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Regulatory Peptides 90 (2000) 93–99

REGULATORY PEPTIDES

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Central natriuretic peptides regulation of peripheral atrial natriuretic factor release

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Received 25 August 1999; received in revised form 7 April 2000; accepted 10 April 2000

Abstract

Atrial natriuretic factor (ANF) and C-type natriuretic peptide (CNP) receptors have been described in encephalic areas and nuclei related to the regulation of cardiovascular as well as sodium and water homeostasis. Stimulation of the anterior ventral third ventricular region of the brain modifies plasma ANF concentration, suggesting the participation of the central nervous system in the regulation of circulating ANF. The aim of this work was to study the effect of centrally applied ANF or CNP on plasma ANF. Normal and blood volume expanded rats (0.8 ml isotonic saline/100 g body weight) were intra cerebralventricularly injected with 1, 10 or 100 ng/μl/min ANF. Blood volume expanded animals were also centrally injected with the same doses of CNP. Blood samples were collected at 5 and 15 min. after intracerebralventricular administration of either ANF or CNP. Centrally applied ANF did not affect circulating ANF in normal blood volume rats. In blood volume expanded animals both ANF (1, 10 or 100 ng/μl/min) and CNP (1 ng/μl/min) decreased plasma ANF concentration after 15 min. Moreover, CNP (10 and 100 ng/μl/min) lowered circulating ANF levels not only at 15 min but also at 5 min. Neither ANF nor CNP elicited any change in mean arterial pressure and heart rate in normal and blood volume expanded rats. These results suggest the existence of a central regulation exerted by natriuretic peptides on circulating ANF levels. Furthermore, this is the first study reporting an effect on plasma ANF induced by centrally applied CNP.

Keywords: Plasma atrial natriuretic factor; C-type natriuretic peptide; Blood volume expansion; Intracerebralventricular injection

1. Introduction

Atrial natriuretic factor (ANF) is a 28 amino acid peptide mainly synthesized by mammalian atrial cardiocytes. This peptide has a direct hypotensive effect by (a) decreasing peripheral vascular resistance through vasodilation and (b) reducing blood volume due to its potent diuretic and natriuretic mechanisms [1,2]. ANF is the main hormone released in response to blood volume expansion (BVE) being the physiological antagonist of the water conservation renin–angiotensin system (RAS).

The natriuretic peptide (NP) family is composed of two other members: brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP). BNP is a 32 amino acid peptide mainly secreted by the ventricles that contributes together with ANF to maintain normal hemodynamics. CNP, a 22 amino acid peptide, is synthesized and released by endothelial cells and it is an important component of an autocrine endothelium-derived vasomodulatory system [3]. Although CNP shares some properties of the other NP, it

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0167-0115/00/$ – see front matter
PII: S0167-0115(00)00115-4

does not have a natriuretic effect and it is the most important NP present in brain [4], where it was originally described.

ANF and BNP are continuously released from the heart, but appropriate mechanical or neuroendocrine stimuli increase their rate of release. Atrial stretch constitutes the main stimulus for NP release together with α-adrenergic stimulation and endothelin-1 [5–7]. The role of glucocorticoids, prostaglandins and acetylcholine, as physiological stimulus contributing to enhance ANF secretion, is still controversial. Endothelial CNP synthesis and secretion is regulated by growth factors [8], cytokines and by the other NPs [9].

All the NPs have been described in brain areas intimately related to the control of cardiovascular function as well as water and sodium homeostasis and hormonal secretions [10]. Both ANF and CNP mRNAs have been reported in the central nervous system (CNS), which supports local synthesis and their role as neuromodulators.

Stimulation of the anterior ventral third ventricular (AV3V) region stimulates natriuresis and increases plasma ANF while it reduces ANF concentration in the brain [11]. Furthermore, lesions induced in the AV3V region abolish peripheral ANF response to acute or chronic volume overload. This area seems to be essential in resting and volume expansion-induced ANF release [12]. These findings suggest that CNS is involved in the regulation of cardiac ANF release. Increasing evidence supports the role of CNP as the main natriuretic peptide in the brain. We have previously reported that CNP modifies catecholamine (CA) metabolism at lower doses than those required for the other NP to elicit the same effect [13]. On this basis the aim of the present work was to study the role of centrally applied ANF or CNP on ANF circulating levels in normal and volume expanded rats. We hypothesize that this NP system located in the CNS could regulate the endocrine cardiac ANF secretion.

