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Vasopressin and angiotensin receptors of the medial septal area of the brain in the control of thirst and salt appetite induced by vasopressin in water-deprived and sodium-depleted rats

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Abstract

In this study we investigated the influence of d(CH_2)$_5$-Tyr (Me)-AVP (A_1AVP) and [Adamanteanacatyl[1],D-ET-D-Tyr[2], Val[4], aminobutyril[6],A[8,9]]-AVP (A_2AVP), antagonists of V_1 and V_2 arginine[8]-vasopressin (AVP) receptors, respectively, as well as the effects of losartan and CGP42112A, antagonists of angiotensin II (ANGII) AT_1 and AT_2, receptors, respectively, on water and 0.3 M sodium intake induced by water deprivation or sodium depletion (furosemide treatment) and enhanced by AVP injected into the medial septal area (MSA). A stainless steel cannula was implanted into the medial septal area (MSA) of male Holtzman rats AVP injection enhanced water and sodium intake in a dose-dependent manner. Pretreatment with V_1 antagonist injected into the MSA produced a dose-dependent reduction, whereas prior injection of V_2 antagonist increased, in a dose-dependent manner, the water and sodium responses elicited by the administration of AVP. Both AT_1 and AT_2 antagonists administered into the MSA elicited a concentration-dependent decrease in water and sodium intake induced by AVP, while simultaneous injection of the two antagonists was more effective in decreasing AVP responses. These results also indicate that the increase in water and sodium intake induced by AVP was mediated primarily by MSA AT_1 receptors.

Keywords: Arginine vasopressin; Vasopressin V_1 antagonist; Vasopressin V_2 antagonist; Angiotensin AT_1 antagonist; Angiotensin AT_2 antagonist; Water intake; Sodium intake; Medial septal area

1. Introduction

Vasopressin (AVP) is a cyclic peptide produced and secreted by the hypothalamus–neurohypophysial system in response to increased plasma osmolarity or to decreased blood pressure/volume (Arroyo et al., 1994). AVP plays an important role in the regulation of the water and sodium balance. Reflex and behavioral responses are both necessary to correct water and sodium imbalances and maintain body fluid homeostasis; AVP participates in these mechanisms (Johnson and Thunhorst, 1997). The V_1AVP receptor is found in several brain structures including the septum (Dorsa et al., 1988; Poulin et al., 1988). The V_1 receptor interacts with a sensitive pertussin-toxin sensitive G-protein in the rat brain septum (Swank and Dorsa, 1991), which may be involved in mediating AVP-induced stimulation of phosphatidylinositol hydrolysis (Shewey et al., 1989; Shewey and Dorsa, 1988), similarly to the case of systemic receptors. Activation of the V_2 receptor in renal collecting ducts by circulating AVP leads to an increase in intracellular cAMP by stimulation of adenylate cyclase activity through protein G_S (Verbalis, 2002). Some

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physiological and behavioral studies support the existence of central nervous system V_2 receptors (Abe et al., 1983; Noszczyk et al., 1993). Adenylate cyclase-linked V_2 receptors might be more sensitive to the regulatory effects of exposure to agonist than phospholipase C-coupled V_1 receptors (Swank and Dorsa, 1991).

The systemic or central administration of angiotensin II (ANG II) increases the secretion of AVP (Renaud et al., 1992; Yamamoto et al., 1978). Regarding thirst, sodium appetite and secretion of AVP, in response to intracerebroventricular (icv) administration of ANG II, several studies have demonstrated that the administration of losartan (an ANG II AT_1 receptor specific antagonist) blocks these responses in rats (Beresford and Fitzsimons, 1992; Rowland et al., 1992). Studies of central administration of AT_2 antagonists have shown variable water and sodium intake responses. Some investigators observed an inhibitory influence on water and sodium intake as well as on AVP release in rats, after administration of AT_2 blockers into the cerebral ventricles (icv) (Cooney, 1994; Cooney and Fitzsimons, 1993; Rowland et al., 1992). The icv administration of an AT_2 antagonist reinforced the drinking and AVP release in response to ANG II (Hohle et al., 1995). Hogarty and Phillips (1991) described a central AVP-mediated drinking response to be inhibited by AT_1 and partly by AT_2 receptors. The reason for the contradictory results with AT_2 antagonists in rats has not been explained yet. It has been suggested that inhibitory results with high doses of some AT_2-selective icv antagonists may be due to an action at the central AT_1 receptors or an in vivo change in the AT_1 antagonist (Cooney and Fitzsimons, 1993).

Considering the importance of the MSA in water and sodium regulation in rats, the present experiments were designed to determine the participation of V_1 and V_2 *v*asopressinergic receptors of the MSA, as well as the effects of AT_1 and AT_2 angiotensin receptors in the thirst and sodium appetite induced by introduction of AVP into the MSA under water deprivation or sodium depletion conditions.

2. Methods

2.1. Animals

Male Holtzman rats weighing 300–350 g were used. The animals were put in individual stainless steel cages with free access to a normal sodium diet (Purina Rat chow 5012), water and a 0.3 M NaCl solution. Temperature was maintained at a constant 23 °C, with a 12:12-h light–dark cycle. The experiments were performed between 9:00 A.M. and 10 P.M.

