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THE INCREASE IN THE CARDIODEPRESSANT ACTIVITY AND VASOPRESSIN CONCENTRATION IN THE SELLA TURCICA VENOUS BLOOD DURING VAGAL AFFERENTS STIMULATION OR AFTER ANGIOTENSIN II INFUSION

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It has previously been demonstrated that the cardiodepressant activity is present in the bovine hypothalamic extract and in the fluid incubating the posterior pituitary lobe "*in situ*". The present study was an attempt to reveal if the cardiodepressant factor and vasopressin were simultaneously released from the pituitary into blood. The samples of venous blood flowing from the sella turcica and, for comparison, from the posterior paw were collected in anaesthetized rats. Blood from the sella turcica was collected with a fine cannula inserted into the internal maxillary vein. The concentration of vasopressin in blood plasma was determined by radioimmunoassay and cardiodepressant activity — using a biological test on a spontaneously discharged pacemaker tissue of the right auricle of the right heart atrium. Stimulation of the central ends of the cut vagus nerves or intra-arterial infusion of angiotensin II simultaneously caused an increase in the cardiodepressant activity and vasopressin concentration in the sella turcica venous blood. The cardiodepressant activity and vasopressin concentration was also enhanced to some degree in blood outflowing from the posterior paw. Present results indicate that both vasopressin and the cardiodepressant factor are released into blood from the posterior pituitary lobe.

Key words: *cardiodepressant activity, vasopressin, blood from the sella turcica*

INTRODUCTION

The release of vasopressin from the posterior pituitary lobe into blood undergoes the control of nervous and humoral factors. Mills and Wang (1, 2) revealed the stimulatory influence of afferent nervous impulsation transmitted by vagus nerves on the release of vasopressin from the posterior pituitary lobe. Further research demonstrated that acetylcholine infused into the hypothalamus stimulates neurons of supraoptic nucleus and increases the

release of vasopressin through nicotinic receptors in the hypothalamus (3) and muscarinic receptors in the posterior pituitary lobe (4). An increase in vasopressin concentration in blood plasma after both intravenous and intra-arterial infusion of angiotensin II has been also found (5—7).

The presence of the cardiodepressant factor has been demonstrated in the bovine hypothalamus (8) and in the fluid incubating the posterior pituitary lobe "*in situ*" in rats (9, 10). Electric stimulation of afferent fibres in vagus nerves caused a marked increase in the release of the cardiodepressant factor from the posterior pituitary lobe, while the stimulation of the superior cervical ganglion decreased the release (11).

The presence of the myocardial depressant factor was also found in blood of animals and humans in the course of posthemorrhagic shock (12—14). The majority of studies concern the factor of negative inotropic effect-MDF (Myocardial Depressant Factor), about a molecular weight < 1.000 d, which reveals negative inotropic activity (12).

The aim of the present study was to find a correlation between the cardiodepressant activity and vasopressin concentration in blood collected from the vicinity of cavernous sinus of the sella turcica and outflowing from the posterior paw during stimulation of the central ends of the cut vagus nerves or after infusion of angiotensin II.

MATERIAL AND METHODS

Experiments were carried out on male rats weighing 380—400 g, F_1 generation of cross--breeding of Buffalo strain males and Wistar strain females from the stock of the Institute of Oncology in Warsaw. The animals were anaesthetized by an intraperitoneal injection of a solution containing 6 mg of chloralose (Roth) and 60 mg of urethane (Fluka AG, CH-9470 Bucks) per 100 g of body weight. Experiments were carried out in three groups of rats.

In group I ($n = 7$) five 30-min samples of blood from the femoral vein and from the vicinity of cavernous sinus of the sella turcica were obtained by a spontaneous constant outflow regulated by changing to the appropriate level of the test tube to which the blood flowed through a cannula inserted into the internal maxillary vein.

In group II ($n = 12$) three 30-min samples of blood from the femoral vein and the vicinity of cavernous sinus of the sella turcica were collected in the same way. During the outflow of the second blood sample central ends of the cut vagus nerves were alternatively stimulated (60 Hz, 2 ms, 10 V, 30 sec trains). Respiratory rate was registered and expressed as breaths per min before and after the vagus nerves stimulation.