2. Materials and methods

Male Wistar rats weighing between 250 and 300 g (from the Faculty of Pharmacy and Biochemistry, University of Buenos Aires) were used in the experiments. Animals were housed in steel cages and maintained at a temperature of 22–24°C in a controlled room with 12 h light–dark cycle (light from 7:00 to 19:00). All rats were given water and commercial Purina chow ad libitum.

Cannulation of the lateral cerebroventricle was performed under anesthesia by means of a David Kopf 900 stereotaxic instrument. Rats were placed on a stereotaxic frame, the skin overlying the midline of the skull was incised and a small hole was drilled through the appropriate area of the skull. A 23-gauge stainless steel cannula was placed in the right lateral ventricle according to the coordinates of Paxinos and Watson [14] atlas (1.3 mm posterior to the bregma, 2.0 mm lateral to midline and 4.0 mm ventral to the skull surface). The cannula was anchored with a stainless steel screw in the skull and covered by dental acrylic. The rats were then allowed to recover from surgery in individual cages for a week.

2.1. Rats with normal blood volume (NBV)

Animals were anesthetized with chloral hydrate (1.3 mg/kg i.p.), the obturator of the intracerebralventricular (i.c.v.) cannula was removed, and a 30-gauge injector was connected to a Hamilton microliter syringe by silastic tubing, and inserted in the guide cannula. The right femoral vein and artery were cannulated with a polyethylene catheter (P40 catheter, Rivero and Cia, Buenos Aires, Argentina).

The animals were randomly divided into the following groups: (a) control group: i.c.v. injected with a bolus of 1 μl of artificial cerebrospinal fluid (aCSF) in 1 min. aCSF has the following composition in mM: NaCl 125, $CaCl_2$ 1.2, $MgCl_2$ 0.9, $NaHCO_3$ 25, Na_2HPO_4 0.5, KH_2PO_4 0.5, glucose 4.3, and urea 6.5; and infused at a rate of 1 μl/min (b) ANF group: i.c.v. injected with 1, 10 and 100 ng/μl in 1 min ANF (rat, 99–126, Peninsula Lab., Belmont, CA, USA) and injected in bolus as previously described. ANF was dissolved in ACSF (total volume 1 μl) to restore an equivalent volume of blood, obtained from rat donors, and to collect venous blood samples (1 ml), respectively. Blood samples for plasma ANF measurement were collected from the femoral vein. Blood volume was restored after each blood collection by the administration of an equal amount of blood from donor rats. Basal: (before the ANF i.c.v. injections), at 5 and 15 min post i.c.v. injections. Blood samples were centrifuged and plasma stored a −70°C.

2.2. Rats with blood volume expansion (BVE)

In a second set of experiments, a BVE (10% of body weight) was performed in others rats 7 days after the surgery for the i.c.v. cannula implantation. BVE was induced in rats in order to stimulate ANF release from atria [15]. The animals were anesthetized with chloral hydrate and the femoral vein catheterized, as described above. Volume overload was achieved by the endovenous infusion of 0.8 ml of isotonic saline/100 g of body weight for 30 min. Immediately after volume expansion control animals received aCSF, and experimental animals received ANF or CNP-22 (rat, Peptides International, Louisville, KY, USA) at doses of 1, 10 or 100 ng dissolved in aCSF and infused as described above.

Blood samples were collected and stored as previously described. Plasma ANF extraction and radioimmunoassay (RIA) were performed as described by Sarda et al. [16]. Briefly, plasma samples were acidified by adding 100 μl/ml of 1 M HCl and passed through Sep-Pak C_{18}-

cartridges (Waters, Milford, MA, USA) previously activated with 5 ml acetonitrile containing 0.1% trifluoroacetic acid (TFA), followed by 5 ml of 0.1% TFA. The cartridges with the adsorbed peptide were washed with 20 ml of 0.1% TFA and then eluted with 3 ml of acetonitrile containing 0.1% TFA. Samples were dried and then stored at −70°C until assayed. Residues were dissolved in 1 ml of 0.1 M phosphate buffer (pH 7.4) containing 0.1% bovine serum albumin, 0.01% sodium azide, 0.05 M NaCl, and 0.1% Triton. Samples were centrifuged and supernatants assayed for ANF RIA. Anti-rat ANF (99–126) was purchased from Peninsula Lab. Inc. (Belmant, CA, USA) and labeled ANF from New England Nuclear (Boston, MA, USA). Plasma ANF levels in rats with NBV are expressed in pg/ml.

