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INCREASE IN CARDIODEPRESSANT FACTOR RELEASE FROM THE POSTERIOIR PITUITARY LOBE AFTER ANGIOTENSIN II INFUSION INTO THE INTERNAL CAROTID ARTERY

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In our previous research the presence of a cardiodepressant factor in the medium incubating the posterior pituitary lobe 'in situ' has been demonstrated. This study presents experiments demonstrating cardiodepressant activity in medium incubating the posterior pituitary lobe 'in situ' and in dialysates of venous blood from the sella turcica region before and during angiotensin II (ANG II) infusion into the internal carotid artery in rat.
Cardiodepressant activity was determined on spontaneously discharging isolated auricle of the right atrium in a two-day-old rat. It has been demonstrated that medium incubating the posterior pituitary lobe which was collected during angiotensin II infusion caused a greater decrease in auricle discharge rate than medium collected before the infusion. Angiotensin II infusion into the internal carotid artery caused a dose-dependent increase in cardiodepressant activity in dialysates of blood outflowing from the sella turcica region. The present results indicate that angiotensin II increase the release of cardiodepressant factor from the posterior pituitary lobe into blood in a dose-dependent manner.

K e y   w o r d s: *Cardiodepressant factor, angiotensin II, posterior pituitary lobe, sella turcica blood, venous blood dialysis.*

INTRODUCTION

A variety of cardiotoxic substances are released into blood during circulatory shock. The best known and best characterized of these cardiotoxic substances appearing in shock blood plasma is myocardial depressant factor (MDF). MDF was initially discovered in 1966 by Brand and Lefer (1) in cat blood plasma during haemorrhagic shock. In later studies MDF has been found in blood plasma of animals and humans in haemorrhagic, endotoxic, cardiogenic, splanchnic ischemia, pancreatitis, burn and traumatic shocks (2, 3).

Moreover, blood plasma MDF originates from the ischemic splanchnic region (i.e. pancreas, intestine, liver). It has also been shown that zymogenic and lisosomal proteases released during shock promote proteolysis and thereby stimulate MDF production (3, 4, 5). The best known action of MDF is its negative inotropic effect (i.e., the depression of myocardial contractility) (6). MDF appears to be a peptide having a molecular weight of 800—1,000 d (6, 7).

Recently, a cardiodepressant factor (CDF) has been also isolated by Hallström *et al.* from the blood plasma of dogs after hypovolemic-traumatic shock (8, 9).

The presence of a cardiodepressant factor was also indicated in our laboratory in the extract from the bovine hypothalamus (10) and in the medium incubating in situ the posterior pituitary lobe (11).

The aim of this study was to find out if cardiodepressant factor release from the posterior pituitary lobe is a dose-dependent of angiotensin II infused into cerebral circulation.

MATERIAL AND METHODS

Animals

The experiments were performed on male rats, weighing 300—320 g, 5—9 months old, the F_1 generation cross-strains of male August and female Wistar from the Institute of Oncology in Warsaw. The animals were anaesthetized by an i.p. injection of a solution containing 6 mg of chloralose (Roth) and 60 mg of urethane (Flucka Ag, CH-9470 Bucks) per 100 g body weight.

Experimental protocols

Two series of experiments were performed.

In the first experiment (n = 10), two 30-min samples of the fluid incubating the posterior pituitary lobe 'in situ' were collected. At the beginning of the second sample collection ANG II (Serva, No Lot 13091, No 51285) at the dose of 100 ng/100 g body weight was administered into the internal carotid artery for the duration of 15 min.

In the second experiment (n = 10) four 30-min dialysate blood samples were collected from the region of the sella turcica. At the begining of the collection of the second, third and fourth blood dialysate sample ANG II at the dose of 10, 30 and 90 ng/100 g b.w./min, respectively, was administered into the interal carotid artery for the duration of 15 minutes (0.04 mL/min).

Collection of the medium incubating the posterior pituitary lobe 'in situ'

