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Arginine^8-Vasopressin Inhibits Centrally Induced Pressor Responses by Involving Hippocampal Mechanisms

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Administration of arginine^8-vasopressin (AVP) or prolyl-leucyl-glycinamide (PLG) into a lateral cerebral ventricle reduced the magnitude of systolic blood pressure increase (pressor response) induced by electrical stimulation of the mesencephalic reticular formation (MRF) in urethane-anesthetized rats. Bilateral destruction of the dorsal hippocampus prevented the action of AVP on the pressor response. However, the effect of PLG was only slightly reduced by hippocampal lesion. Microinjection of AVP in the dentate area of the dorsal hippocampus mimicked the action of intracerebroventricularly administered peptides. The effect of a single injection of AVP lasted at least for 60 min. Neither hippocampal damage nor peptide administrations resulted in changes in mean arterial blood pressure (basal BP).

Bradycardiac response accompanied the BP increase during MRF stimulation. Hippocampal damage or intracerebroventricular administration of AVP and PLG failed to affect the cardiac response. Injection of AVP into the hippocampus tended to reduce the magnitude of cardiac responses caused by MRF stimulation.

It is suggested that the inhibition by AVP of a pressor response produced by MRF stimulation involves the dorsal hippocampus. The action of PLG or related peptides seems to be, at least in part, through mechanisms not involving the hippocampus.

INTRODUCTION

Much data has been collected during the last decade suggesting that the hypothalamic neurosecretory peptide hormone vasopressin (antidiuretic hormone) profoundly influences brain processes related to learning, memory, sleep, drug addiction and tolerance to opiates (for review see refs. 5 and 11). It has also been observed that subcutaneous administration of this peptide facilitates cardiac responses that accompany classical conditioning or passive avoidance behavior in the rat[3,4]. The question that was raised by these latter findings is whether the cardiac response changes were correlates of the behavioral actions of vasopressin or were due to a direct peptide effect on brain centers involved in the regulation of the cardiovascular system. In order to investigate this question a model was developed to study cardiovascular responses evoked by the excitation of CNS structures. The posterior hypothalamus or the mesencephalic reticular formation was stimulated electrically with various frequencies or current intensities in urethane-anesthetized rats and the stimulation-induced increase in blood pressure (pressor response) served as the measure of centrally regulated cardiovascular response[2]. Lysine^8-vasopressin and a fragment of this peptide, desglycinamide^9-lysine^8-vasopressin, administered intravenously markedly attenuated the pressor response evoked by posterior hypothalamic stimulation and increased the threshold to evoke a pressor response by the stimulation of the mesencephalic reticular formation[2]. Subsequently it was shown that these actions of the peptides are of a central nature. Intracerebroventricular administration of arginine^8-vasopressin (AVP) markedly reduced the magnitude of a pressor and bradycardiac response evoked by the stimulation of the mesencephalic reticular formation. This reduction appeared to be dose-dependent in the range of 3–25 ng[26,27].

Noradrenaline is considered as an inhibitory

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neurotransmitter in central cardiovascular regulation[8,9]. Intracerebroventricularly administered AVP increases the turnover rate of noradrenaline in limbic-midbrain areas and in the lower brainstem[23]. Modulation of noradrenergic transmission, primarily at the terminals of the dorsal noradrenergic bundle system, was shown to be involved in the action of AVP on memory consolidation[14]. The dentate gyri of the hippocampus which receive vast noradrenergic innervation from the dorsal bundle system[24], play an important role in this peptide–noradrenergic transmitter interaction. Local injection of AVP into this area facilitated memory consolidation and increased noradrenaline turnover rate in situ[15]. In addition, extensive damage of the dorsal hippocampus prevented the action of vasopressin on avoidance extinction[25].

The aim of the present experiments was to investigate whether an action of AVP in the hippocampus is involved in the inhibition of a pressor response evoked by CNS excitation. Therefore the influence of intracerebroventricularly administered AVP on pressor and bradycardiac response evoked by electrical stimulation of the mesencephalic reticular formation was investigated in rats with extensive dorsal hippocampal lesions. In addition, the effect of prolyl-leucyl-glycinamide (PLG, OXT_{7-9}), the C-terminal linear tripeptide fragment of oxytocin, was investigated in the lesioned rats. PLG appeared to share an inhibitory action of centrally induced pressor response with AVP[26,28], but it failed to affect forebrain noradrenaline turnover rate[29]. Finally, the effect of local injection of AVP into the dentate gyrus of the hippocampus was also assessed.