In rats with BVE, results are expressed as the ratio between plasma ANF concentration at 5 or 15 min/plasma ANF concentration at time zero (BVE when the induced secretion of cardiac ANF is maximum). Those ratios express the variations of plasma ANF concentration after i.c.v. injection of ANF or CNP in BVE rats.

2.3. Systemic blood pressure (SBP) and heart rate (HR) measurements

In order to study i.c.v. applied ANF and CNP on SBP and HR, other set of experiments was performed. The animals were prepared as described above and randomly divided into the following groups: (a) ANF and (b) CNP groups. SBP was measured using a blood pressure transducer (Statham 923 Db) by inserting a cannula into the right femoral artery and being recorded on a Grass Model 7D polyghraph. Heart rate was computed from the arterial pressure signal by a cardiotachometer.

2.3.1. Rats with NBV

SBP was continuously recorded along all the experimental period. ANF or CNP were injected in three consecutive periods (1, 10 and 100 ng doses, dissolved in aCSF), into the i.c.v. cannula as previously described. After each injection a resting period of 10 min. was allowed before the next dose.

2.3.2. Rats with BVE

In other experiments ANF or CNP effects were studied in BVE rats. BVE was induced as previously described. SBP was recorded continuously along all the experimental period. After 30 min. of BVE period, the rats were i.c.v. injected with ANF or CNP following the same protocol as previously described.

Results are expressed as the mean±SEM. Statistical analysis was performed by one way analysis of variance (ANOVA) and the *t*-test modified by Bonferroni. Values of $P < 0.05$ or less were considered statistically significant.

Table 1
Changes in mean arterial pressure (ΔMAP) (mmHg) in rats with normal blood volume (NBV) or blood volume expansion (BVE) after different doses of i.c.v. injected ANF ($n = 3$) or CNP ($n = 4$)

Dose (ng)	ΔMAP (mmHg)			
	0	1	10	100
ANF				
NBV	0.0±0.0	0.0±0.0	0.0±0.0	−3.3±3.0
BVE	−1.0±1.0	1.0±1.0	3.7±1.2	1.0±4.9
CNP				
NBV	0.0±0.0	0.0±0.0	−6.0±2.3	1.3±1.3
BVE	0.7±1.5	−2.0±3.7	3.0±2.5	2.0±1.2

3. Results

In order to study the possible regulation exerted by central NP on MAP and ANF release, different concentrations of ANF or CNP were i.c.v. injected in normal and BVE rats.

Tables 1 and 2 show the changes in mean arterial pressure (ΔMAP) and heart rate, respectively, in NBV and BVE rats. Neither ANF nor CNP elicited any significant change in ΔMAP in any studied group. Mean arterial pressure (MAP) and heart rate (HR) were measured in NBV and BVE rats in basal conditions. There were significant differences in MAP between both groups (115.3±3.5 vs. 129.8±4.3 mmHg, $P < 0.01$, $n = 7$). In the other hand, HR was not significantly affected by volume expansion (460±17 vs. 452±19 beats per minute, $n = 7$).

Centrally applied ANF at any given doses (1, 10 or 100 ng) did not modify plasma ANF in NBV rats (74±4 pg/ml, $n = 20$) (Table 3). However, ANF circulating levels were dramatically increased in BVE rats (356%,

Table 2
Changes in heart rate (HR) beats per minute (bpm) in rats with normal blood volume (NBV) or blood volume expanded (BVE) after different doses of i.c.v. injected ANF ($n = 3$) or CNP ($n = 4$)

Dose (ng)	Heart rate (bpm)			
	0	1	10	100
ANF				
NBV	−3±3	5±3	0±0	−3±3
BVE	−6±6	−6±6	3±3	3±3
CNP				
NBV	−2±2	10±10	−5±2	−2±2
BVE	−8±5	−2±2	3±3	6±6

Table 3
Plasma ANF levels in rats with normal blood volume (NBV).