When anaesthetized rats were immobilized on an operating board, ear bars were introduced and the upper jaw was fixed in a clamp. The skin and subcutaneous tissues of the submandibular region were infiltrated with a 2% Polocaine hydrochlorici solution (Polfa) and the mendible, the muscles of the floor of the mouth and the soft palate were divided along the mid-line. A hole was made with a dental drill in the sphenoid bone to expose the dura between the posterior margin of

the optic chiasma and the pons. The technique of Worthington (12) of parapharyngeal approach to the pituitary was followed, except that no heparin was injected. After a longitudinal incision had been made in the dura mater with a special fine angular knife and the anterior lobe of pituitary gland was carefully removed with a stainless steel tube (0.5 mm external diameter) connected to a suction pump as described previously (13). The anterior lobe was removed in the direction from median eminence to pons. Care was taken not to touch the surface of the posterior lobe with the suction tube. During the removal of the anterior lobe, the posterior lobe was kept in position with the aid of a fine glass rod. The whole preparation was carried out under a binocular dissecting stereomicroscope P.Z.0., magnification $25 \times$. Special care was also taken in order not to interrupt the vessels between the posterior pituitary lobe and the diaphragm of the hypophysis in order to preserve the blood supply to the posterior lobe. The whole area was then washed several times with 0.95% NaCl solution. With the aid of a micromanipulator two fine polyethylene tubings were placed behind the posterior lobe, a fine polyethylene tube (0.5 mm diameter) was positioned 3 cm over the median eminence. The incubation medium was dropped from the tube so that the pituitary and median eminence were constantly covered with incubation medium.
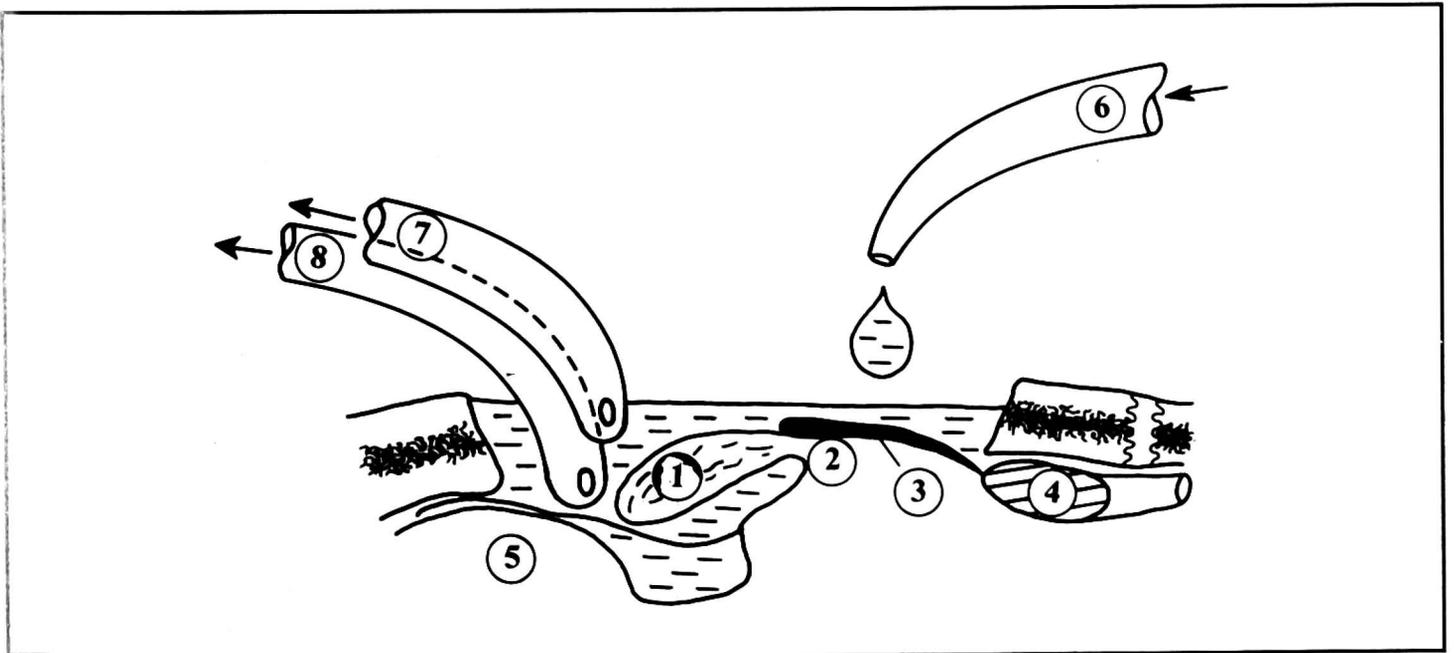

Fig. 1. Sagital section of the rat ventral hypothalamus during incubation of the posterior pituitary lobe 'in situ'. 1 — posterior pituitary lobe, 2 — pituitary stalk, 3 — clot in pituitary portal vessels, 4 — optic chiasma, 5 — pons, 6 — inflow tubing, 7 — outflow tubing for continuous exchange of the incubation medium, 8 — outflow tubing for the exchange of the whole volume of the incubation medium.

