phenylephrine and 1 μg sodium nitroprusside to test the completeness of SAD. Rats then were injected with 100 ng AII, icv, as described above.

Experiment 7: Effect of icv AII on Blood Pressure, Heart Rate, and Splanchnic and Femoral Nerve Activity (FNA) in α-Chloralose Anesthetized Rats

Rats (n = 6) were prepared for SpNA recordings as described above. In a second group (n = 6), the inguinal area contralateral to the side where the femoral catheters had been inserted was exposed. Usually, three branches of the femoral nerve could be isolated in the vicinity of the femoral artery and vein. The branch yielding the best signal was used. Tests with phenylephrine and sodium nitroprusside for sympathetic activity yielded weak but measurable responses. Since the recorded nerve activity was dominated by bursts originating from motor fibers within the nerve bundle, the injections of AII (100 ng, icv) were performed in both groups under α-chloralose anesthesia 1 day after surgery. The SpNA recordings in this experiment served as control for the effect of anesthesia on the central AII effects, since recordings of sympathetic nerve activity in the other experiments all were done in conscious animals.

Experiment 8: Effect of AII-Induced Drinking on Blood Pressure, Heart Rate, and Splanchnic Nerve Activity in Rats

Rats (n = 6) were prepared for SpNA recording as described above. A small pot filled with tap water was placed into the cage and the animals were allowed to drink during the experiment. AII (100 ng) was injected icv as usual. Blood pressure, heart rate, and SpNA were recorded for 1 hour after the central application of AII.

Drugs

Angiotensin II (AII) and substance P were purchased from Bachem, Bubendorf, Switzerland, arginine vasopressin (AVP) was from Serva, Heidelberg, FRG, phenylephrine was from Sigma, München, FRG, and sodium nitroprusside was from Merck, Darmstadt, FRG. The vascular AVP antagonist $d(CH_2)_5AVP$ was kindly provided by Dr. M. Manning, Toledo, Ohio, and prazosin was provided by Pfizer, Karlsruhe, FRG. Hexamethonium bromide was purchased from Serva, Heidelberg, FRG. All drugs except prazosin were dissolved in isotonic saline and diluted to the appropriate concentrations before use. Prazosin was dissolved in a solution containing 5% glycerol and 5% glucose.

Statistics

Results are reported as means ± SEM. For statistical evaluation, Student's t-test was used for paired and unpaired observations, and BMDP7D analysis of variance (ANOVA) with Bonferroni's method of multiple pairwise comparison was used, when appropriate. A significance level of $P < 0.05$ was accepted.

Results

Experiment 1

Effect of icv AII on Blood Pressure, Heart Rate, SpNA, RNA, and ANA (Table 1, Figs. 2–4)

The icv injection of AII at doses of 1, 10, and 100 ng increased blood pressure with a latency of 15–20 seconds after the injection, and a maximum after 1–

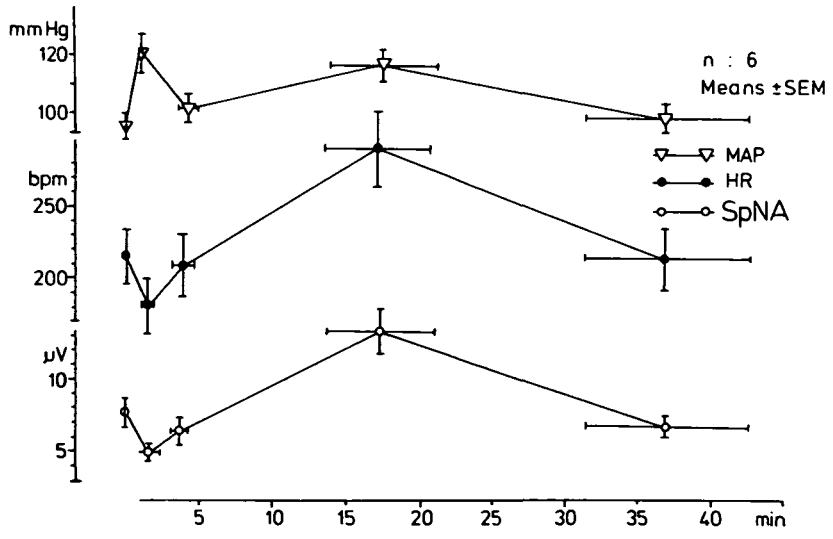

FIGURE 2. *Biphasic responses in mean arterial blood pressure (MAP, mm Hg), heart rate (HR, beats/min), and mean rectified splanchnic nerve activity (SpNA, μV) to 10 ng AII, icv, in a group of conscious rats (n = 6). Note the time course of events with the rapid initial fall in heart rate and nerve activity and the late increase with a maximum about 17 minutes after the AII injection. The latter was not seen in all animals tested (n = 10).*

TABLE 1
Effect of icv AII on Blood Pressure, Heart Rate, and Efferent Sympathetic Nerve Activity in Conscious Rats