MATERIALS AND METHODS

Male Wistar rats (CPB—TNO, Zeist, The Netherlands), weighing 190–240 g, were used. The rats were housed under a scheduled light–dark regimen (light on between 06.00 and 19.00 h) and provided with ad libitum food and water.

Centrally induced pressor response was studied in urethane-anesthetized (1.3 g/kg, i.p.) animals. A polyethylene catheter was introduced into the left iliac artery to measure arterial blood pressure by means of a Statham P23 AC transducer attached to a Grass polygraph (79C). A 0.1% solution of heparin (Leo Pharmaceutical Products, Ballerup, Denmark) dissolved in saline was administered through the catheter in order to prevent clotting. Heart rate was monitored with a biotachometer triggered by the pulse pressure. During the experiment rectal temperature was monitored with a thermistor connected to a telethermometer (Yellow Springs 46 TUC). Body temperature was maintained at 37 °C by application of radiant heat.

The rats were placed in a David Kopf stereotaxic instrument and a guide cannula (outer diameter 600 μm) was stereotaxically implanted in a lateral ventricle. The coordinates were as follows: AP + 7.3; RL 1.2; DV + 7.0 according to Albe-Fessard et al.[1]. A microsyringe with a needle protruding 100 μm from the guide cannula was used for intraventricular injection. Subsequently, a bipolar stainless steel electrode (diameter 150 μm), insulated except for the flat end, was inserted in the mesencephalic reticular formation (AP + 1.4; RL 1.5; DV + 3.0). Stimulation was carried out by means of rectangular biphasic pulses from a Grass S88 stimulator. Current was isolated by means of a Grass SIU 5 stimulus isolation unit and regulated with Grass constant current units. Five-second trains of current were applied with an intertrain interval of 60 s. The duration of pulses was 1 ms and the interval between the electronegative and positive pulses was also 1 ms. Frequencies of stimulation were 10, 30, 50, 70 and 90 Hz. In order to obtain a comparable base-line pressor response the current intensity that caused an increase in systolic blood pressure of 50 mm Hg was determined at 50 Hz stimulation frequency. The average current intensity in intact rats was 70 μA varying between 40 and 100 μA. The determined current intensity was then used for stimulation at the other frequencies. The various frequencies were applied randomly in such a way that each stimulation frequency was used only once in a stimulation series. The maximal systolic blood pressure increase (pressor response) and the maximal heart rate change as induced by the 5-s current train were measured at each stimulation frequency.

The experimental schedule was as follows: immediately after the first series of stimulation a peptide or vehicle was injected into a lateral cerebral ventricle or bilaterally in the dentate gyrus of the hippocampus. The stimulation sequence was then repeated 20, 40 and 60 min after injections.

In the first series of experiments 7 days before the

stimulation studies the dorsal hippocampus was lesioned in a group of rats. The animals were anesthetized with ether and placed in a David Kopf stereotaxic apparatus. A stainless steel electrode (diameter 200 μm), insulated except for a 200 μm tip, was used. The electrode was inserted into two points of each hippocampus in order to produce bilateral destruction of hippocampal tissue of total width. The stereotaxic coordinates were as follows: AP + 4.6; RL 1.0; DV + 7.6 and RL 2.5; DV + 7.5. A copper rod of 5 mm diameter, inserted in the anus, served as indifferent electrode. Lesioning current (12.0 μA for 20 s) was applied by means of a radiofrequency lesion maker (Grass LM 4). Control rats were subjected to the same operation procedure except that current was not applied.

In the second series of experiments injections were given bilaterally into the dentate gyrus of the hippocampus instead of the lateral cerebral ventricle. For this purpose a twin guide cannula directed to the dentate gyri bilaterally was inserted stereotaxically. The coordinates were as follows: AP + 4.5; R and L 1.75; DV + 7.2.

Arginine[8]-vasopressin (AVP; pressor activity 471 IU/mg) and Pro–Leu–Gly-NH_2 (PLG) were freshly dissolved in 0.9% saline containing 1% of 0.01 N HCl. Acidified saline vehicle was used as a control. The injection volume was 1 μl for lateral ventricular injection and 0.5 μl for intrahippocampal injection. AVP and PLG were administered intraventricularly in a dose of 25 ng. Intrahippocampal injections contained 1 ng of AVP. The doses of peptides were selected on the basis of former observations: AVP administered intraventricularly in a dose of 25 ng appeared to be effective in suppressing the blood pressure response, while the dose of 1 ng was well below the minimally effective dose of 6.25 ng[27]. Intracerebroventricularly injected PLG in a dose of 25 ng was maximally effective[28].