Rats	Basal	5 min	15 min
Controls ($n = 6$)	70±11	64±10	61±11
ANF 1 ng ($n = 4$)	75±10	64±5	72±11
ANF 10 ng ($n = 5$)	78±7	77±7	83±5
ANF 100 ng ($n = 5$)	73±8	77±8	78±5

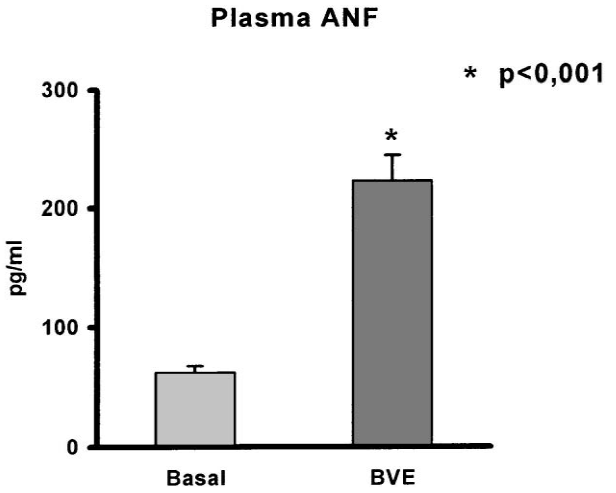

Fig. 1. Plasma ANF concentrations in rats in basal conditions and after a blood volume expansion (BVE) with 0.8 ml of isotonic saline/100 g of body weight ($n = 34$). The columns are the means, and the vertical bars are the SEM; n = number of cases.

$P < 0.001$, $n = 34$) in line with previous investigations showing that cardiac ANF is induced by volume overload [17,18] (Fig. 1).

Fig. 2 shows the variations in plasma ANF in BVE rats after NPs administration. In control and i.c.v. ANF injected rats the 5 min/0 min and the 15 min/0 min ratios indicate that plasma ANF was significantly decreased by centrally applied 1 ng ANF (33%, $P < 0.05$, $n = 4$), 10 and 100 ng ANF (50%, $P < 0.001$, $n = 5$ in both groups), compared with aCSF injected rats (controls, $n = 6$).

The ratios for centrally applied CNP in BVE rats are shown in Fig. 3. At the lowest dose tested (1 ng) CNP induced a significant reduction of plasma ANF at 15 min (50%, $P < 0.005$, $n = 4$). However, higher doses of CNP (10 and 100 ng) elicited a marked reduction of circulating ANF at 5 min, showing a faster response to i.c.v. injected CNP (40%, $P < 0.05$, $n = 5$ in both groups). The decrease was also observed at 15 min (50%, $P < 0.001$, $n = 5$ in both groups).

4. Discussion

The present study shows that: (1) the i.c.v. injection of ANF in anesthetized rats in basal conditions (NBV) did not affect either the peripheral (cardiac) ANF release or the mean blood pressure or heart rate, in line with previous findings [19,20]; (2) centrally applied ANF at doses of 1, 10 and 100 ng significantly decreased peripheral ANF release 15 min after BVE and (3) centrally applied CNP