In group III ($n = 14$) five 30-min samples of blood from the femoral vein and the vicinity of cavernous sinus of the sella turcica were obtained in the way described above. During collection of the second blood sample angiotensin II (Serva, No L 13091, No 51285) in the dose of 100 ng/100 g of body weight was injected into the internal carotid artery for the duration of 10 minutes.

Stimulation of vagus nerves

Before the stimulation vagus nerves were separated from the surrounding tissues in the neck, cut and the central ends were laid on bipolar silver electrodes. The electrodes were connected to a Grass stimulator model S 4 K. The cut vagus nerves were stimulated alternatively through a commutator with 30 sec trains of electric pulses (60 Hz, 2 ms and 10 V) on and 30 sec off breaks for 30 min during the collection of the second blood sample. The electric pulses were monitored on a ST-509 A oscilloscope (Radiotechnika, Wrocław).

Blood Sampling

In order to obtain blood samples one polyethylene cannula was inserted into the peripheral end of the femoral vein and the second cannula into the internal maxillary vein in the vicinity of cavernous sinus of the sella turcica. At the beginning of the experiment 10 ml of Lock's solution with heparin (400 UJ/ml) was injected into the femoral vein. Then 30-min blood samples were collected by a spontaneous constant outflow regulated by the appropriate level of the test tube to which the blood flowed from the femoral vein or from the internal maxillary vein. After collection of each sample 2 ml of Lock's solution was injected into the femoral vein. Blood was centrifuged, the obtained plasma was divided into two parts and deep-frozen (−70°C). One portion was used for the determination of vasopressin by radioimmunoassay (15) and the second was assigned for the biological test on a spontaneously discharged pacemaker tissue of the right auricle of the right heart atrium of a two-day-old rat.

At the end of each experiment 1% solution of trypan blue was injected in the vicinity of the cavernous sinus of the sella turcica *via* a cannula inserted into the internal maxillary vein. The heads of the animals were cut off and kept in 10% formalin for several days. The brains were then removed from the skull and the posterior pituitary lobes were verified under a stereomicroscope. Only animals showing the staining of the posterior pituitary lobe were included in our results. Staining of the posterior pituitary lobe has proved proper insertion of the cannula into the vicinity of the cavernous sinus of the sella turcica, and proper blood collection.

Determination of Cardiodepressant Activity

Cardiodepressant activity was determined on pacemaker tissue of the isolated right auricle of the right heart atrium of a two-day-old rat. Two-day-old rats (5.5 g) were decapitated. The heart was isolated and the auricle of the right heart atrium was dissected under a stereomiscroscope and placed on a platinum wire electrode in a 100 µl chamber in Ringer-Lock's solution at 20—22°C. Ringer-Lock's solution contained the following in mmol/l H_2O: NaCl-153; KCl-5.6; $CaCl_2$-3.3; $NaHCO_3$-1.7; glucose 5.5 and was oxygen saturated. The solution additionally contained atropine sulphate 5×10^{-6} mol/l. Ringer-Lock's solution was constantly exchanged at a rate of 50 µl/20 sec. After keeping the isolated atrium auricle for 15—30 min in the chamber it discharged spontaneously at a constant rate. The contractions of the atrium auricle were constantly observed under a stereomicroscope and the spontaneous discharge of the pacemaker tissue was recorded on the ECG apparatus specially adapted for this purpose. (*Fig. 1*).