At the conclusion of the experiments the rats were killed by decapitation and the brains were removed. After fixation in a 4% formalin solution, 100 μm slices were prepared and stained with 0.1% thionin. The localizations of the stimulation electrodes, the injection cannulas and the hippocampal lesions were determined microscopically.

The results are given as the mean ± S.E. of the differences between the magnitudes of post- and pre-

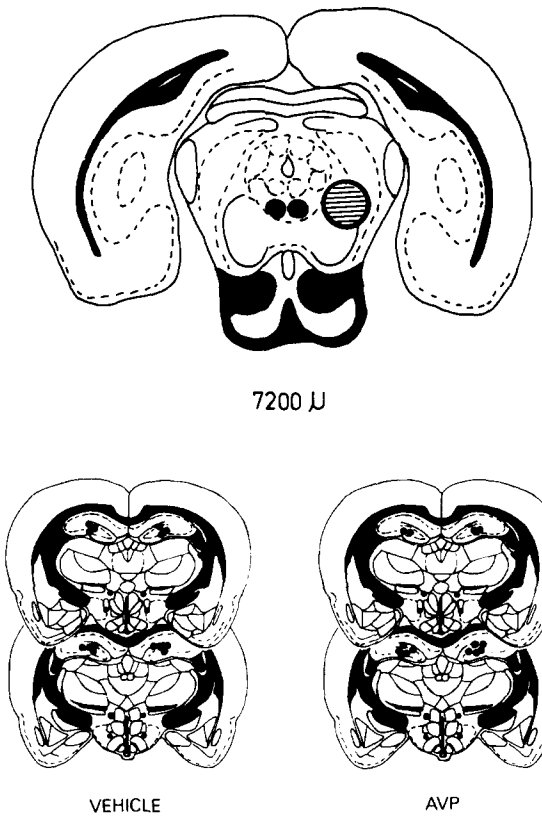

Fig. 1. Schematic representation of the localization of the stimulating electrodes in the mesencephalic reticular formation of the rat (upper drawing) and the localization of bilateral microinjections of vehicle and arginine[8]-vasopressin (AVP) in the dentate gyrus of the hippocampus in the rat. The striped circle represents the extent of electrode placements from where pressor responses can be evoked, and the black dots in the hippocampus show the site of injections. Drawing according to Palkovits[19] (upper figure: frontal section 7200 μm dorsal to the commissura anterior; lower drawings: frontal sections at 3300 μm (top) and 3600 μm (bottom) caudal to the commissura anterior).

treatment responses (Δ pressor and heart rate response) except when otherwise stated. Statistical analysis of the data was performed by paired and two-tailed *t*-tests. The test of Dunnett (parametric) or Steel (non-parametric) was applied for multiple comparisons[10]. In addition, two-way analysis of variance was also used.

RESULTS

Histology

The localizations of stimulation electrodes, the bilateral hippocampal lesions and of hippocampal injections are shown in Figs. 1 and 2. The stimulation