Dose		Responses: Baseline	Responses: Maximal response	Responses: % Change in nerve activity	Time: Latency (sec)	Time: Max (min)	Time: Return (min)
			Splanchnic nerve				
1 ng	MAP	93.3 ± 4.4	+17.5 ± 2.1*		15 ± 2	1.9 ± 0.4	11.8 ± 2.5
$n = 10$	HR	235 ± 17	−12 ± 21		30 ± 14	2.1 ± 0.3	4.8 ± 0.7
	SpNA	7.8 ± 1.1	−1.9 ± 1	(−24)	21 ± 5	2.0 ± 0.4	3.7 ± 0.6
10 ng	MAP	95.5 ± 5.0	+25.0 ± 2.6*		15 ± 2.2	1.2 ± 0.1	20.2 ± 4.8
	HR	218 ± 19	−38 ± 6*		21.7 ± 4	1.6 ± 0.4	7.5 ± 1.1
	SpNA	7.9 ± 1.0	−4.8 ± 0.6†	−60	26 ± 8	1.7 ± 0.8	5.3 ± 1.2
100 ng	MAP	100.0 ± 5.0	+22.5 ± 2.1†		18 ± 5	1.4 ± 0.1	29.5 ± 3.7
	HR	220 ± 23	−42 ± 3†		25 ± 7	4.9 ± 1.4	14.8 ± 3.5
	SpNA	8.1 ± 0.9	−3.5 ± 0.7†	−43	18 ± 3	6.6 ± 3.3	11.5 ± 1.9
			Renal nerve				
100 ng	MAP	90.0 ± 3.4	+28.3 ± 5.3*		23 ± 2	1.1 ± 0.2	
$n = 6$	HR	220 ± 25	−62 ± 13†		25 ± 8	4.3 ± 1.6	
	RNA	13.0 ± 1.6	−4.7 ± 1.1†	−36	30 ± 5	2.6 ± 1.0	
			Adrenal nerve				
100 ng	MAP	86.3 ± 6.3	+30.0 ± 2.04*		30 ± 1	1.0 ± 0.1	
$n = 4$	HR	283 ± 35	−55 ± 5‡		40 ± 7	5.8 ± 1.6	
	ANA	14.3 ± 0.9	−2.5 ± 0.7‡	−18	53 ± 8	5.8 ± 0.5	

Results are expressed as means ± SEM; MAP, mean arterial blood pressure (mm Hg); HR, heart rate (beats/min); SpNA: splanchnic nerve activity (μV); RNA, renal nerve activity (μV); ANA: adrenal nerve activity (μV).
* $P < 0.001$, † $P < 0.01$, ‡ $P < 0.05$, when compared with control values before AII injection.

2 minutes. In some animals, a second smaller peak was noted after 13–17 minutes. The initial peak was accompanied by a fall in heart rate and a marked decrease in SpNA of −24% after 1 ng, −60% after 10 ng, and −43% after 100 ng AII. The second peak, if present, usually was associated with increases in heart rate and SpNA, as shown in Figure 2. Control injections of the vehicle (0.9% NaCl) did not produce any significant changes of the parameters measured.

The fall in sympathetic activity associated with the initial pressor peak was also observed in the renal and adrenal nerves (Table 1). Representative recordings are shown in Figures 3 and 4.

Experiment 2

Effect of icv Substance P on Blood Pressure, Heart Rate, and Splanchnic, Renal, and Adrenal Nerve Activity (Table 2; Figs. 3 and 4)

The icv injection of 1 μg substance P increased blood pressure with a latency of about 1 minute, the

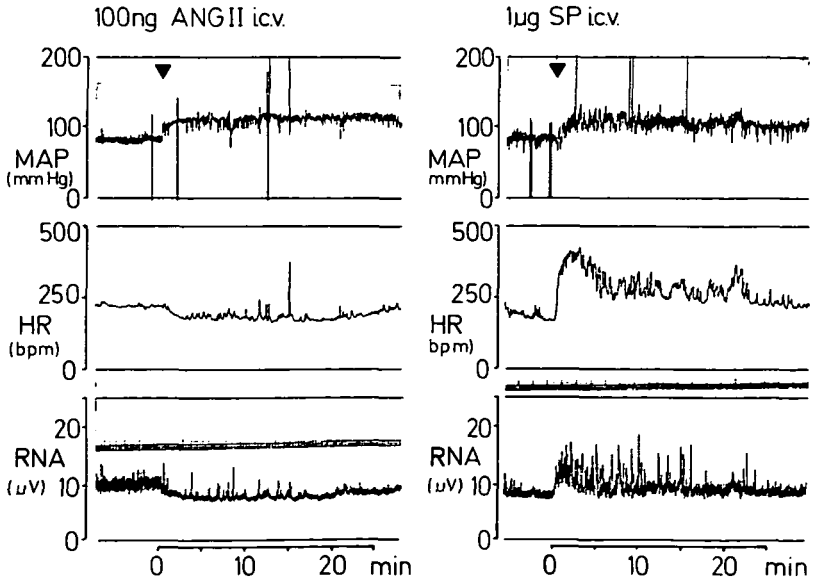

FIGURE 3. *Representative recordings of the changes in mean arterial blood pressure (MAP), heart rate (HR), and mean rectified renal nerve activity (RNA) after central AII and substance P injections in conscious rats.*

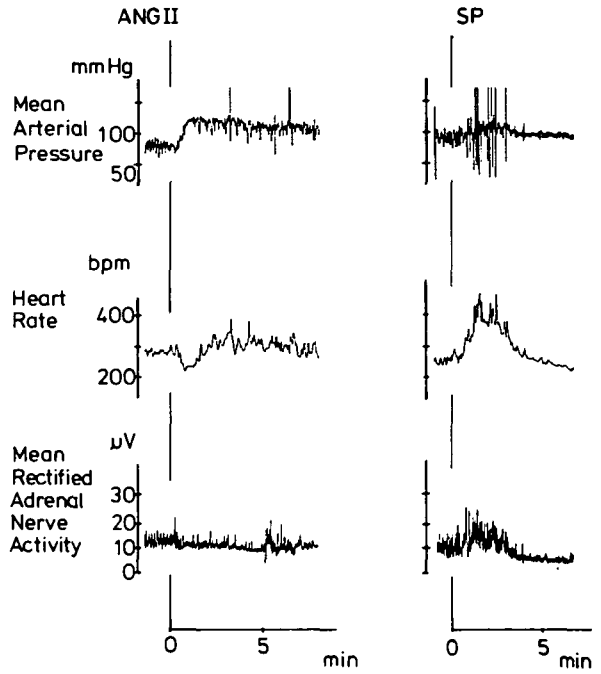

FIGURE 4. *Representative recordings of the changes in blood pressure (MAP), heart rate (HR), and adrenal nerve activity (ANA) after icv injections of AII (100 ng) and substance P (1 μg) in conscious rats.*

peak was reached after about 5 minutes. This response was accompanied by a marked rise in heart rate, SpNA, RNA, and ANA. Representative recordings are shown in Figures 3 and 4. In all instances, the rises in heart rate and sympathetic nerve activity preceded the blood pressure increases. A behavioral arousal reaction, with enhanced locomotion, grooming, and scratching, was usually associated with the pressor response.