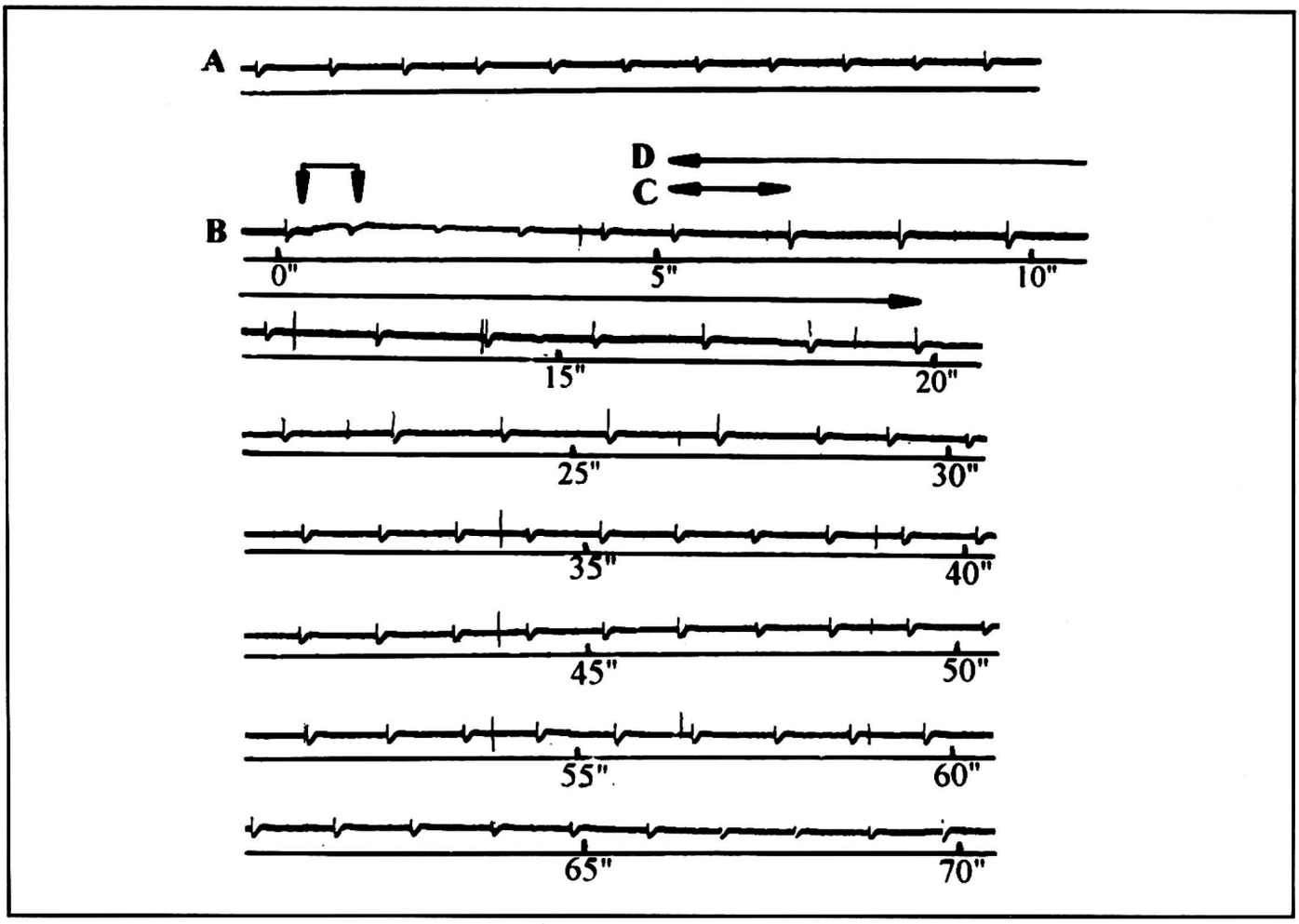

Fig. 1. Records of spontaneous discharges of isolated right auricle of the right heart atrium of a two-day-old rat. A — control records. B — records after injection of blood plasma into the chamber ⌐↓↓⌐. C — the longest cycle after a sample injection. D — ten successive cycles beginning with the longest cycle after a sample injection.

The frequency of 10 successive spontaneous discharges of the pacemaker tissue before introduction of the studied plasma sample into the chamber was calculated in Hz. The samples of plasma were introduced into the chamber in the volume of 20 µl. The frequency of spontaneous successive discharges of the pacemaker tissue was recorded over a period of 2 min. Each sample was tested on 6 preparations. The results were calculated in cycles per second, taking into consideration 10 successive cycles in which the difference of frequencies after introduction of the studied sample into the chamber in relation to the control frequency was the greatest. Cardiodepressant activity was expressed as a percentage of a decrease in the pacemaker tissue discharges.

Statistical Evaluation of the Results

The concentration of vasopressin was expressed in pg/ml. The spontaneously discharged pacemaker tissue was expressed in percentage of the control frequency of the discharged pacemaker tissue. All the results have been presented as mean $\pm$ standard deviation from the mean (S.E.M.). Correlation between the content of vasopressin and decrease in discharges rate of the pacemaker tissue was carried out in each sample for each experiment. Student's t-test was used for the statistical analysis. $P < 0.05$ was considered as the minimal level of significance.