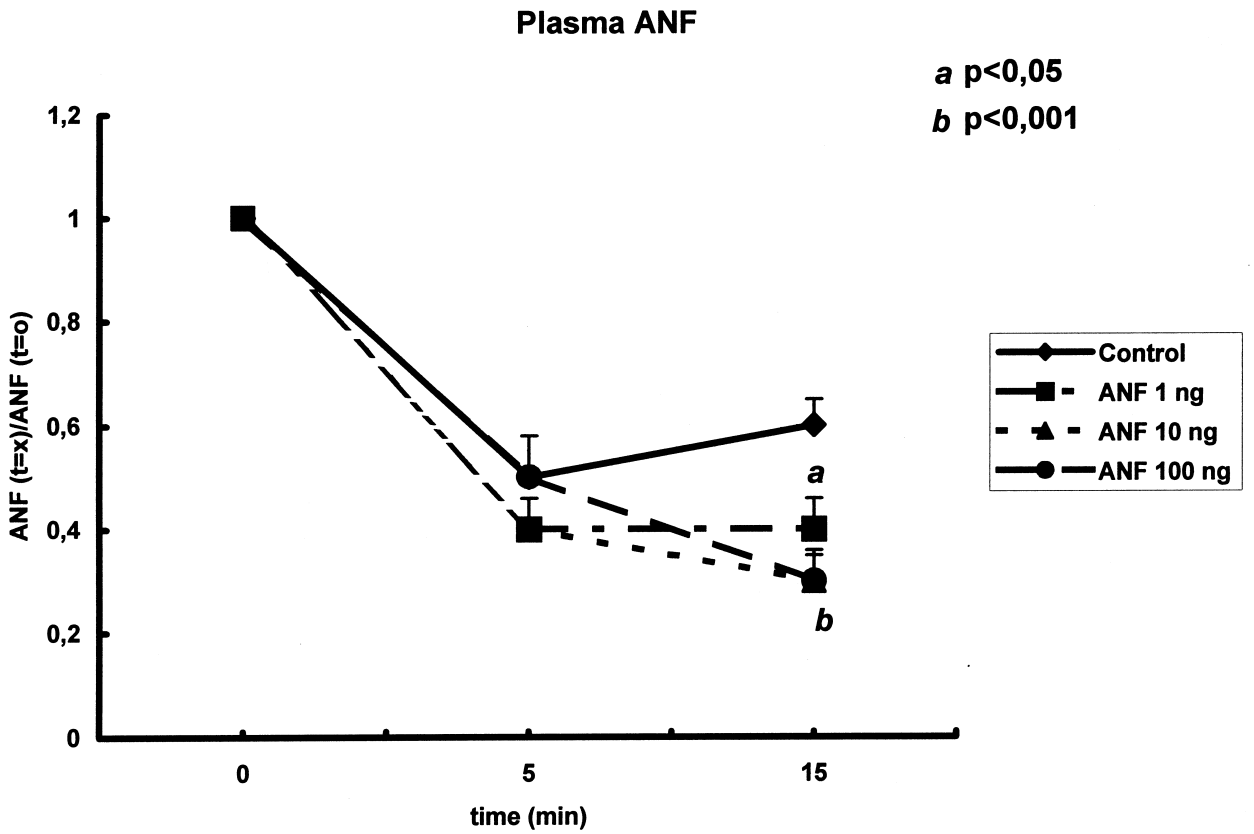

Fig. 2. Plasma ANF ($t = x$)/plasma ANF ($t = 0$) ratios in controls ($n = 6$) and ANF 1, 10 and 100 ng/μl i.c.v. injected rats ($n = 4$, 5 and 5, respectively). Time = 0: blood volume expansion (BVE), when the induced secretion of cardiac ANF is maximum; and $t = x$ is 5 or 15 min after BVE. (a and b) Significant changes versus controls. Results are expressed as mean ± SEM; n = number of cases.