Experiment 3

Effect of icv AII, and Substance P on Cardiac Output (Table 3)

After the injection of 100 ng AII, icv, cardiac output tended to fall; however, this change did not achieve statistical significance until 2.5 minutes had elapsed. The calculated total peripheral resistance was increased throughout the observation period. In contrast, substance P (1 μg icv) produced an early increase in cardiac output (30 seconds), which was no longer significant after 5 minutes. The calculated total peripheral resistance remained unchanged throughout the observation period.

Experiment 4

Effects of icv AII and Substance P on Plasma Catecholamines (Fig. 5)

Plasma catecholamines, measured at the time of the respective pressor peaks, were influenced differently by the two peptides. After the injection of 100 ng AII, icv, noradrenaline was reduced by 34% and adrenaline remained unchanged, compared to saline-injected controls. Substance P (10 μg icv) increased noradrenaline by 65% and adrenaline by 302%.

Experiment 5

Blood Pressure, Heart Rate, and Splanchnic Nerve Activity after icv AII, in LE and DI Rats: Effects of Peripheral Interference with AVP Receptors and α_1-Adrenoceptors, and of Ganglion Blockade (Table 4; Fig. 6)

Injection of 100 ng AII, icv, produced the same pattern of changes in LE rats as observed in WI rats

TABLE 2
Effect of icv Substance P (1 μg) on Blood Pressure, Heart Rate, and Efferent Sympathetic Nerve Activity in Conscious Rats

		Responses			Time		
		Baseline	Maximal response	% Change in nerve activity	Latency (sec)	Max (min)	Return (min)
				Splanchic nerve			
$n = 6$	MAP	88.3 ± 4.0	+29.2 ± 3.6*		54 ± 18	5.3 ± 0.3	25.7 ± 4.3
	HR	292 ± 39	+128 ± 14*		48 ± 12	5.3 ± 0.9	26.2 ± 4.1
	SpNA	8.0 ± 1.2	+6.8 ± 0.6*	+85	36 ± 6	4.8 ± 0.9	24.8 ± 3.8
				Renal nerve			
$n = 6$	MAP	85.0 ± 3.9	+24.2 ± 2.7*		55 ± 5	3.8 ± 0.5	
	HR	268 ± 26	+145 ± 27*		35 ± 5	2.8 ± 0.5	
	RNA	13.3 ± 1.7	+19.5 ± 6.7*	+147	35 ± 5	2.3 ± 0.5	
				Adrenal nerve			
$n = 4$	MAP	92.5 ± 1.4	+23.8 ± 3.8*		53 ± 14	3.8 ± 0.3	
	HR	273 ± 21	+168 ± 20*		29 ± 11	2.6 ± 0.5	
	ANA	10.8 ± 1.5	+6.8 ± 1.4*	+63	33 ± 10	2.6 ± 0.2	

Results are expressed as means ± SEM; abbreviations as defined in footnote to Table 1.
* $P < 0.001$, compared with control values before substance P injection.

TABLE 3
Effect of icv AII and Substance P on Cardiac Output and Total Peripheral Resistance in Conscious Rats ($n = 6$)

		Control before injection	Responses to AII/SP 30 sec	2.5 min	5 min	10 min	15 min after injection
AII (100 ng)	MAP	96.4 ± 2.7	+26.0 ± 2.8‡	+27.3 ± 3.5‡	+23.7 ± 3.2‡	+18.3 ± 3.9‡	+18.0 ± 3.7‡
	CO	120.8 ± 11.2	−16.3 ± 7.8	−27.2 ± 5.6*	−22.0 ± 4.1	−19.1 ± 6.2	−21.6 ± 3.0
	TPR	086 ± 0.08	0.06 ± 0.2†	+0.7 ± 0.2†	+0.5 ± 0.1†	+0.5 ± 0.2†	+0.4 ± 0.1†
SP (1 μg)	MAP	80.4 ± 8.3	+19.0 ± 1.3‡		+16.0 ± 2.6‡	+6.7 ± 2.4*	+4.0 ± 1.6
	CO	154.8 ± 25.7	+106.6 ± 31.8†		+37.6 ± 16.2	+9.9 ± 18.7	+4.2 ± 11.5
	TPR	0.56 ± 0.09	−0.15 ± 0.01		−0.04 ± 0.05	−0.02 ± 0.06	−0.02 ± 0.06
Saline	MAP	82.0 ± 7.5	+1.7 ± 1.7	+1.7 ± 1.0	+0.7 ± 1.0	−0.3 ± 1.3	−2.0 ± 2.3
	CO	142.7 ± 17.0	+2.0 ± 10.7	+0.8 ± 9.8	−0.3 ± 9.8	+4.5 ± 7.9	−3.3 ± 7.9
	TPR	0.58 ± 0.07	−0.02 ± 0.02	−0.02 ± 0.02	−0.02 ± 0.02	−0.02 ± 0.03	−0.02 ± 0.02