RESULTS

Before stimulation of the vagus nerves the respiratory rate was 56 ± 6 per min ($n = 12$), at the beginning of stimulation it decreased and was 26 ± 4 inspirations per min ($n = 12$).

Control vasopressin concentrations were 318 ± 223 pg/ml ($n = 7$) in the cavernous blood plasma and 110 ± 5 pg/ml ($n = 7$) in the femoral vein plasma collected during 30 minutes. Control decrease in discharges of the pacemaker tissue was $11.9 \pm 0.7\%$ in the cavernous blood plasma and $10.68 \pm 0.8\%$ in the femoral vein plasma (*Fig. 2*). Vasopressin concentration and decrease in discharges of the pacemaker tissue in the cavernous blood plasma ($r = 0.57$, $P < 0.01$) and in the femoral vein plasma ($r = 0.44$, $P < 0.05$) were correlated.

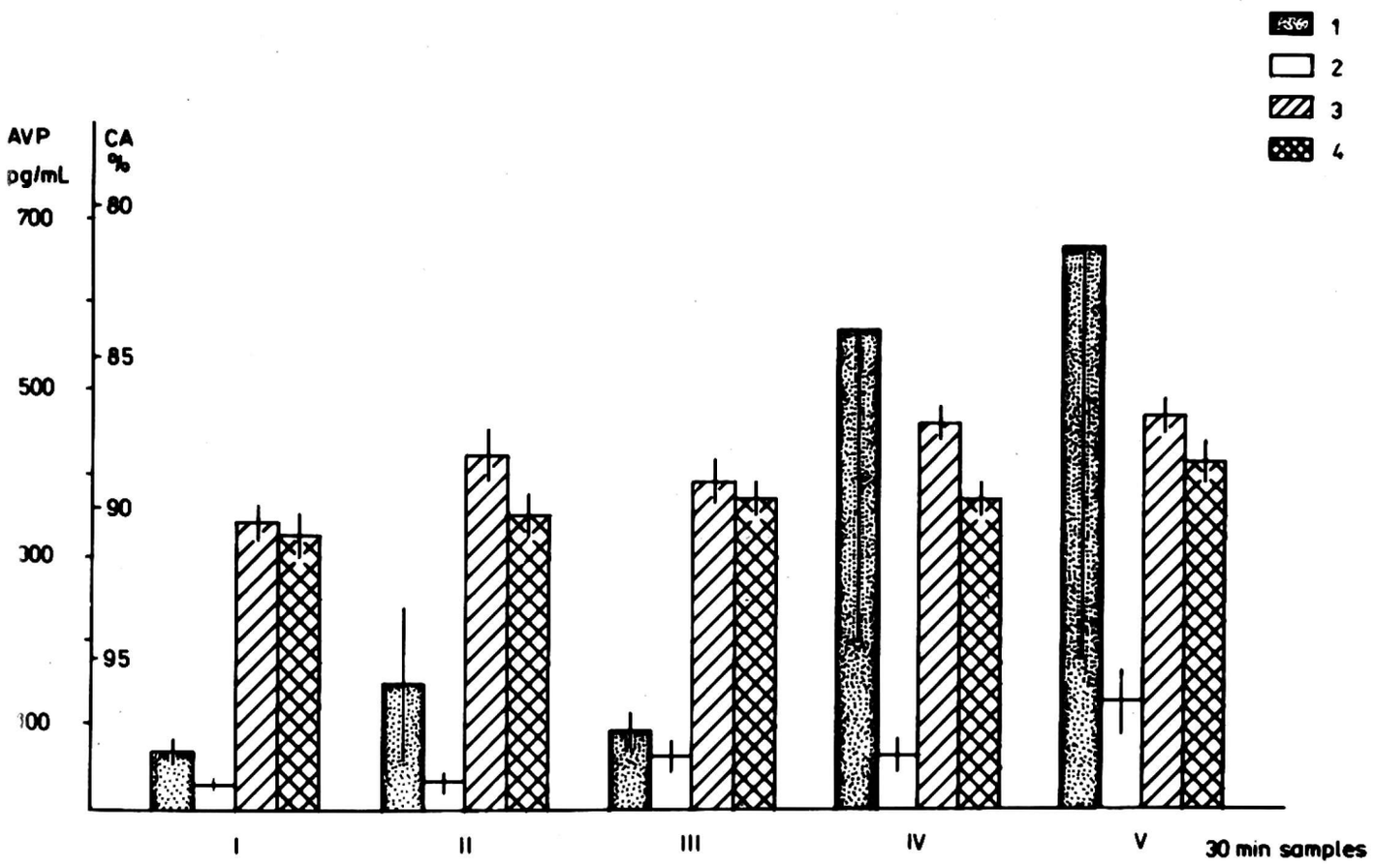

Fig. 2. Vasopressin concentration (AVP) and cardiodepressant activity (CA) in the blood from the internal maxillary vein and the femoral vein (mean $\pm$ SE, $n = 7$) 1 — vasopressin in the internal maxillary vein; 2 — vasopressin in the femoral vein; 3 — cardiodepressant activity in the internal maxillary vein; 4 — cardiodepressant activity in the femoral vein; I—V blood samples.

Stimulation of the vagus nerves caused an increase in both vasopressin and the cardiodepressant activity. Vasopressin reached a maximum of 1772 ± 857 pg/ml in the cavernous blood plasma and 355 ± 141 pg/ml in the femoral vein plasma. The greatest decrease in discharges rate of the pacemaker tissue were $15.5 \pm 1.2\%$ induced by the cavernous blood plasma and $12 \pm 0.4\%$ induced by

the femoral vein plasma (*Fig. 3*). There was a correlation between vasopressin concentration and the cardiodepressant activity in the cavernous blood plasma ($r = 0.8$, $P < 0.001$). There was no correlation between vasopressin concentration and the cardiodepressant activity in the femoral vein plasma ($r = 0.33$, $P > 0.05$).