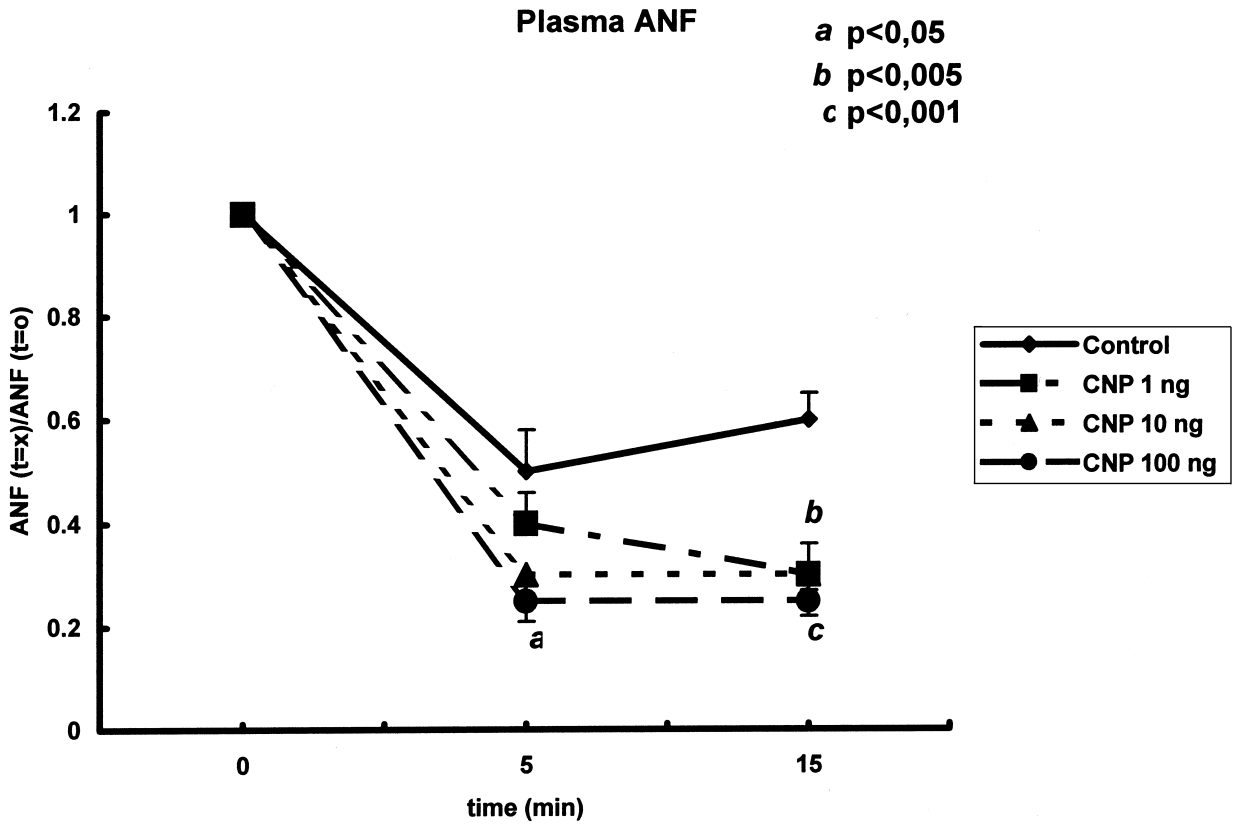

Fig. 3. Plasma ANF ($t = x$)/plasma ANF ($t = 0$) ratios in controls ($n = 6$) and CNP 1, 10 and 100 ng/μl i.c.v. injected rats ($n = 4$, 5 and 5, respectively). Time = 0: blood volume expansion (BVE) time, when the induced secretion of cardiac ANF is maximum; and $t = x$ is 5 or 15 min after BVE. (a, b and c) Significant changes versus controls. Results are expressed as mean ± SEM; n = number of cases.

(1, 10, 100 ng) significantly decreased cardiac ANF release at 15 min after BVE meanwhile the higher doses (10 and 100 ng) decreased peripheral ANF release at 5 and 15 min after BVE demonstrating a faster inhibitory effect of the centrally injected peptide on cardiac ANF secretion.

The release of NPs from the heart is stimulated by mechanical (atrial stretch) as well as neuroendocrine stimuli (endothelin-1 and α-adrenergic stimulation) [6,21]. Glucocorticoids, acetylcholine and prostaglandins have also been involved in NP secretion [2,7]. However, little is known about the possible role of the CNS in the regulation of cardiac ANF secretion. Both, ANF and CNP have been described in the brain. They are synthesized and released in several areas and nuclei of the CNS. Dense ANF binding sites have been reported in circumventricular organs such as the area postrema, choroid plexus, organum vasculosum lamina terminales (OVLT) and subfornical organ. Neural connections also exist between subfornical organ, organum vasculosum lamina terminalis (OVLT) and the paraventricular nucleus of the hypothalamus [10]. Furthermore, NP receptors have been described in association with angiotensin II (Ang II) receptors in discrete encephalic areas and nuclei intimately related to the control of cardiovascular, renal and hydromineral homeostasis [22].

Evidence exists for the presence of ANF in CSF of several species but the concentration is ~20–50 times lower than in plasma (0.5–1 pmol) [23,24]. On the other hand, CNP is the major natriuretic peptide in human CSF being almost undetectable in plasma [25].

In patients with brain injuries the elevated plasma ANF levels suggest that they trigger a central mechanism that modulates peripheral ANF release [26]. Centrally administered ANF into the third or lateral ventricle inhibits salt intake in salt-depleted normally hydrated rats in a dose-dependent manner, suggesting a physiological role for ANF in the regulation of thirst induced by both osmotic and peptidergic stimuli [27]. Moreover, anti-ANF serum administered i.c.v. significantly potentiates water intake in 24 h water-deprived or Ang-II stimulated rats in comparison with that of animals receiving 2 μg ANF i.c.v. [28]. Antunes-Rodrigues et al. [12] showed that lesions in the median eminence or neural lobe of the pituitary gland, that interrupts neuronal pathways projecting from the AV3V region to the neurohypophysis, blocks BVE-induced ANF release.