Results are expressed as means ± SEM; MAP, mean arterial blood pressure (mm Hg), CO, cardiac output (ml/min); TPR, total peripheral resistance (mm Hg·min/ml); Statistics: ANOVA with Bonferroni's multiple pairwise comparison.
* $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$.

in the previous experiments. Intravenous pretreatment with the vascular AVP receptor antagonist $d(CH_2)_5AVP$ abolished the pressor responses to 100 ng AVP, iv (43.4 ± 4.8 mm Hg vs. 1.3 ± 0.8 mm Hg). The pressor responses to 100 ng AII, icv, were reduced from 22.0 ± 2.0 mm Hg in the control group to 14.2 ± 0.8 mm Hg in the AVP antagonist-pretreated group, whereas the corresponding changes in heart rate and SpNA were not significantly different between the two groups (Fig. 6). In the DI rats, the pressor response to 100 ng AII, icv, was 11.4 ± 2.7 mm Hg (Fig. 6). The changes in heart rate and SpNA were not uniform. In 9 of 11 animals, a decrease in heart rate (−54.4 ± 9.9 beats/min) and a dramatic fall in SpNA (−9.0 ± 2.2 μV) were observed, whereas, in two animals, heart rate increased by +30 and +40 beats/min and SpNA increased by +10 and +13 μV.

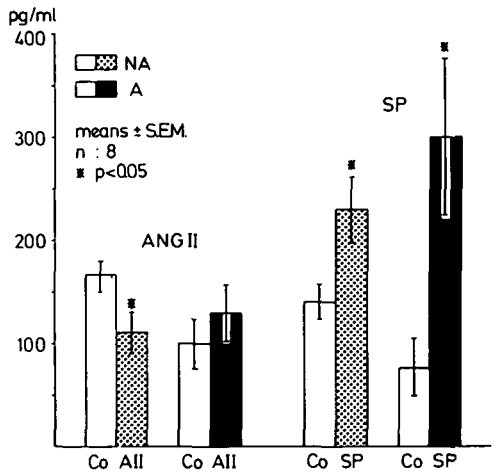

FIGURE 5. *Effect of icv injections of 100 ng AII (left) and 10 μg substance P (right) on plasma catecholamines in conscious rats. NA, noradrenaline; A, adrenaline; Co, control vehicle injections; ANG II, angiotensin II; SP, substance P.*

The effects of peripheral vascular AVP receptor, α_1-adrenoceptor, and ganglion blockade are summarized in Table 4. At the time of the icv AII injection, the pressor responses to iv AVP were completely blocked in the $d(CH_2)_5AVP$-pretreated animals, as were the pressor responses to iv phenylephrine after prazosin pretreatment. In the LE rats, peripheral AVP receptor blockade reduced the pressor responses to 100 ng AII by 60%, whereas peripheral α_1-adrenoceptor blockade did not have a significant effect, and ganglion blockade even potentiated the AII pressor responses. However, combined pretreatment with $d(CH_2)_5AVP$ and prazosin completely prevented the central AII pressor responses. In the DI rats, prazosin or hexamethonium each practically eliminated the central pressor responses to AII.

Experiment 6

Effect of icv AII on Blood Pressure, Heart Rate, and Splanchnic Nerve Activity in Conscious Chronically Baroreceptor-Denervated (SAD) Rats (Table 5; Figs. 7 and 8)

In the SAD rats, the heart rate and SpNA responses to iv phenylephrine and iv sodium nitroprusside were markedly reduced but not totally abolished, compared to sham-operated controls, indicating that the denervation was not complete (Table 5). After injection of 100 ng AII, icv, the pressor responses were potentiated to 49.2 ± 10.3 mm Hg ($p < 0.05$) in the SAD rats, whereas heart rate remained unaltered. The fall in SpNA persisted in the same magnitude as in the sham-operated controls (−3.83 ± 0.84 μV, Fig. 7). A representative recording is shown in Figure 8.

TABLE 4
Effect of Blockade of Peripheral α_1-Adrenoceptors, Vascular AVP Receptors, and of Ganglion Blockade on the Pressor Responses to 100 ng AII, icv, in Conscious Rats

	Blood pressure responses						
	Day 1				Day 2		
	Baseline MAP	AII, icv	Prazosin, iv	AII Prazosin, iv	Baseline MAP	Hexamethonium, iv	AII, icv Hexamethonium, iv
LE $n = 8$	88 ± 5	+24 ± 3	−14 ± 2	+20 ± 2	83 ± 7	−22 ± 2	+47 ± 9*
DI $n = 10$	90 ± 4	+7 ± 2	−15 ± 1	+2 ± 1†	88 ± 3	−24 ± 2	+1 ± 1†

	−Blood pressure responses, Day 3					
	Baseline MAP	AII, icv	$(CH_2)_5$AVP, iv	AII, icv d$(CH_2)_5$AVP, iv	Prazosin, iv	AII, icv $(CH_2)_5$AVP + prazosin, iv
LE $n = 8$	88 ± 4	+25 ± 4	−8 ± 2	+10 ± 2†	−13 ± 2	±0

Results are expressed as means ± SEM; MAP, mean arterial blood pressure (mm Hg); LE, Long Evans rats; DI, diabetes insipidus rats. Doses were: AII, 100 ng, icv; prazosin, 100 μg/kg per min, iv; hexamethonium, 12 mg/kg + 600 μg/kg per min, iv.
* $P < 0.05$; † $P < 0.01$, compared with AII control injections.

Experiment 7

Effect of icv AII on Blood Pressure, Heart Rate, and Splanchnic and Femoral Nerve Activity (FNA) in α-Chloralose-Anesthetized Rats (Table 6)

Under α-chloralose anesthesia, the central effects of AII on blood pressure and heart rate were shortened and reduced, compared to those in conscious rats (cf Table 1). The fall in SpNA was reduced but present in all animals. In contrast, FNA was found to increase in four of six rats tested, being unchanged in the two remaining animals. The onset of the increase in FNA was later than the onset of the pressor response (Table 6).