The longer tubing with an opening on its side touched the diaphragm of the hypophysis, the shorter one was situated 1.5 mm above the posterior lobe. The medium in which the pars posterior was incubated was constantly aspirated through the shorter tubing. This tubing was connected to a glass tube with methanol (1:2.5 vol/vol of methanol) and dextran (6 mg of dextran MW = 110,000). The glas tube was connected to a suction pump and the incubation fluid was constantly aspirated. The longer outflowing tubing was connected with the glass tube at the end of each 30-min interval so that the whole volume of the incubating medium could be aspirated (Fig. 1). Samples of the incubation medium collected during the first 30 min were discarded. The incubation medium prepared according to McIlwain and Rodnight (14) had the following composition: NaCl — 120; KCl — 4.8; KH_2PO_4 — 1.2; $MgSO_4$ — 1.3; $CaCl_2$ — 2.8; $NaHCO_3$

— 26; glucose — 10.0 (mmol/L) pH 7.4 and dropped at the rate of 1 mL/h. After the precipitation of proteins each medium sample with methanol was centrifuged at 10 000 g and the supernatant was lyophilized and stored at — 20°C until bioassay.

Dialysate blood sampling

In order to obtain blood dialysate samples from the vicinity of the pituitary one polyethylene cannula was inserted into the heart end of the internal maxillary vein and the second cannula into the maxillary vein in the vicinity of cavernous sinus of the sella turcica. Blood was drawn from the region of *sella turcica* through the polyethylene cannula (and a tube) to the minidialysator with the use of the peristaltic pump. It was than returned to the organism through the cannula inserted into the heart end of the maxillary vein (*Fig. 2*). At the beginning of the experiments 2 mL of Lock solution with heparin (400 UJ/mL) was injected into the internal maxillary vein.

The whole amount of dialysing fluid was exchanged every 30 min for 2 hrs by draining it directly into a test tube. Four 1 mL samples of dialysate were obtained this way. Before refilling the minidialysator with dialysing fluid its cover was rinsed with Mc Ilwain-Rodnight solution. At the end of each experiment 1% solution of trypan blue was injected through a cannula inserted into the internal maxillary vein. The brains were then removed from the skull and the dye in the posterior pituitary lobes were verified under a stereomicroscope. Only these dialysate samples which were collected from animals showing the staining of the posterior pituitary lobe were included into the 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.
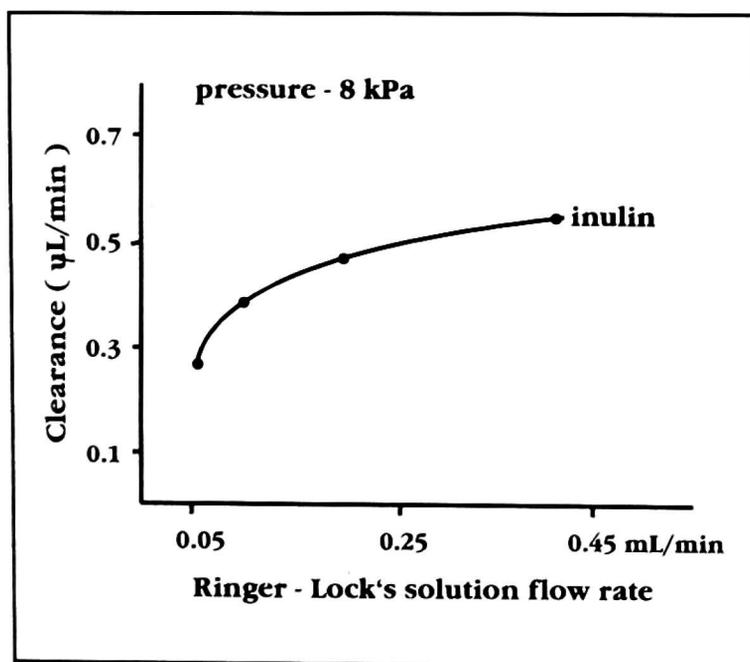

Fig. 2. Clearance of inulin at various Ringer-Lock solution flow rates. At a constant pressure of 8 kPa Ringer-Lock solution and inulin were dialysed: 0.05 mL/min, 0.1 mL/min, 0.2 mL/min, 0.4 mL/min. The volume of ultrafiltrate outflowing from the minidialysator housing was measured. Ultrafiltrate was hydrolised and fructose content was determined using colorimetric method.