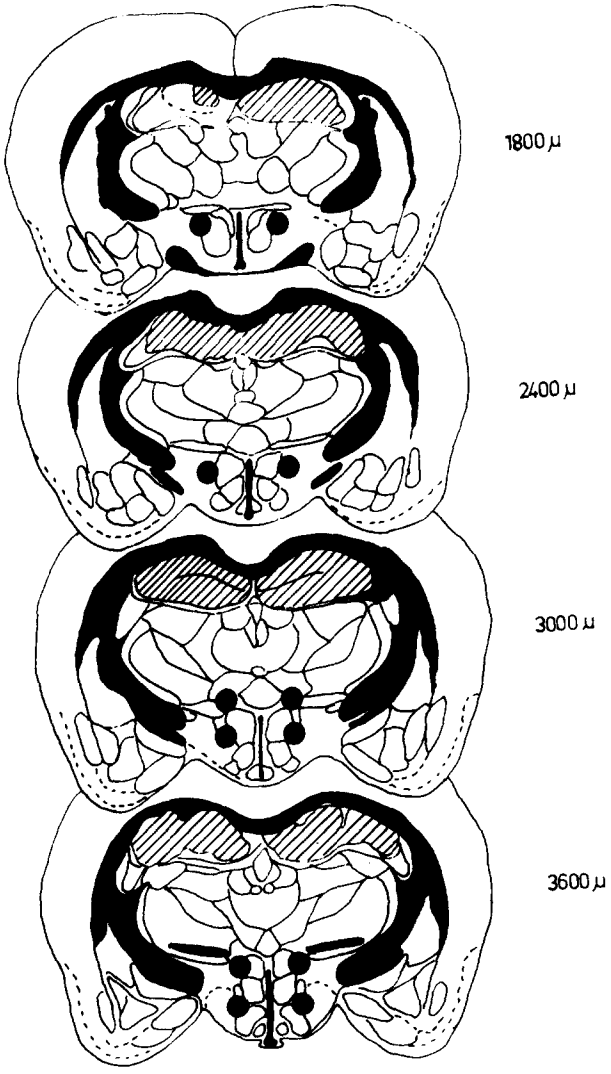

Fig. 2. Schematic representation of the maximal extent of bilateral lesions (striped) of the dorsal hippocampus of the rat. Drawing according to Palkovits[19] (frontal sections at 1800, 2400, 3000 and 3600 μm dorsal to the commissura anterior.

sites in 56 rats from where the pressor response could be evoked were found in the MRF at the level of the cuneiform nucleus. Sites were localized both in the nucleus and dorsal to it (Fig. 1, upper drawing). The extent of bilateral lesions of the dorsal hippocampus in 14 rats is depicted in Fig. 2. The lesions destroyed the dorsal hippocampus proper in full width at least in one section. The lesions were always restricted to the hippocampus. The injection sites in 14 rats were always localized in the dentate area of the dorsal hippocampus (Fig. 1, lower drawing).

Effects of intraventricular peptide administration in hippocampal-lesioned rats

The mean arterial blood pressures of anesthetized rats bearing bilateral lesions or sham lesions in the dorsal hippocampus were of the same order of magnitude (116.3 ± 3.0 and 113.2 ± 4.2 mm Hg respectively). After experimental procedures preceding vehicle or peptide administration, blood pressure remained in the same order of magnitude in lesioned (117.8 ± 3.9 mm Hg) and sham-lesioned (117.9 ± 2.5 mm Hg) rats. However, the heart rate of lesioned rats increased from 367.1 ± 10.0 bpm to 411.2 ± 11.4 bpm. A similar change was observed in sham-lesioned rats (368.4 ± 14.1 to 411.0 ± 10.0 bpm). Two-way analysis of variance indicated a significant effect of experimental procedures ($F = 42.8$; df = 1/80; $P < 0.01$), but no difference between lesioned and sham-lesioned rats was found. Intracerebroventricular injection of the vehicle or of AVP or PLG failed to affect mean arterial pressure 20, 40 and 60 min later. The heart rate of rats receiving vehicle or PLG remained practically unchanged 20, 40 and 60 min after treatment both in lesioned and sham-lesioned rats (data are not shown). Heart rate of rats that received AVP, however, showed a more pronounced decline in lesioned than in sham-lesioned rats ($F = 5.18$; df = 1/36; $P < 0.05$). The heart rate of lesioned rats receiving AVP was 421.7 ± 9.8 bpm just before the treatment and 381.1 ± 15.0 bpm 60 min later. The corresponding values in sham-lesioned rats which received AVP were 420.4 ± 9.6 and 407.3 ± 7.9 bpm, respectively.

Electrical stimulation of the mesencephalic reticular formation elicited a frequency dependent rise in systolic blood pressure (pressor response) and a fall in heart rate both in hippocampal-lesioned and sham-lesioned rats. There were no differences in these stimulation-induced cardiovascular responses (Table I). Analysis of variance indicated a significant effect of stimulation frequency on both responses ($P < 0.05$) while the effect of hippocampal damage was not significant. The current intensities that induced a pressor response of 50 mm Hg at 50 Hz frequency were in the same order of magnitude in both the lesioned (89.9 ± 5.4 μA) and sham-operated rats (75.2 ± 8.3 μA). Since changes in blood pressure were minimal at 10 Hz stimulation frequency, while skeletal muscle contractions started to occur at 90 Hz, the

TABLE I

Increase in systolic blood pressure (pressor response) and decrease in heart rate (cardiac response) to electrical stimulation of the mesencephalic reticular formation in rats with extensive bilateral lesions in the dorsal hippocampus

Values for pressor response are maximal differences in systolic blood pressure between the values before and during stimulation, and those for cardiac response are maximal differences in heart rate before and during stimulation. Values are means ± S.E. (n = 7 for all groups).