Experiment 8

Effect of AII-Induced Drinking on Blood Pressure, Heart Rate, and Splanchnic Nerve Activity in Rats (Fig. 9)

When rats were allowed to drink after an icv injection of 100 ng AII, a further rise in blood pressure (+12.5 ± 1.1 mm Hg) of rapid onset was observed in all animals. Heart rate and SpNA, both of which decreased immediately after the AII injection, recovered quickly, and rose to above control levels during the drinking response (+120.0 ± 18.9 beats/min and +2.83 ± 0.57 μV, respectively). A representative recording is shown in Figure 9.

Discussion

Differences between AII and Substance P

A consistent and unexpected feature of this study was the initial fall in splanchnic, renal, and adrenal sympathetic nerve activity immediately after the central injection of AII in conscious rats. A generalized sympathetic stimulation must therefore be ruled out as an initiating factor for the central pressor action of this peptide in rats. The additional finding of a decrease in heart rate and plasma noradrenaline at the time of the AII-induced pressor peak, and the

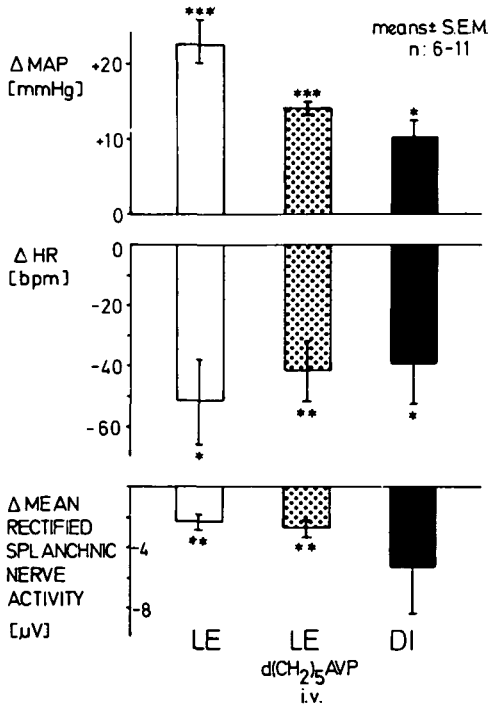

FIGURE 6. *Maximum responses in blood pressure (MAP), heart rate (HR), and splanchnic nerve activity to 100 ng AII, icv, in conscious Long Evans (LE) rats (n = 6 each group) and diabetes insipidus (DI) rats (n = 11). The columns in the middle depict the respective changes in LE rats after intravenous (iv) pretreatment with the vascular vasopressin receptor antagonist d$(CH_2)_5$ AVP. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.*

TABLE 5
Effect of Chronic Sinoaortic Deafferentiation (SAD) on Blood Pressure, Heart Rate, and Sympathetic Nerve Responses to iv Phenylephrine and Sodium Nitroprusside in Conscious Rats

		SAD			Sham		
		Baseline	Response	Response per mm Hg Δ MAP	Baseline	Response	Response per mm Hg Δ MAP
PE	MAP	97.0 ± 1.2	+51.0 ± 7.3*		106.7 ± 3.8	+35.8 ± 1.5	
(1 μg iv)	HR	324.0 ± 17.8	−48.0 ± 2.0†	0.94	302 ± 21.8	−88.0 ± 4.9	2.46
	SpNA	9.2 ± 0.6	−1.6 ± 0.4*	0.03	12.8 ± 1.4	−4.3 ± 1.2	0.12
NIPR	MAP	99.1 ± 1.0	−55.0 ± 1.6*		105.8 ± 4.0	−42.5 ± 5.0	
(1 μg, iv)	HR	310.0 ± 22.6	+74.2 ± 17.8*	1.35	270.0 ± 22.2	+118.3 ± 14.5	2.78
	SpNA	9.4 ± 0.9	+2.9 ± 1.2*	0.05	12.0 ± 1.2	+11.0 ± 2.7	0.26

Results are expressed as means ± SEM; $n = 6$ per group. MAP, mean arterial blood pressure (mm Hg); HR, heart rate (beats/min); SNA, splanchnic nerve activity (μV); PE, phenylephrine; NIPR, sodium nitroprusside.
* $P < 0.05$, † $P < 0.01$, compared with sham-operated group.

fact that pharmacological interference with the sympathetic nervous system in the periphery had little influence on the pressor response to AII (prazosin), or even potentiated it (hexamethonium), support this conclusion.

The response pattern to AII was in contrast with that observed after substance P. Central pressor effects comparable to AII were associated with marked increases in heart rate, SpNA, RNA, ANA, and circulating catecholamines. Together with previous findings that the substance P-induced blood pressure increases could be completely prevented by peripheral α_1-adrenoceptor blockade (Unger et al., 1981), or antagonized by ganglionic blockade (Petty and Reid, 1982), this result indicates that substance P increases blood pressure centrally by a generalized sympathetic stimulation. When applied directly to the hypothalamus, SP causes a rise in blood pressure (Unger et al., 1983) and augments hypothalamic blood flow (Klugman et al., 1980). The latter effect was abolished by a variety of procedures, including central chemical sympathectomy with 6-hydroxydopamine, central adrenoceptor or cholinoreceptor blockade, or destruction of a so-called intracerebral noradrenergic pathway.