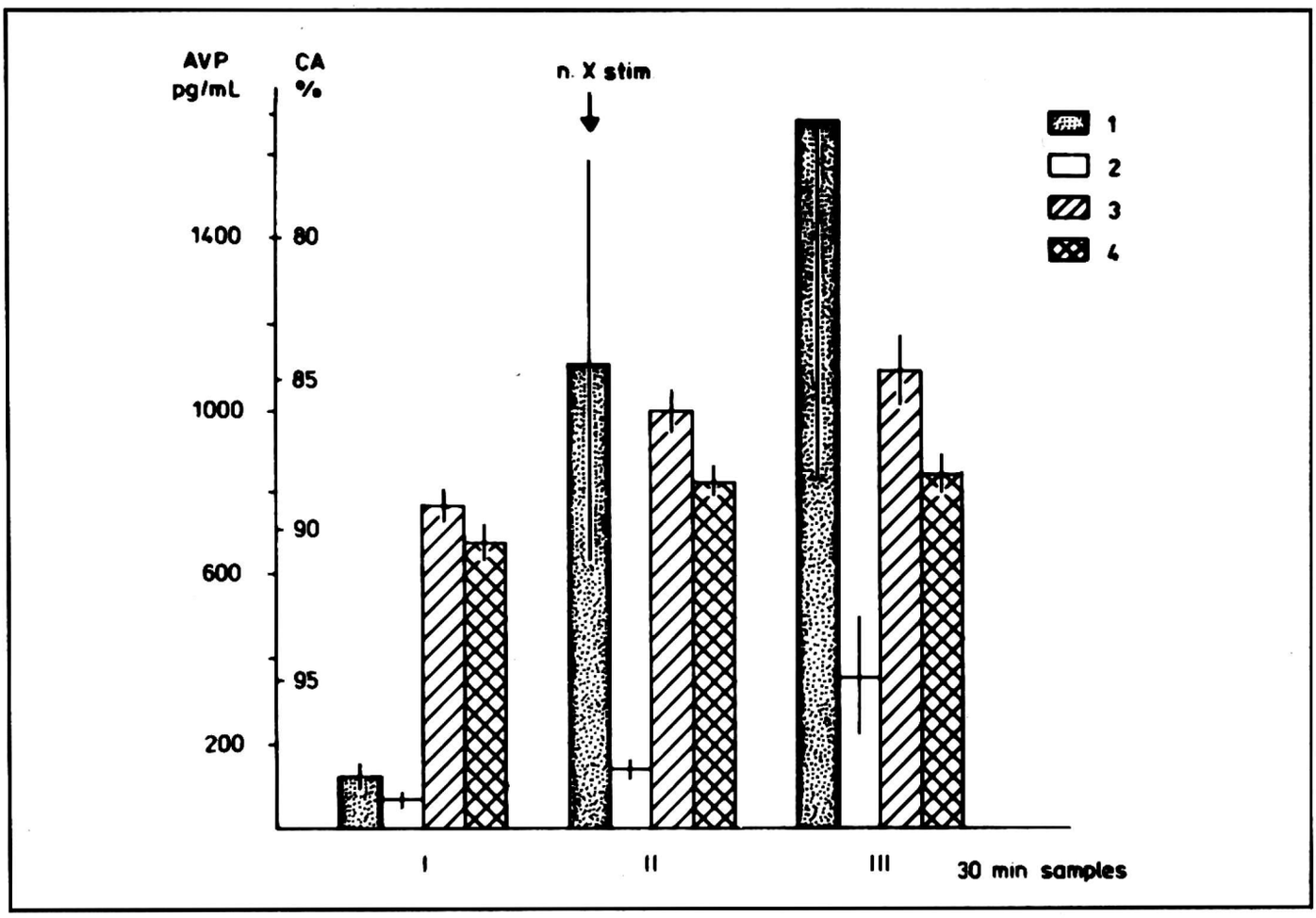

Fig. 3. Vasopressin concentration (AVP) and cardiodepressant activity (CA) in the blood from the internal maxillary vein and the femoral vein before (I samples), during (II samples), after (III samples) the electrical stimulation of the vagus nerves (mean $\pm$ SE, $n = 12$). 1 — vasopressin in the internal maxillary vein; 2 — vasopressin in the femoral vein; 3 — cardiodepressant activity in the internal maxillary vein; 4 — cardiodepressant activity in the femoral vein.

Angiotensin II also caused an increase in vasopressin concentration and the cardiodepressant activity in group III of animals. Vasopressin reached a maximum of 1632 ± 1285 pg/ml in the cavernous blood plasma and 107.2 ± 34.2 pg/ml in the femoral vein blood plasma collected over a period of 30 min during and after angiotensin II injection. The greatest decrease in discharges rate of the pacemaker tissue were $14 \pm 0.6\%$ in the cavernous blood plasma and $10.6 \pm 0.8\%$ in the femoral vein plasma (*Fig. 4*). Vasopressin concentration and the cardiodepressant activity in the cavernous blood plasma ($r = 0.64$, $P < 0.001$) and the femoral vein plasma ($r = 0.63$, $P < 0.001$) were correlated.