Minidialysator characteristics

Minidialysators have been manufactured according to our design by EURO-SEP-Ltd Warsaw. They have two tips Luer's needles for connecting from one side through a cannula with a vein and from the side - with a peristaltic pump. At the side of the minidialysator there are two tips for Luer's needles for the exchange of the dialysing fluid (*Fig. 2, Tabl I*). Minidialysators were tested in *in vitro* experiments. Inulin clearance *in vitro* is presented in figure 3, and *in vitro* ultrafiltration in *Fig. 4*.
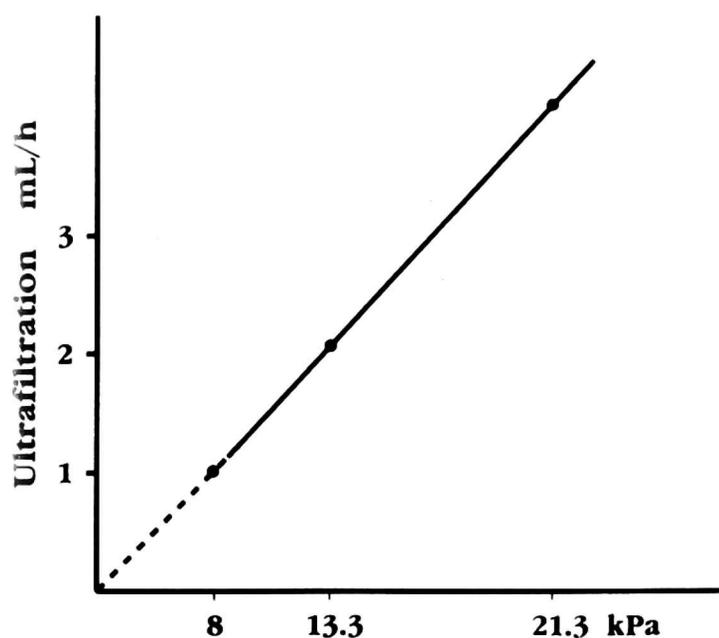
Fig. 3. In vitro ultrafiltration. Ringer-Lock solution was dialysed for 1, 2 and 3 hours and volume of ultrafiltrate outflowing from the minidialysator housing was measured at 8 kPa, 13.3 kPa and 21.3 kPa.
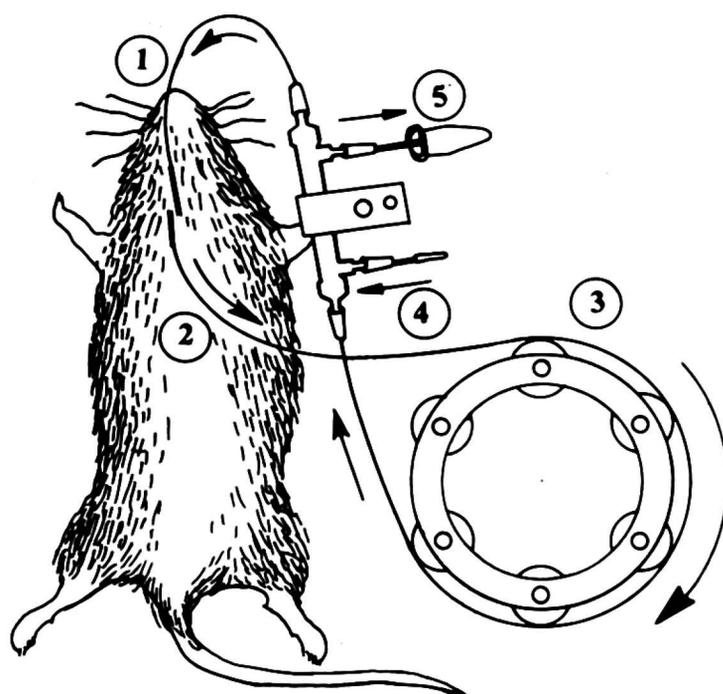
Fig. 4. Dialysis of venous blood outflowing from the cavernous sinus vicinity of the *sella turcica* in rats. 1 — cannula inserted into the heart end of the internal maxillary vein. 2 — cannula inserted into the *sella turcica* end of the internal maxillary vein. 3 — peristaltic pump. 4 — inflow tube for filling minidialysator housing. 5 — outflow tube for collecting dialysating medium from the minidialysator housing.

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. Each heart was isolated, the auricle of the right heart atrium was dissected under stereomicroscope and placed on a platinum wire electrode in a 100 µL chamber in Ringer-Lock solution at 20—22°C. Ringer-Lock solution contained 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 contained additionally atropine sulphate 5×10^{-6} mol/L. Ringer-Lock 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 contracted spontaneously at a constant rate. Lyophilized 30 min samples of the fluid incubating the posterior pituitary lobe or blood dialysate samples were dissolved in 0.3 mL redistiled water and injected into the 100 µL chamber in the volume of 20 µL. The contractions of the atrium auricle were observed under a stereomicroscope and the spontaneous discharge of pacemaker tissue was recorded on the ECG apparatus specially adapted for this purpose. The changes of discharges frequency analysed by the computer and expressed as a percentage of the greatest decrease in discharge rate in relation to the control using especially developed software. Discharge rate of the pacemaker tissue was recorded during 20s before and 100s after administration of the studied sample. Each sample was tested on six preparations.