Stimulation frequencies	*Pressor response (mm Hg)*		*Cardiac response (beats/min)*	
	lesion	*sham-lesion*	*lesion*	*sham-lesion*
10 Hz	2.9 ± 0.8	2.3 ± 1.9	— 0.6 ± 2.7	+ 2.3 ± 2.8
30 Hz	17.4 ± 1.8	15.4 ± 1.1	—18.0 ± 2.3	— 26.9 ± 4.1
50 Hz	50.1 ± 1.7	50.6 ± 1.8	—58.9 ± 12.0	— 74.1 ± 11.0
70 Hz	89.1 ± 2.7	85.7 ± 2.7	—84.3 ± 19.6	— 85.0 ± 17.1
90 Hz	98.1 ± 4.5	98.6 ± 1.2	—92.4 ± 21.1	—102.6 ± 19.6

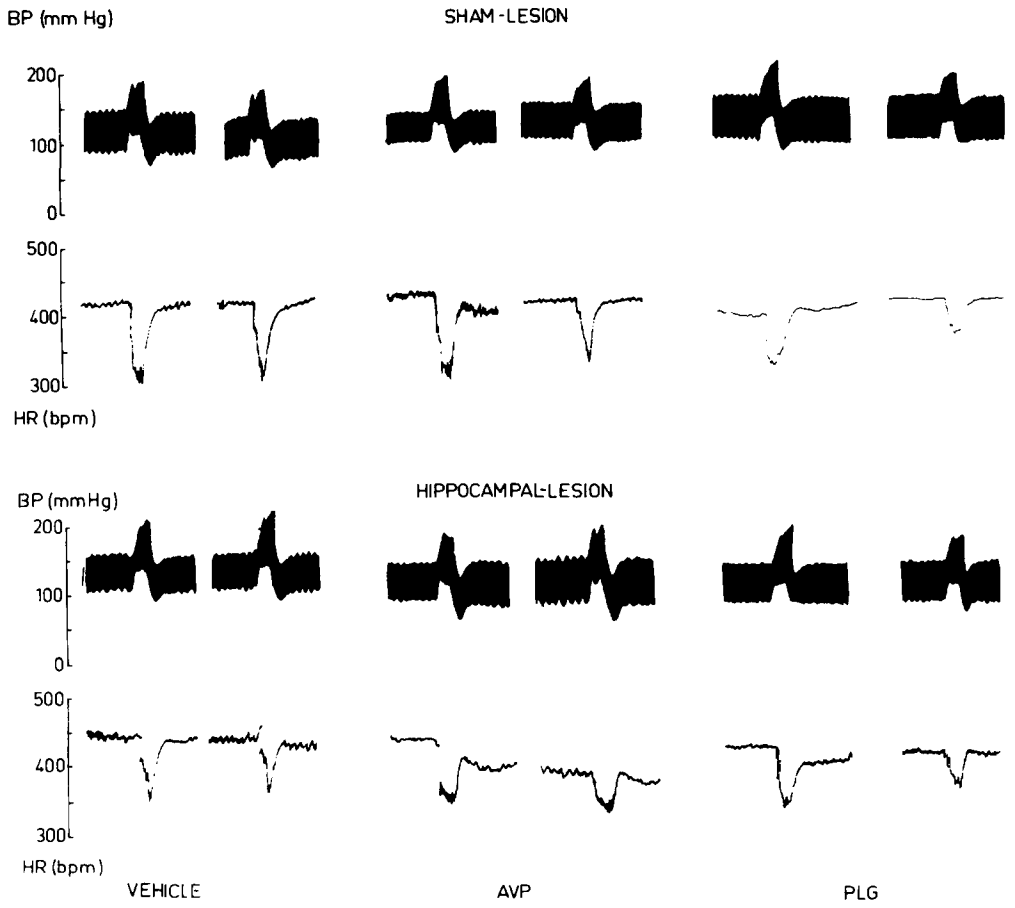

Fig. 3. Blood pressure and heart rate recordings in urethane-anesthetized rats bearing bilateral lesions or sham-lesions in the dorsal hippocampus before, during and after a 5 s electrical stimulation of the mesencephalic reticular formation. The rats received vehicle, arginine^{8}-vasopressin (AVP; in a dose of 25 ng), or prolyl-leucyl-glycinamide (PLG; 25 ng) into a lateral cerebral ventricle 20 min earlier. The frequency of the electrical stimulation was 50 Hz.

TABLE II

The effect of intracerebroventricularly administered arginine^8-vasopressin (AVP) and prolyl-leucyl-glycinamide (PLG) on the magnitude of pressor response evoked by electrical stimulation of the mesencephalic reticular formation in rats with bilateral dorsal hippocampal damage

Surgery was performed 7 days prior to the experiments. Dose of the peptides was 25 ng. Δ Pressor response values are mean difference ± S.E. in the magnitude of systolic blood pressure increase before and 20, 40 and 60 min after treatment as expressed in mm Hg. The frequency of electrical stimulation was 30, 50 and 70 Hz. n = 7 for each group.