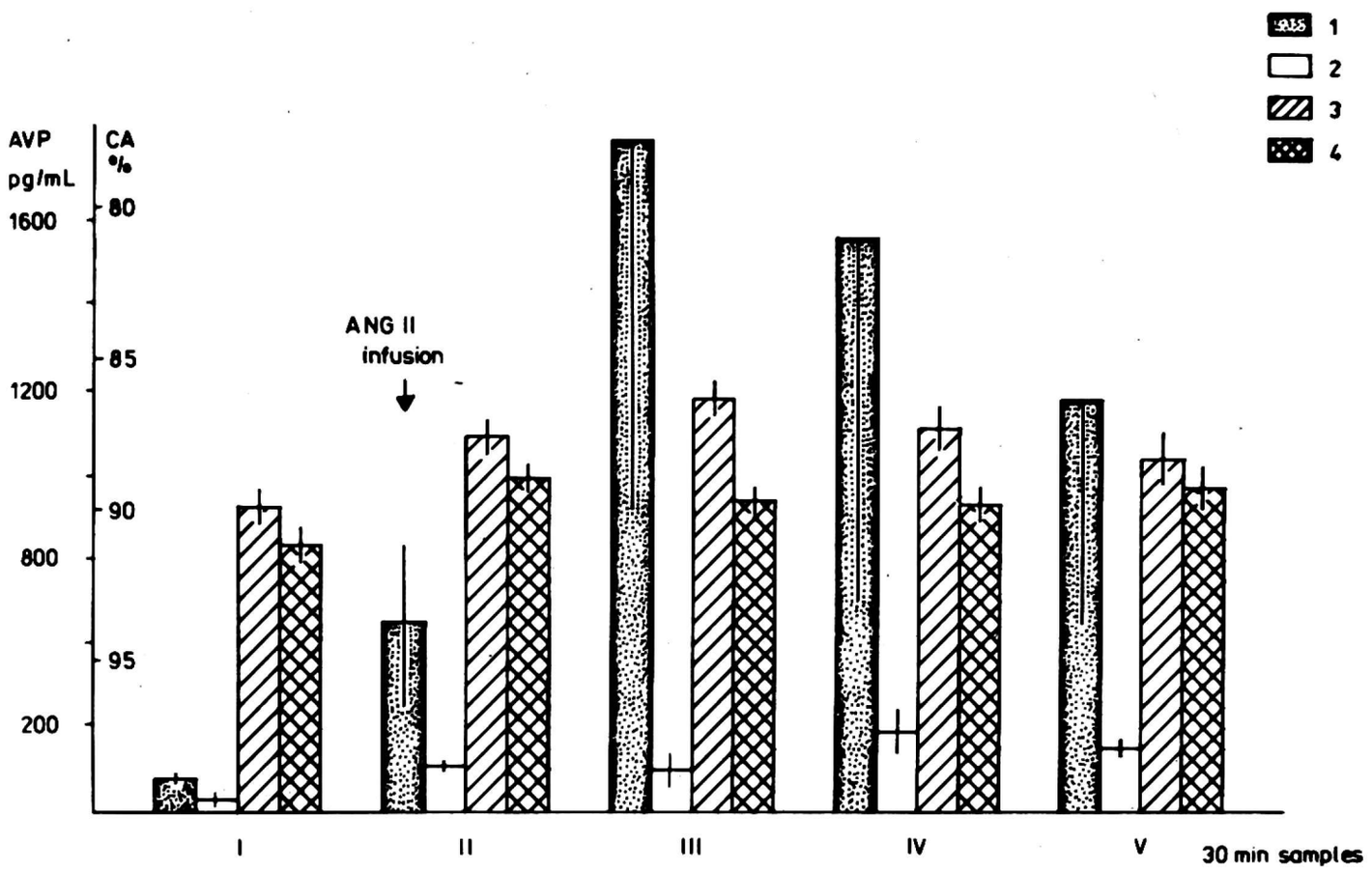

Fig. 4. Vasopressin concentration (AVP) and cardiodepressant activity (CA) in the blood from the internal maxillary vein and the femoral vein before (I samples), during (II samples), after (III, IV, V samples) angiotensin II infusion. (mean $\pm$ SE, $n = 14$). 1 — vasopressin in the internal maxillary vein; 2 — vasopressin in the femoral vein; 3 — cardiodepressant activity in the internal maxillary vein; 4 — cardiodepressant activity in the femoral vein.

Due to the fact that vasopressin concentration and the cardiodepressant activity were higher in blood plasma from the sella turcica than in the femoral vein blood plasma, it is likely, that both vasopressin and the cardiodepressant factor are released into blood in the sella turcica region.

DISCUSSION

In previous papers results concerning the release of the cardiodepressant factor into the fluid incubating the posterior pituitary lobe "*in situ*" have been presented. This factor, possessing a small molecular weight (ca. 1,000 d), exerts a negative chronotropic effect on the pacemaker tissue of the right auricle of the right heart atrium in a two-day-old rat (9, 10).

The present experiments indicate that in the rat the release of vasopressin and the cardiodepressant factor to the blood outflowing from the region of the sella turcica may be simultaneous, but the magnitude of vasopressin or the cardiodepressant factor release can be different. Moreover, vasopressin undergoes degradation in the circulatory system to a greater extent than the

cardiodepressant factor. In the presented experiments it was found that stimulation of the central ends of the cut vagus nerves or angiotensin II infusion simultaneously increased the release of both vasopressin and the cardiodepressant factor into the sella turcica venous blood and into the peripheral blood. However, it was found that during vagus nerves stimulation the increase in the cardiodepressant activity was associated but not significantly correlated with the increase in vasopressin release into the peripheral blood plasma. The stimulation of the vagus caused a higher release of vasopressin and a higher cardiodepressant activity than angiotensin II infusion.

Our earlier studies have indicated that the stimulation of the central ends of the cut vagus nerves caused an increase in cardiodepressant activity in the medium incubating the posterior pituitary lobe (16). It is known from other studies that the stimulation of the cut vagus nerve causes an increased release vasopressin from the posterior pituitary lobe into blood (1, 2, 17, 18).