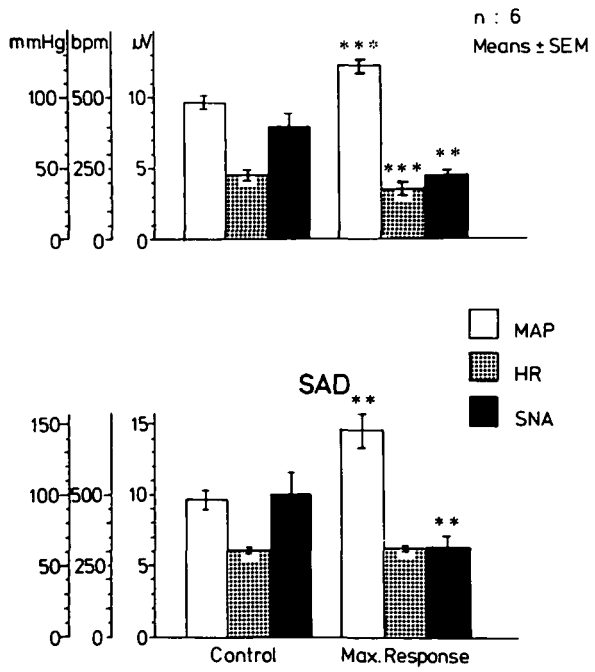

FIGURE 7. *Responses in mean arterial blood pressure (MAP), heart rate (HR), and mean rectified splanchnic nerve activity (SpNA) to 100 ng AII, icv, in sham-operated (top) and chronically sinoaortic-denervated (SAD, bottom) conscious rats.* $^{**}P < 0.01$, $^{***}P < 0.001$.

It is therefore, conceivable that some neuropeptides such as SP could exert their central cardiovascular actions by changing blood flow in discrete cardiovascular control centers of the brain, thereby changing the function of, e.g., hypothalamic circuits, whereas such a mechanism seems less likely for angiotensin.

In contrast to AII, SP has not been found to release AVP when applied centrally (Unger et al., 1981), although increases in vasopressinergic neuron activity in the nucleus supraopticus after intraventricular injection of SP have been reported (Clarke et al., 1980). However, we have observed a selective dose-dependent release of the stress-related (Lang et al., 1983b) neurohormone oxytocin from the pituitary gland after icv injections of substance P (Unger et al., 1983).

Differences between the two peptides were also found with respect to their effects on cardiac output and total peripheral resistance. AII decreased cardiac output and increased total peripheral resistance, whereas substance P produced a short-lasting initial rise in cardiac output.

Thus, in agreement with previous results obtained in mongrel dogs by Ferrario et al. (1972) and Brosnihan et al. (1979), central AII increases blood pressure in the rat by a rise in total peripheral resistance, rather than by an increase in cardiac output as was observed with substance P.

Evidence for Sympathetic Activation following Central AII

Our finding of reduced abdominal sympathetic activity appears to be at variance with a number of

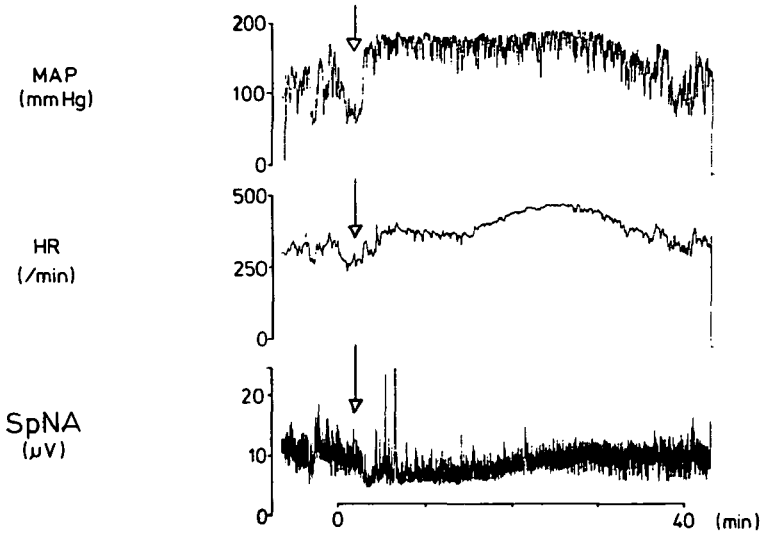

FIGURE 8. *Representative recording of the changes in mean arterial blood pressure (MAP), heart rate (HR), and mean rectified splanchnic nerve activity (SpNA) after injection of 100 ng AII, icv, in a conscious rat 4 weeks after sinoaortic denervation (SAD). Note the lability of the basal blood pressure and the marked pressor response associated with a rise in heart rate and a fall in SpNA.*

previous reports, including our own, in several species including the rat, rabbit, cat, dog, and monkey, in which neurally mediated vasoconstriction was postulated to be responsible for at least part of the increase in blood pressure after central administration of AII [for review, see Severs and Daniels-Severs (1973), Brody and Johnson (1980), and Schölkens et al. (1983)].

However, most of these discrepancies can be explained by the lack of directly obtained data on sympathetic nerve activity in conscious animals, and by factors such as anesthesia, dose, and route of administration of AII, time of measurements or sampling, and different species used in the various experiments. For instance, in the dog, not only do the central AII-sensitive sites appear to be different from those in rats, but also the sympathetic contribution to the central AII pressor effects may be greater (Severs and Daniels-Severs, 1973). Even in this species, direct measurements of sympathetic activity following central AII application are scarce, and have yielded contradictory results. Whereas Fukiyama (1972) observed an initial, nonsustained excitation of SpNA and RNA, with a subsequent fall in RNA following intravertebral arterial infusion of AII in anesthetized mongrel dogs, Ferrario et al. (1972) reported variable changes in SpNA (increase or no change) and a decrease of renal nerve discharge in the same experimental model.

The decrease in RNA which occurred in these experiments and in our own study could help to explain two consistently observed phenomena following central AII receptor stimulation, namely, the suppression of plasma renin activity (Reid and Day, 1977) and the increase in sodium excretion (Severs et al., 1971; Brooks and Malvin, 1982).