Surgery	*Treatment*	*ΔPressor response*								
		20 min			*40 min*			*60 min*		
		30 Hz	*50 Hz*	*70 Hz*	*30 Hz*	*50 Hz*	*70 Hz*	*30 Hz*	*50 Hz*	*70 Hz*
Lesion	vehicle	—0.9±1.5	— 1.4±0.8	— 2.1±2.4	—1.0±1.3	— 5.1±1.3	— 4.4±2.3	—3.3±1.4	— 7.9±1.3	— 7.4±1.5
	AVP	—0.6±1.0	— 4.9±1.7	— 4.7±1.8	—1.7±1.3	— 6.7±1.0	— 8.7±1.8	—3.1±1.5	— 9.7±1.2	—12.6±1.5
	PLG	—2.9±2.0	— 8.3±2.5*	—11.3±1.5**	—2.4±3.6	—11.7±2.6*	—18.3±2.7**	—6.3±2.8	—15.3±3.6*	—22.1±2.6**
Sham-lesion	vehicle	2.4±1.5	— 0.3±1.0	— 1.3±2.0	1.1±2.8	— 2.6±2.4	— 4.0±1.8	—0.6±1.5	— 5.4±2.2	— 5.3±1.9
	AVP	—5.1±1.0**	—17.0±1.6**	—22.0±3.5**	—6.7±1.3**	—20.9±2.5**	—32.3±3.3**	—8.9±1.4**	—26.4±3.5**	—39.7±4.2**
	PLG	—3.9±2.0	—18.3±2.5**	—16.6±1.7**	—5.0±1.2*	—27.3±3.2**	—27.3±2.4**	—6.1±1.2**	—29.0±3.2**	—33.7±2.4**

* $P < 0.05$, ** $P < 0.01$ vs vehicle-treated rats (Multiple comparison test of Dunnett).

TABLE III

Changes in the magnitude of pressor and bradycardiac response induced by electrical stimulation of the mesencephalic reticular formation of rats following bilateral microinjection of arginine^8-vasopressin (AVP) or vehicle into the dentate area of the dorsal hippocampus

Values are mean ± S.E. of differences in the magnitude of systolic blood pressure increase (Δ pressor response in mm Hg) or heart rate decrease (Δ cardiac response in beats/min) before and after treatment. The dose of the peptide was 1 ng. n = 7 for each group.

Treatment–stimulation interval	*Stimulation frequency*	*Δ Pressor response*		*Δ Cardiac response*	
		AVP	*vehicle*	*AVP*	*vehicle*
20 min	30 Hz	— 5.7 ± 1.4**	+1.0 ± 1.4	— 8.4 ± 4.2	—14.9 ± 5.7
	50 Hz	—26.1 ± 2.1**	—2.3 ± 2.1	—32.4 ± 9.5	—16.7 ± 6.3
	70 Hz	—31.9 ± 1.9**	—1.7 ± 1.6	—36.9 ± 11.7	—15.9 ± 7.0
40 min	30 Hz	— 6.6 ± 1.8*	—0.6 ± 2.0	— 9.6 ± 5.4	—19.7 ± 7.7
	50 Hz	—26.9 ± 1.9**	—5.1 ± 1.6	—38.4 ± 11.0	—26.9 ± 7.6
	70 Hz	—40.4 ± 3.1**	—5.4 ± 1.9	—53.3 ± 15.1	—25.3 ± 9.9
60 min	30 Hz	— 8.0 ± 2.2*	—2.3 ± 1.6	— 8.3 ± 5.2*	—25.0 ± 6.0
	50 Hz	—29.7 ± 1.6**	—7.6 ± 1.6	—45.6 ± 11.1	—34.4 ± 9.6
	70 Hz	—44.6 ± 4.5**	—9.0 ± 1.5	—45.9 ± 13.4	—21.9 ± 12.0

* $P < 0.05$; ** $P < 0.01$ (t-test, two-tailed), significance of differences vs vehicle-treated rats.

influences of treatments were evaluated only at the frequencies of 30, 50 and 70 Hz.