An increased release of vasopressin into blood by angiotensin II infused into the internal carotid artery in the amount of 10—60 μg/kg/min was found by Claybaugh et al. (6) and Shimizu et al. (7). Angiotensin II causes an increase in vasopressin release from both the pituitary (17) and hypothalamus (19, 20).

A reduced volume of circulating blood and a decrease in arterial pressure is an effective stimulus releasing both vasopressin (21) and the cardiodepressant factor (14). At the beginning of our experiment the animals were given 10 ml of Lock's solution intervenously to present the reduction of circulating blood volume resulting from blood sample collecting.

In our studies vasopressin concentration in the control blood exceeded the value known from the literature data (22). It is probably due to the fact that in our experiments vasopressin was determined in blood flowing directly from the sella turcica, as the cannula collecting blood was inserted into the maxillary vein and its end was situated in the vicinity of the cavernous sinus. Blood obtained this way contained more vasopressin than blood outflowing from the posterior paw. Moreover, urethane applied as an anasthetic in our experiments increases the release of neurohormones from the posterior pituitary acting at the level of neurosecretory endings (23) and also influences the volume of body fluids, and through the volume receptors, additionally increases the release of neurohormones (24).

Some authors have revealed that intravenous infusion of vasopressin decreases the heart contraction rate (25—27). Bradycardia induced by vasopressin in rats is caused by reflex decrease of sympathetic tone to the heart or by the increase in vagal tone (25). It is supported by the fact that vasopressin given centrally causes as increase in arterial blood pressure and tachycardia (28).

Other authors performing experiments on the isolated rat heart have concluded that vasopressin contracts coronary vessels which causes the heart

muscle hypoxia and a decrease in the heart contraction rate (29, 30). Hof (31), however, has indicated that the reduction of the coronary blood flow under the influence of of vasopressin does not cause a decrease in the heart contraction rate.

The research carried out by Lefer and Inge (32) on isolated papillary muscle demonstrated that vasopressin at the concentration of 10^{-5} to 10^{-8} mol/L does not exhibit cardiodepressant activity. Also Brizzee et al (33) in their experiments performed on the Langendorff isolated rat heart preparation indicated that vasopressin has no chronotropic effect. In our previous experiments, similarly, vasopressin had no influence on the frequency of the isolated auricle contractions rate (34). Our and other studies reveal that cardiodepressant activity of plasma is not caused by vasopressin.

Neuropeptides present in the posterior pituitary lobe, such as substance P, leu-enkephalin, met-enkephalin angiotensin II, atrial natriuretic factor, vasopressin, oxytocin and delta sleep-inducing peptide in a concentration from 2.1×10^{-7} to 10^{-3} mol/l had no effect on the contraction frequency of the isolated auricle of the heart right atrium of a two-day-old rat (34).

In the present study the cardiodepressant activity of plasma was not brought about by acetylcholine, because atropine sulphte (5×10^{-6} mol/l) was added to Ringer-Lock's solution perfusing the auricle.

Various biologically active substances are also released into blood during circulatory shock combined with a decrease in arterial blood pressure. The best known cardiodepressant substance is MDF (Myocardial Depressant Factor) discovered intially by Brand and Lefer in 1966 in blood of cats during posthemorrhagic shock (12). MDF is a peptide or glycopeptide of molecular weight 500—1,000 d (35) and acts inotropically negatively on the isolated papillary muscle (12—14).

In recent years the cardiodepressant factor (CDF) was also revealed by Halström et al (36, 37) in blood of animals during post-traumatic shock. The authors have demonstrated that negative intropic effect of this factor is connected with the blockade of the calcium inward current.

In this study we have proved a correlation between the concentration of vasopressin and the cardiodepressant activity in venous blood plasma from the vicinity of cavernous sinus of the sella turcica and in the blood outflowing from the posterior paw.

After stimulation of the vagus nerves or angiotensin II infusion the increase in the concentration of vasopressin and the cardiodepressant activity in the blood plasma from the vicinity of the sella turcica is higher than from the peripheral vein. It indicates that both vasopressin and the cardiodepressant factor are released into blood from the posterior pituitary lobe.

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