Recently, Tobey et al. (1983) compared renal and splenic nerve activity after intracarotid and icv administration of AII in anesthetized cats, and found differential changes in sympathetic outflow, depending on the site of application. The increase in nerve discharge was confined to the splenic nerve, and there was little or no change of activity in the renal nerve. They concluded that discrete and nonuniform effects on sympathetic activity with alterations in visceral blood flow distribution contributed to the central pressor responses to AII.

In the rat, conclusions regarding a sympathetic

TABLE 6

Effect of icv AII (100 ng) on Blood Pressure, Heart Rate, and Splanchnic and Femoral Nerve Activity in α-Chloralose Anesthetized Rats

		Responses			Time		
		Baseline	Maximal response	% Change in nerve activity	Latency (sec)	Max (min)	Return (min)
				Splanchnic nerve			
$n = 6$	MAP	71.7 ± 6.4	+17.5 ± 4.8†		13 ± 2	1.8 ± 0.4	4.2 ± 1.0
	HR	305.0 ± 31.1	−38.3 ± 18.5		23 ± 8	1.4 ± 0.4	3.3 ± 0.9
	SpNA	8.2 ± 1.0	−1.3 ± 0.2†	−16%	20 ± 5	1.0 ± 0.4	3.2 ± 1.0
				Femoral nerve			
$n = 6$	MAP	95.0 ± 3.7	+11.7 ± 2.1†		17 ± 3	2.0 ± 0.3	14.0 ± 2.9
	HR	318.3 ± 31.6	−26.0 ± 8.7*		28 ± 8	2.4 ± 0.6	9.3 ± 3.3
	FNA	8.5 ± 1.4	+3.3 ± 1.7	(+39%)	60 ± 38	2.4 ± 1.2	4.7 ± 1.7

Results are expressed as means ± SEM. MAP, mean arterial blood pressure (mm Hg); HR, heart rate (beats/min); SpNA, splanchnic nerve activity (μV); FNA, femoral nerve activity.

* $P < 0.05$; † $P < 0.01$, compared with control values before AII injection.

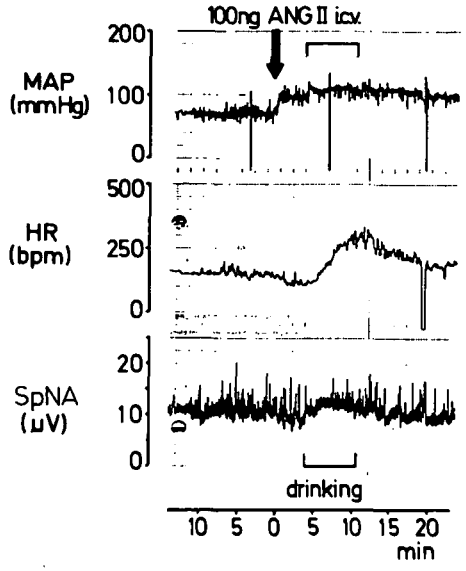

FIGURE 9. *Representative recording of the changes in mean arterial blood pressure (MAP), heart rate (HR), and mean rectified splanchnic nerve activity (SpNA) after injection of 100 ng AII, icv, and during AII-induced drinking.*

contribution to the central pressor action of AII have been based on circumstantial evidence from ablation experiments, pharmacological interference with the sympathetic nervous system, plasma catecholamine determinations, or measurements of regional blood flow (see reviews cited above), but not on direct measurements of sympathetic nerve activity. The results were not unequivocal. For instance, the combination of adrenalectomy and sympathetic nerve destruction by 6-hydroxydopamine abolished only part of the pressor response (Falcon et al., 1978), as did peripheral α-adrenoceptor blockade (Unger et al., 1981), whereas peripheral ganglionic blockade with hexamethonium caused little or no change (Brody and Johnson, 1980), or even increased the pressor response (Severs et al., 1970; Lappe and Brody, 1984), as was also found in this study. Further, peripheral sympathectomy with 6-hydroxydopamine did not attenuate the pressor peak following icv AII. This effect was found to be due to increased sensitivity to circulating AVP (Hoffman et al., 1977). On the other hand, when increased sympathetic tone was inferred on the basis of increased regional vascular resistances following central AII, the data were either obtained after infusion of the peptide into the carotid artery with mixed central and direct peripheral vascular effects of the peptide (Lappe and Brody, 1984), or the data were not adequately controlled for other vasoconstrictor mechanisms, such as circulating AVP, and reference to the exact time course of the initial events following the central AII application.

Specificity of the Central Effects of AII on Sympathetic Activity

From our data, it seems that the initial decrease in SpNA, RNA, and ANA is a specific feature of the central response to AII. However, this effect could also be brought about by factors not directly related to AII receptor stimulation in the brain. First, there could have been leakage of the peptide from the CSF into the circulation, giving rise to a systemic AII pressor response with reflexly inhibited sympathetic tone and heart rate. Second, the reduced sympathetic nerve activity could be a baroreceptor reflex-mediated event to counteract the rise in blood pressure, as pointed out by Ferrario et al. (1972). The first possibility has been addressed in the past by us and other investigators (Severs and Daniels-Severs, 1973; Schelling et al., 1980) and can be excluded, since penetration of peptides such as AII and saralasin from the cerebrospinal fluid into the blood occurs only at considerably higher doses and has never been detected immediately, but only after a lag time of several minutes following peptide application into the lateral brain ventricle (Schelling et al., 1980). Moreover, we have found previously that peripheral blockade of vascular AII receptors with saralasin (10 μg/kg per min, iv)—which leads to a reduction of more than 60% of the pressor responses to 100 ng AII injected iv—does not affect the pressor responses to the same dose of AII-injected icv (Unger et al., unpublished observation).