Statistical analysis

Data are reported as means $\pm$ SE. Student's t-test was used for statistical analysis. $P < 0.05$ was considered as significant.

Table I. Characteristics of minidialysator used for the *sella turcica* blood dialysis

Technical Data of the Minidialysator	
Ultrafiltration coefficient (mL/h/mm Hg)	5.5
Inulin clearance *in vitro* (µL/min)	0.52
Active surface (m²)	0.1
Lumen/wall thickness of capillary (µm)	200/0.8
Number of capillaries	270
Lenght of capillary (mm)	59
Inner diameter of a capillary (mm)	0.2
Priming volume: blood (mL)	0.8
Priming volume: dialysate (mL)	1.6
Membrane material	Cuprophan[R]
Housing material	Lustran-San[R]
Polting compound	Polyurethane
Net weight (g)	8 g
Maximae working pressure	500 tor

Inulin clearance was determined *in vitro* at Ringer-Lock solution and inulin flow rate of 0.45 mL/min.

RESULTS

Cardiodepressant activity of the medium incubating the posterior pituitary lobe 'in situ'

Fig. 5 presents changes of spontaneous discharges rate of the pacemaker tissue under the influence of medium incubating the posterior pituitary lobe *'in situ'* in rats. Medium incubating the posterior pituitary lobe which was collected during angiotensin II infusion caused a greater in discharges rate ($55 \pm 0.06\%$, $P < 0.01$, $n = 10$) than medium collected before angiotensin II infusion ($40.6 \pm 0.05\%$, $P < 0.01$, $n = 10$). Mean difference frequency cardiodepressant activity of the medium incubating the posterior pituitary lobe before angiotensin II infusion and during angiotensin II infusion is statistically significant ($P < 0.01$)

Cardiodepressant activity of blood dialysate from the sella turcica

Fig. 6 shows examples illustrating changes in spontaneous discharges rate of pacemker tissue of the isolated auricle after administration of Ringer-Lock solution, medium incubating the posterior pituitary lobe during angiotensin II infusion at doses of 100 ng/100 g body weight, dialysate of the blood from the *sella turcica* during angiotensin II infusion at doses of 10 ng/100 g b.w./min and 90 ng/100 g b.w./min.