Evidence suggests that NPs behave as an inhibitory system, their effects are not usually seen in basal conditions but expressed in induced systems. In agreement with this assertion, our results show that centrally applied

ANF did not affect basal circulating ANF levels but both, ANF and CNP, decrease volume overload-induced plasma ANF. Changes in ANF circulating levels induced by centrally applied ANF or CNP are unlikely to be mediated by changes in cerebral blood flow since ANF infusion has no effect on cerebrovascular circulation [29,30].

Neuroendocrine or neural mechanisms may mediate central ANF and CNP effects on cardiac ANF release. The neuroendocrine mechanism may involve: (a) the inhibition of endothelin release, since that peptide is found in several structures of the brain; (b) the well-known ANF inhibitory effect on resting and CRH-stimulated ACTH secretion that eventually decrease circulating glucocorticoids [31] and (c) an interaction with posterior pituitary hormones as AVP or oxytocin. Recent evidence indicates that BVE activates putative ANFergic neurons that stimulate the release of oxytocin from the neurohypophysis that would act on oxytocin receptors on the heart mediating the release of ANF [32]. In our experiments the pharmacological doses of ANF could abolish oxytocin release.

A great body of evidence supports the view that NPs inhibit noradrenergic neurotransmission in CNS as well as in the adrenal medulla. We have previously reported that NPs inhibit basal as well as evoked NE release and synthesis and decrease CA turnover [33,34] these effects being mediated by biological type A and B receptors coupled to guanylate cyclase activation on cGMP generation as second messenger. Furthermore ANF and CNP increase neuronal NE uptake. The effect of CNP is achieved with lower doses than those used for ANF to elicit the same effects. On the other hand, centrally applied ANF has been reported to reduce sympathetic renal as well as splanchnic activities in sinoaortic denervated rats [35]. Taken together these findings suggest that the inhibition of noradrenergic neurotransmission is likely to be implicated in the decreased plasma ANF levels induce by centrally applied NP in situations of volume overload.

Little is known about central CNP actions on peripheral ANF release. In most species, including man and rat, the brain content of CNP is greater than that of BNP and ANF [10]. In a previous work we reported that CNP displays similar effects to those found for ANF in NE release, being the CNP effect higher than those of the others natriuretic peptides [13]. Furthermore, the threshold concentration for CNP to affect evoked NE release was 1 pM which is within the physiological range. In the present work i.c.v. injection of CNP elicited a faster response (5 min at doses of 10 and 100 ng) than that of ANF injection (15 min at the same doses). In addition, CNP showed the inhibitory effect on plasma ANF release even at the lowest dose (1 ng). The last observation is possibly related to the fact that NPR-B is the most abundant NP receptor subtype in the CNS. The binding affinity of NPR-B is higher for CNP than for ANF.

In agreement with previous investigations [19,36,37], our results indicate that blood pressure and heart rate were unaffected by centrally administered ANF. In addition, we also found that CNP did not elicit any change on those hemodynamic parameters. These findings support the view that the inhibitory effect of centrally applied ANF or CNP on peripheral ANF release is not related to changes in blood pressure or heart rate.

It is possible that the effects of ANF and CNP may be exerted on the same central areas, where NPR-A and NPR-B are co-localized. We have previously demonstrated that ANF and CNP act in the same areas and nuclei in the CNS eliciting similar effects [38]. Although all NPs can bind to the three receptors subtypes with different affinity, it must be pointed out that the NPR-B receptor is the most abundant subtype in the CNS.

In conclusion, the present results suggest the existence of a feedback mechanism that regulates cardiac ANF release mediated by central ANF and CNP in encephalic areas close to the AV3V region, where the largest accumulations of ANF-containing cells were found, including preoptic and periventricular nuclei, and the anterior wall of the third ventricle with the associated OVLT, a critical area in the regulation of fluid homeostasis and cardiovascular function. This response is elicited only in response to acute volume expansion but not in basal conditions in agreement with previous findings. To our knowledge this is the first work to report an effect of centrally applied CNP on cardiac ANF release. CNP exerted a rapid inhibitory response even at the lowest concentration further supporting the hypothesis that CNP is the main member of the natriuretic peptide system in the brain.

Acknowledgements

We wish to thank Dr. Martín Rodríguez Fermepín, Dr. Susana Gorzalczany and Miss Carmen S. Cavallero for their excellent technical assistance. This work was supported by grants from the University of Buenos Aires (FA 134), Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET) (PID-3235) and ANPCYT (PMT-PCC116).

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