Table II summarizes the influences of AVP, PLG and vehicle administration on the pressor and bradycardiac responses in rats with bilateral lesions in the dorsal hippocampus and sham-operated rats. In comparison to the pressor responses during the pre-injection stimulation, a slight decrease in the magnitude of the responses was observed at 40 and 60 min, but both in lesioned and sham-lesioned rats receiving vehicle. Intracerebroventricularly administered AVP significantly reduced the pressor response at all frequencies and every time following the treatment in sham-operated rats. However, no effect of AVP was found in rats with dorsal hippocampal lesions. Administration of PLG into one lateral cerebral ventricle also attenuated the pressor response in sham-operated rats. This peptide also had significant inhibitory effects in hippocampal-lesioned rats. The reduction of the pressor response was, however, less at 50 and 70 Hz stimulation frequencies in lesioned rats in comparison to the sham-lesioned ones. The magnitude of the differences amounted approximately to 50% at 50 Hz and 30% at 70 Hz stimulation frequency. The differences appeared to be always significant at 0.05 level or less (t-test). Fig.3 shows actual blood pressure and heart rate recordings in lesioned and sham-lesioned rats receiving vehicle, AVP or PLG intracerebroventricularly.

Bradycardiac responses to MRF stimulation were slightly reduced by intracerebroventricular administration of the vehicle in both the lesioned and sham-lesioned rats. As compared to these controls neither AVP nor PLG affected the magnitude of the bradycardiac response (data are not shown).

Effect of hippocampal peptide injection

Bilateral injection of AVP in an amount of 1 ng into the dentate area of the dorsal hippocampus failed to alter mean arterial pressure and heart rate. However, the magnitude of the pressor response produced by MRF stimulation was markedly reduced by hippocampal injection of AVP. The pressor response of the vehicle-injected rats was somewhat reduced 40 and 60 min after treatment, particularly at stimulation frequencies of 50 and 70 Hz ($P < 0.05$; paired t-test), when compared to the pretreatment responses. This reduction might be related to some local action of the treatment such as injection volume or acidity of the vehicle. Administration of AVP significantly decreased the response magnitude at all test periods and stimulus frequencies as compared to the controls that received the vehicle (Table III).

Table III also shows the action of AVP or vehicle treatment on the bradycardiac response to MRF stimulation. Compared to the magnitude of the cardiac response to pretreatment MRF stimulation a significant reduction occurred following vehicle admin-

istration at all test periods and stimulation frequencies. The differences were significant at $P < 0.05$ or $P < 0.01$ level (paired t-test). This pattern of response reduction was intensified by AVP administration at the frequencies of 50 and 70 Hz. The differences between peptide- and vehicle-treated rats failed to reach the 5% significance level. Interestingly, the reduction of the cardiac response at 30 Hz stimulation frequency was less pronounced in AVP-treated rats throughout the 3 stimulations, but the difference was significant only at 60 min.

DISCUSSION

The main finding of this study is that an inhibitory effect of centrally acting AVP on a pressor response induced by MRF stimulation involves dorsal hippocampal mechanisms. It was found that bilateral lesions of the dorsal hippocampus prevent the attenuation of the pressor response evoked by electrical stimulation of the MRF in urethane-anesthetized rats upon administration of AVP into one lateral cerebral ventricle. Furthermore, local administration of AVP into the dentate gyri mimicked the action of intracerebroventricularly injected peptide. The tripeptide PLG that also reduces the magnitude of centrally evoked pressor responses[26,28] retained its inhibitory effect in rats bearing dorsal hippocampal damage although the effect was somewhat diminished. Accordingly, the site of action of this oxytocin-related peptide is different from that of vasopressin. The effectiveness of PLG in lesioned rats, albeit in reduced degree, reinforces the notion that an intact hippocampus is essential for the action of AVP. If hippocampal damage would have altered cerebrospinal circulation or the sensitivity of other structures towards the neuropeptides, comparable changes in the activity of PLG and AVP might have been expected. However, it remains to be explained whether the somewhat reduced potency of PLG in lesioned rats was due to decreased sensitivity of other brain site(s) for PLG or whether the phenomenon was related to altered cerebrospinal circulation.