Fig. 5. Influence of medium incubating 'in situ' the posterior pituitary lobe on the spontaneous discharges rate of the heart auricle. Angiotensin II infusion into right internal carotid artery (100 ng/100 g b.w.) significantly decreased spontaneous discharges. (Value are means $\pm$ SE, P<0.01 vs control value, n = 10).
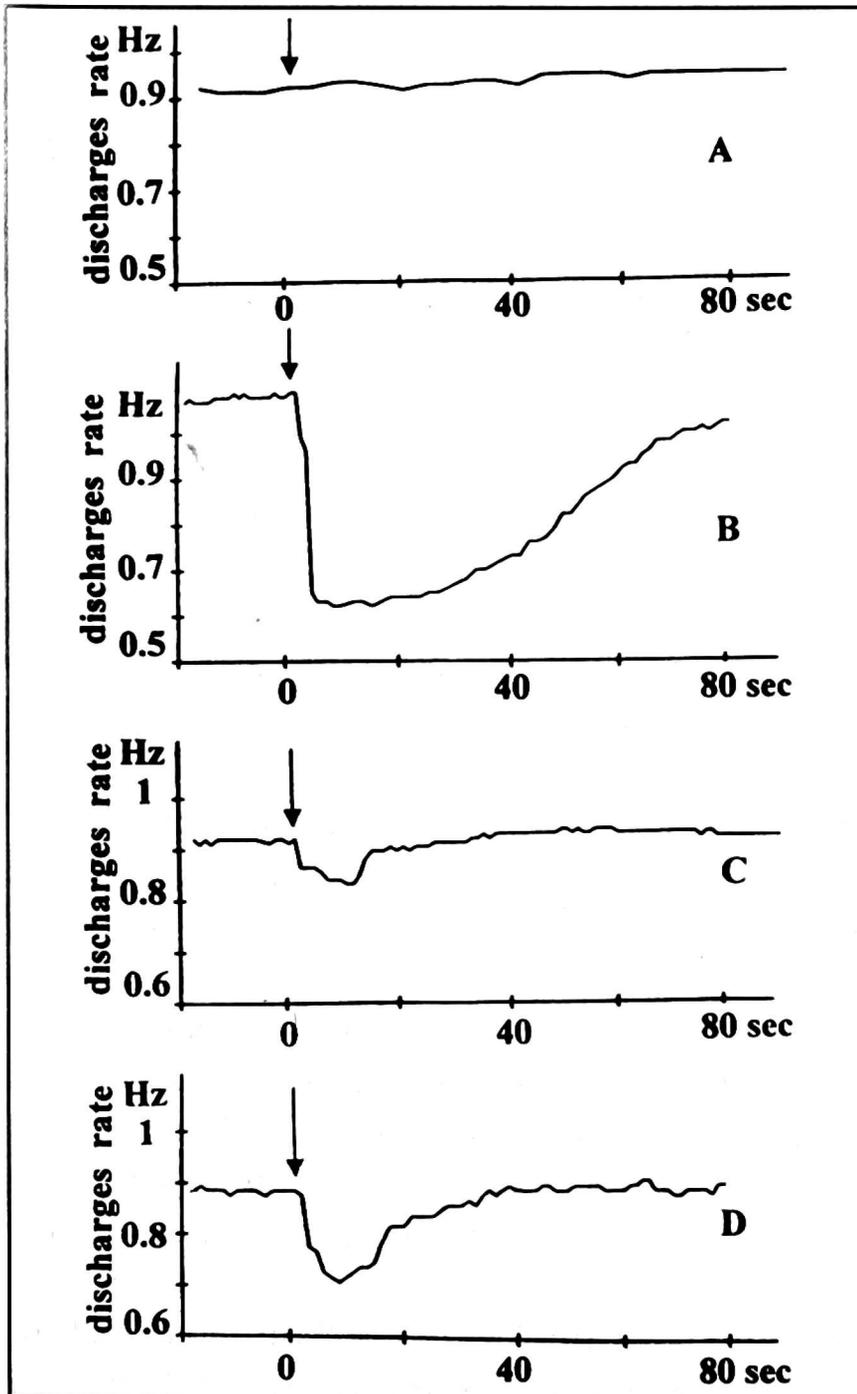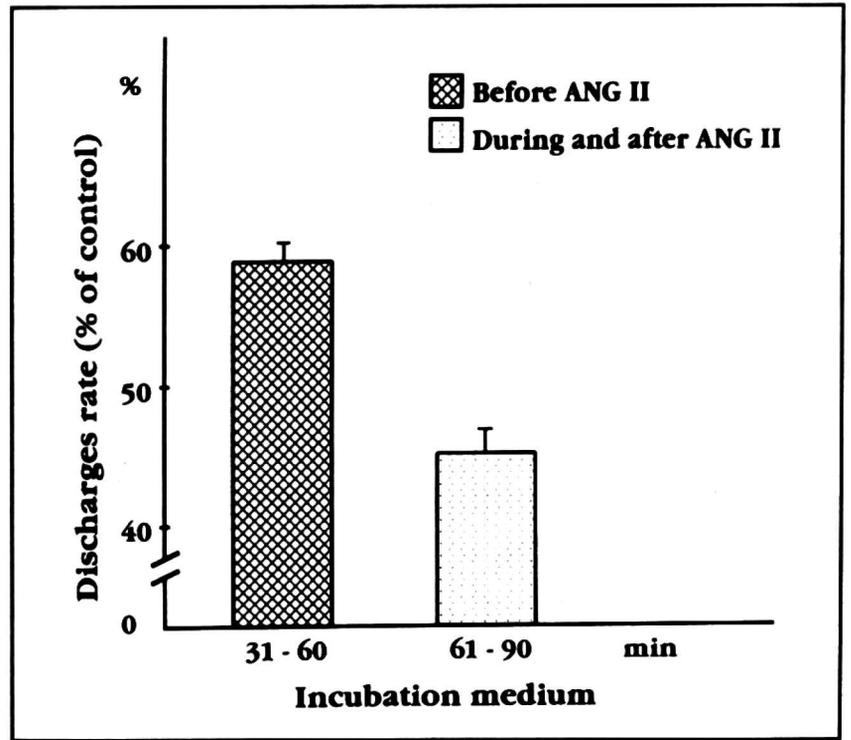
Fig. 6. Examples of records illustrating changes in spontaneous discharges rate of pacemaker tissue of the isolated auricle to administration: Ringer-Lock solution (A), medium incubating the posterior pituitary lobe during and after agniotensin II infusion at doses 100 ng/100 g body weight (B), dialysate of the blood from the sella turcica during angiotensin II infusion at doses 10 ng/100 g b.w./min (C), and doses 90 ng/100 g b.w./min (D). Arrows indicate time of 20 µL sample administration into the chamber with spontaneously discharging isolated auricle of the right atrium.