The second possibility of a baroreceptor reflex-mediated event cannot be ruled out entirely, but appears unlikely on the basis of the data obtained in this study. First, there was no correlation between the increase in blood pressure and the fall in SpNA, as one might have expected if the latter was reflex mediated. Second, the fall in SpNA, but not in heart rate, persisted in the chronically baroreceptor-denervated animals, despite a marked attenuation of the reflex SpNA responses to blood pressure increases by phenylephrine and decreases by sodium nitroprusside. Third, the fall in SpNA persisted to the same degree after complete blockade of vascular AVP receptors, and was present in most DI rats, despite a significant reduction of the pressor responses to AII. Finally, comparable centrally evoked pressor responses to substance P (this study) and to AVP (Unger et al., in press) were not associated with decreases, but with marked increases in SpNA, RNA, and ANA.

Other cardiovascular reflexes, for instance, those mediated by cardiac mechanoreceptors (Bishop et al., 1984), must be considered as well. It is conceivable that the increase in arterial blood pressure induced a distension of the cardiac ventricles and activated their receptors with subsequent sympathetic inhibition. To exclude this possibility, one would have to study the sympathetic responses to central AII, while at the same time preventing any blood pressure increase. This experiment was not completed in the present study, since our preliminary attempts showed that all manuevers to prevent the central pressure response to AII also simultaneously markedly altered blood pressure, heart rate, and sympathetic activity prior to the administration

of the peptide. These complex responses precluded a comparison with the original preparation.

Nevertheless, even if mediated in part by cardiovascular reflex activation such as the heart rate response, the initial decrease in sympathetic activity of the splanchnic, renal, and adrenal regions appears to be specific for AII, when compared to other centrally acting pressor peptides such as substance P or AVP.

Hemodynamic Implications

The question regarding the hemodynamic consequences of this finding remains to be investigated further. Reduced sympathetic tone within nerves controlling distinct vascular areas does not necessarily mean vasodilation and increased blood flow, if, as with AII, a pressor hormone is released simultaneously into the circulation. On the other hand, the fact that the reduction of sympathetic activity occurs in the absence of AVP-induced vasoconstriction, as seen in the $d(CH_2)_5$AVP-treated LE rats and in DI rats, indicates that this effect is independent of AVP and could give rise to regionally increased blood flow. It is also possible that central AII selectively increases the sympathetic drive to other vascular territories, e.g., the skeletal muscle or the skin. Increased vascular resistance in these regions could account for the persistence of (reduced) pressor responses in the absence of AVP-mediated vasoconstriction, as has been observed here and in a number of previous studies [see Severs et al. (1970), Hutchinson et al. (1976), Haack and Möhring (1978), and Unger et al. (1981)]. Accordingly, in these cases, peripheral interference with the sympathetic nervous system by ganglionic blockade or α_1-adrenoceptor blockade completely abolished the central pressor responses to AII. This demonstrates the total dependence of the pressor response on the integrity of the sympathetic nervous system, when AVP is absent or not effective.

It could be interpreted that the increase in femoral nerve activity, together with the fall in splanchnic nerve activity that we observed in anesthetized rats, supports the idea of a regionally restricted sympathetic stimulation by central AII. However, this finding must be interpreted with caution for the following reasons: first, the sympathetic component within the femoral nerve bundle was small compared to its motor and sensory fibers (a fact which precluded testing of the FNA responses in conscious animals); second, the increase in femoral nerve activity did not occur in all animals tested; third, the rise in blood pressure had a shorter latency than the corresponding increase in FNA.

With respect to the changes observed upon drinking, one could speculate that stimulation of central AII receptors not only gives rise to drinking behavior itself, but also initiates the drinking response with a behavioral ("appetitive behavior," exploration) and hemodynamic (blood pressure increase) adjustment. The act of drinking which then ensues, changes the hemodynamic situation to a typical "drinking pattern" with further increases in blood pressure, increases in heart rate, and recruitment of additional sympathetic nerves in areas in which the nerve activity was initially suppressed. The additional rise in blood pressure, induced by drinking, has previously also been reported by Falcon et al. (1978). Since we observed the "drinking pattern" as such also in the DI rats upon spontaneous drinking, it appears to be independent of the original stimulus. Interestingly, a late marked increase in SpNA upon icv AII injections was also observed in some but not all animals in the absence of drinking. This response was usually associated with a second smaller peak in blood pressure and with tachycardia, but never with the initial pressor peak. Thus, it appears, that late activation of initially suppressed sympathetic nerves can help to maintain the pressor response to central AII, even in the absence of drinking.

Substance P, on the other hand, initiates a behavioral hemodynamic and neuronal pattern which has more similarities to the classical defense-type reaction described by (among others) Folkow and Rubinstein (1965), after electrical stimulation of distinct hypothalamic areas in the cat. This could be plausible on the basis of the involvement of this peptide in central pain processing.

In conclusion, we have described two distinct hemodynamic and neuronal patterns following the injection of equipressor doses of AII and substance P into the lateral brain ventricle of conscious rats. The pressor responses to substance P were associated with behavioral arousal, together with increases in heart rate, cardiac output, and a generalized sympatho-adrenal stimulation. The AII response pattern was more complex, with an initial decrease in heart rate and splanchnic, renal, and adrenal sympathetic nerve activity, followed by a rise in heart rate and splanchnic discharge during water ingestion. The cardiovascular and sympathetic response pattern produced by central AII could thus be considered as a prerequisite for the drinking reaction, one of the many ways in which this peptide contributes to body fluid homeostasis, whereas the response pattern to substance P could be instrumental in adjusting the organism to react to unpleasant stimuli such as pain.

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