The effectiveness of AVP to reduce the pressor response following local microinjection into the dentate area of the dorsal hippocampus provided direct evidence of the hippocampal localization of its action. It is of course not possible to exclude the involvement of hippocampal regions other than the dentate area as site(s) of action of AVP. As was mentioned in the Introduction, the selection of the dentate gyrus was deliberate on the basis of former behavioral findings[6,14]. A coincidence in the localization of a behavioral and cardiovascular modulatory action of AVP, however, cannot be considered as a unique finding. It has already been shown that integration of behavioral (somatomotor) responses of alerting, aggressive display and flight and of cardiovascular response elicited as a preparatory reaction in the alerting stage of the somatomotor reaction is localized in the same hypothalamic, central gray and tegmental areas[13]. The hippocampal localization of behavioral actions of AVP concerns modulation of memory, namely improved retention of avoidance response due to facilitated consolidation[14] or reversal of experimentally induced memory loss (amnesia[6]). If one accepts the view that improved memory function means a more effective behavioral adaptation, a parallel inhibitory action of AVP on the pressor response may be interpreted as a protective effect of the peptide to prevent cardiovascular overactivity in response to environmental challenge. The physiological implication of this assumption, however, has yet to be proven. It should however be mentioned that the hippocampus receives vasopressinergic fibers from hypothalamic neurosecretory nuclei[7,21]. This neuronal system may serve as the anatomical substrate of a physiological action.

The local neural mechanisms of action of AVP on pressor responses induced by MRF stimulation are not yet known. The action of AVP on memory processes in the dentate gyrus seems to involve an increased noradrenergic transmission in situ[14], probably due to a presynaptic peptide effect[15]. Such a peptide–catecholamine interaction may also be involved in the modulation of centrally induced hypertensive response. This assumption is supported by the proposed inhibitory action of noradrenaline on central cardiovascular regulation[8,9].

Although supramedullary modulation of medullary cardiovascular regulatory areas is well recognized[13], the role of the hippocampus as a cardiovascular modulatory structure is not yet clear. The present experiments showed that dorsal hippocampal damage fails to affect mean arterial blood pressure, heart rate and pressor and bradycardiac response to

MRF stimulation in urethane-anesthetized rats. It seems therefore that the hippocampus does not exert tonic modulatory actions on cardiovascular regulation but, in the absence of the structure, transient modulatory effects like that caused by AVP are prevented. The transient cardiovascular modulation by AVP was related to acute challenges of the system as mimicked by MRF stimulation, but mean arterial blood pressure was not affected either following intracerebroventricular[26,27] or local hippocampal administration of the peptide. These latter observations are in contrast with the recent findings by Pittman et al.[20]. They reported dose-related increase in systolic blood pressure by 25 ng up to 5 μg of AVP administered into a lateral cerebral ventricle. The response was of a rapid onset. Although the dose of AVP administered intracerebroventricularly in the present study was only 25 ng, former observations failed to reveal any action of AVP on mean arterial pressure up to a dose of 500 ng in urethane-anesthetized rats[27]. The use of anesthesia by Pittman et al.[20] which included pentobarbital and ethanol besides urethane may have changed the permeability of the CSF–blood barrier, thereby allowing a leakage of the peptide into the periphery

Failure of hippocampal damage to prevent the action of PLG may suggest that it reduces pressor response differently, through mechanisms that do not involve the hippocampus. Recent observations show an action of PLG following fourth cerebral ventricular injection. It was also found that injection of PLG into the dorsal raphe nucleus results in a reduction of pressor responses induced by MRF stimulation (Versteeg et al., submitted). However, PLG may also act at the site of stimulation. The stimulation area in the MRF dorsally to the cuneiform nucleus contains dopaminergic cell bodies that belong to the A8-catecholamine cell group[18]. It is known that the peptide alters dopamine turnover rate[29].

In contrast to previous findings[27], heart rate responses during MRF stimulation were not significantly reduced by AVP in these experiments. It is likely that this discrepancy could be ascribed to the large variation in the magnitude of this cardiovascular response as indicated by large standard errors of means rather than to specific procedures (lesion, sham-lesion, local injections) of the present experiments. The observations, however, reinforce the notion that heart rate changes are not the consequence of blood pressure increase (reflex bradycardia)[27]. It is, rather, conceivable that the stimulation of MRF also activated vagal cardio-inhibitor mechanisms.

The interest of studying the involvement of neuropeptides, in particular of hypothalamic neurosecretory peptides, in central cardiovascular regulation is steadily increasing. An extensive network of vasopressinergic and oxytocinergic nerve fibers terminate in the brainstem and medullary cardiovascular regulatory areas[7,21,22]. Changes in brain vasopressin concentration were observed in a stroke-prone substrain of spontaneously hypertensive rats (SHR)[16], in hypertension-prone and -resistant Sabra rats[12], and in SHR rats following stress[17]. If one accepts a view that stimulation-induced pressor responses may be considered as models for acute neurogenic hypertension, reduction of the pressor response by AVP may be considered as a protective mechanism. However, it remains to be shown whether a dysfunction of central vasopressinergic system eventually in conjunction with central noradrenergic inhibitory mechanisms[30] is of importance in the etiology of neurogenic hypertension.

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