Intra-arterial infusions of angiotensin II produced dose-related increase in cardiodepressant activity in the dialysate of the blood from the *sella turcica.* Cardiodepressant activity of the dialysate from the *sella turcica* increased from the control value of $12 \pm 0.05\%$ (sample I) to $14.31 \pm 0.07\%$ (sample II); $16.72 \pm 0.07\%$ (sample III), and $19.94 \pm 1\%$ (sample IV) during angiotensin II infusion at dose of 10, 30 and 90 ng/100 g b.w./min, respectively (*Fig. 7*).
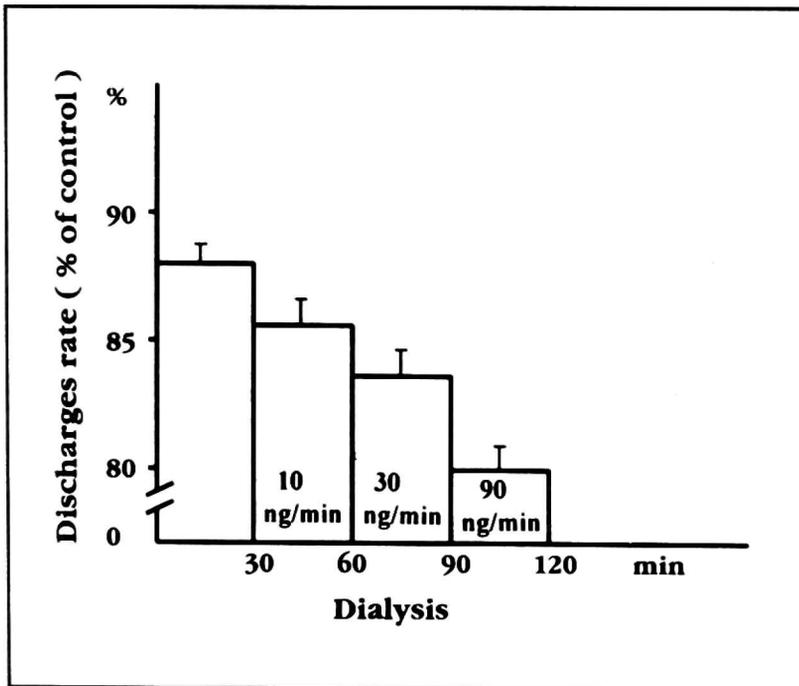

Fig. 7. Dose response change in discharges rate of the isolated auricle of the right atrium after administration of 20 µL of blood dialysate from the *sella turcica* caused by angiotensin II intra-arterial infusion. Angiotensin II at doses 10, 30, 90 ng/100 g b.w./min was infused at the beginning of the 30—60, 61—90, 91—120 min dialysis and caused a dose-dependent increase in cardiodepressant activity in dialysates. (Value are means $\pm$ SE, *$P < 0.05$ vs before angiotensin II infusion, n = 8)

DISCUSSION

Our previous reports presented results showing that a cardiodepressant factor is present in extract from bovine hypothalamus (10) and in medium incubating *in situ* the posterior pituitary lobe (11, 15). Electric stimulation of afferent fibres in vagus nerves or angiotensin II infusion significantly increased cardiodepressant factor release from the posterior pituitary lobe into the blood (15, 16).

Cardiodepressant factors have been reported to be released into the general circulation in all types of circulatory shock (1, 4, 6, 17). One of the best known shock factors is myocardial depressant factor, which exerts a depressant effect on myocardial contractility (18). This factor is produced in the ischemic splanchnic region primarily in the pancreas and has a molecular weight of 500 — 1,000 d (1, 3, 19). Cardiodepressant factor was also found in incubated pancreas homogenates and in the isolated perfused pancreas (19, 20).

Some investigators have shown in *in vivo* and *in vitro* experiments that a cardiodepressant factor may be released from the small intestine during intestinal ischemia (21, 22).

In recent years a cardiodepressant factor (mol wt < 1,000 d) has been also revealed by Hallström *et al.* (8, 9, 23) in the plasma ultrafiltrates of dogs after

hypovolemic-traumatic shock. The authors reported that negatvie inotropic and chronotropic effect of CDF is connected with blockade of the calcium inward current.

The present experiments showed that the medium incubating *in situ* the posterior pituitary lobe in rats collected during angiotensin II infusion had higher cardiodepressant activity than medium collected prior to angiotensin II infusion. It was also shown, that angiotensin II produce a dose-dependent elevation in cardiodepressant activity in the blood dialysate outflowing from the region of the *sella turcica* (hypothalamus, pituitary). Results of this study suggest that simultaneous release of cardiodepressant factor and vasopressin from the posterior pituitary lobe into blood is induced by angiotensin II. The dose of angiotensin II administered in our experiment are in agreement with those previously utilized in rats (100—900 ng/kg/min (24)).

Angiotensin II is involved in the central regulation of vasopressin secretion (25, 26). Bonjour and Malvin first reported that the intravenous infusion of angiotensin II (10 ng/kg/min) caused significant increase in plasma levels of vasopressin (27). An increase in vasopressin release was also reported after intra-arterial infusion (28, 29) as well as intracerebroventricular administration (30, 31). These results accord well with the data of *in vitro* studies showing enhanced release of vasopressin to the incubation medium containing a part of the hypothalamus together with the pituitary (32, 33). Subsequent studies have provided evidence that circulating angiotensin II stimulates the vasopressin release via binding to receptors in the circumventricular organs (34).

In our experiments intra-arterial infusion of angiotensin II increased also the release of cardiodepressant factor from the posterior pituitary lobe into incubating medium and into blood outflowing from the region of *sella turcica*.

Intravenous infusion of vasopressin decreases the heart rate (35, 36). Osborn *et al.* (35) observed that vasopressin-induced bradycardia in rats is associated with the reduction of tonic activity of sympathetic fibres or with the increase in tonic activity of vagal nerve fibres runnning to the heart. The bradycardia may be also a consequence of the vasopressin-induced reduction in coronary blood flow (37, 38) since this hormone is reported to be without effect on the rate of myocardial contraction *in vitro* (39, 40). In our experiments, similary, vasopressin in concentration from 2×10^{-7} mol/L to 2×10^{-4} mol/L had no effect on an isolated auricle rate (43). Our results are in agreement with other ones, indicating that cardiodepressant activity of medium incubating the posterior pituitary lobe is not caused by vasopressin.

Some investigators have observed that angiotensin II causes an increase in oxytocin (18) as well as Substance P release (41).

Oxytocin is a neuropeptide which has a positive inotropic effect on isolated papillary muscles (42). Our previous investigations showed that oxytocin had no effect on contraction frequency of the isolated heart auricle (43).

Some pharmacological studies of substance P in isolated perfused heart and isolated right atrium (44) have shown that substance P has a negative chronotropic effect. On the contrary, substance P administered both peripherally and centrally causes tachycardia (45, 46). In our studies substance P had no direct chronotropic effects on the isolated auricle (43).

It has also been found *in vitro* experiments that other neuropepides present in the posterior pituitary lobe, such as, leu-enkephalin, met-enkephalin, angiotensin II, delta sleep inducing peptide and atrial natriuretic factor in concentration from 2.1×10^{-7} do 1×10^{-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 (43).

In the present study, cardiodepressant activity was not induced by acetylcholine because the atropine sulphate (5×10^{-6} mol/L) was present in Ringer-Lock solution, in which the auricle was bathed.

The data presented in this report indicate that cardiodepressant substance (s) released from the posterior pituitary lobe differ from MDF produced during haemorrhagic shock. MDF appears to originate to a large degree from the ischemic pancreas (4) whereas the cardiodepressant factor originates from the posterior pituitary lobe. MDF is a peptide or glucopeptide having a molecular weight of 500 — 1,000 d (4, 7). Cardiodepressant factor from the posterior pituitary lobe is also probably a peptide (11). It passes through the dialysing membrane (20 kDa cutoff) of minidialysator, therefore its molecular weight does not exceed 20 kDa. Both MDF and cardiodepressant factor circulate in the blood and depress the heart. MDF accumulates in the blood during the late stage of shock and exerts direct negative inotropic effect, whereas cardiodepressant factor exerts direct negative chronotropic effect.

In summary, angiotensin II produced an increase in cardiodepressant activity in the fluid incubating the posterior pituitry lobe '*in situ*'. It also tended to increase in cardiodepressant activity in the dialysate from the blood outflowing from the region of the *sełła turcica* in a dose-dependent manner. During shock cardiodepressant factor released simultaneously with vasopressin probably decreases the heart contraction rate and inhibits the unfavourable effect of vasopressin on coronary blood flow.

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