2.2. Brain surgery

Rats were anesthetized with an Equithesin anesthetic cocktail (0.97 g sodium pentobarbital and 4.25 g chloral hydrate in 100 mL distilled water; 0.33 mL/100 g body weight) and placed in a Kopf stereotaxic instrument. Stainless steel cannulae (0.6 mm outer diameter, 0.33 mm inner diameter) were implanted just above the MSA, using the bregma as reference point. Stainless cannula introduction points were made in the rats' heads and, at these points, cranial bone trepanning was performed with a spherical drill, opening holes with an approximate diameter of 1.5 mm. Stainless steel cannulae were implanted into the MSA using the following coordinates: 0.20 mm caudal to the bregma, 0.0 mm lateral to the sagittal line, and 10.2 mm below the duramater, in conformity to the rat brain atlas of Paxinos and Watson (1986). The tip of the cannula was positioned at a point 0.5 mm above the MSA. Cannulae were attached to the skull using acrylic cement and small screws. Insertion of a close-fitting stylet kept the lumen free of debris and clots. Three days before and 3 days after surgery, the animal received prophylactic doses of penicillin. After brain surgery, the animals returned to their individual metabolic cages, with access to granular chow, tap water, and 0.3M NaCl solution for 1 week, until the day of the experiment. The procedures conformed to the National Institutes of Health Guide for Care and Use of Laboratory Animals.

2.3. Drugs

Furosemide was dissolved in water with pH adjusted to 9.0 with 1 M NaOH. The other drugs were dissolved in sterile isotonic saline immediately before each experiment. Injections into rat brains were made using a Hamilton-type syringe (5 μL) connected to a PE-10 polyethylene tube and an injector needle (0.3 mm o.d.) that was 0.5 mm longer than the cannula fixed to the skull. A volume of 0.5 μL was delivered over 20–30 s. The drugs used were: Arginine^8–vasopressin (AVP), [Adamanteanacatyl^1,D-ET-D-Tyr^2, Val^4, aminobutyril^6,Arg^{8,9}]-vasopressin (A_2AVP) (both Sigma Chemical Co, St Louis, MO, USA), d(CH_2)$_5$-Tyr (Me)-AVP (A_1AVP) (Bachem Inc., Torrance, CA, USA), Losartan (DuPont, Merck, Wilmington, DE, USA), CGP42112A (RBI, Natick, MA, USA) and Furosemide (Elkins-Sinn, Cherry Hill, NJ, USA).

2.4. Induction and measurement of water intake

Rats had access to water and food ad libitum and were put in the metabolic cages at least 5 days before the experiments began. The amount of water ingested in the various experiments was measured with 0.1 mL-graduated glass burettes adapted with a metal drinking spout. Intake was induced by water deprivation during the 24 h that preceded the experiment. Before the experiment, the burettes containing water were removed from the cages.

To observe the effects of AVP on water intake in water-deprived rats, 10, 20, 40, 80 and 160 nmol of AVP in saline was injected just before offering water burettes to the animals. AVP doses were used in random order in the experiments. In the first two experiments, the first half were control rats, receiving vehicle injections, and the second half received drug injections with the defined dose. The opposite occurred in the following two experiments: the first half received the drug and the second, control (saline).

To observe the effects of AVP and ANGII, antagonists, A_1AVP, A_2AVP, losartan and CGP42112A (10, 20, 40, 80 and 160 nmol) and the vehicle (0.15 M NaCl) were administered, either individually or combined, with 40 nmol AVP injections. When antagonists were combined, they were injected 10 min before AVP. Water burettes were offered immediately after brain injections. Intake recordings started immediately after AVP or vehicle injection and continued for 4 h. The interval between successive drug injections was at least 5 days.

2.5. Induction and measurement of 0.3 M NaCl intake

The amount of 0.3 M NaCl ingested in the various experimental situations was measured with 0.1 mL-graduated glass burettes adapted with a metal drinking spout. The animals had no access to food during the ingestion experiments. Rats had access to water and 0.3 M NaCl tubes 24 h a day for 5 days before the experiments.

The rats were subjected to a basal ingestion of 0.3 M NaCl in response to two 10 mg/kg subcutaneous injections of furosemide, separated by a 2 h interval. The cages were immediately washed after furosemide treatment so that rats could be confined in a sodium-depleted environment. The normal food was replaced by a sodium-depleted diet and the rats were kept without 0.3 M NaCl for 24 h (water burettes were not removed). After this period, rats had access to water and 0.3 M NaCl solution.

The same procedures as those used to assess the effects of drug injections on water intake were followed in sodium-depleted rats, to observe effects on sodium intake.

The recording of sodium intake started immediately after MSA injections with AVP or vehicle and continued for 4 h. Manipulations were spaced at least 5 days apart.

2.6. Histological analysis

At the end of the experiments, the animals received an injection of 2 μL of fast green dye into the MSA. They were deeply anesthetized with ether and perfused transcardially with saline followed by 10% formalin. The brains were removed, frozen and then cut into 20–30 μm sections; stained with cresyl violet, and analyzed by light microscopy to confirm MSA injection sites.

Typical MSA injection sites, as shown in Fig. 1, are centered in the intermediate and caudal areas of the medial septum. In some rats there was a small amount of fast green dye in the lateral ventricles and lateral septal area, and these were excluded from the analysis. From a total of 76 rats used in this study, 64 rats had histologically confirmed injections into the MSA, and they were analyzed statistically and included in the results.

2.7. Statistical analysis

The results are reported as mean+−SE. Repeated-measure analysis of variance was performed to determine the overall main effect and/or interaction. Significant effects were further evaluated by Newman–Keuls post hoc test with the level of significance set at $p<0.05$.

3. Results

3.1. Effects of A_1AVP, A_2AVP, Losartan or CGP42112A on water intake induced by AVP in dehydrated rats

Injections of AVP into the MSA of water-deprived rats increased significantly the water intake in a dose-dependent manner. The AVP dose for the subsequent experiments was chosen close to the median effect (40 nmol). Pretreatment with A_1AVP (10, 20, 40, 80 and 160 nmol) produced a statistically significant decrease, whereas pretreatment with A_2AVP (10, 20, 40, 80 and 160 nmol) produced a statistically significant increase in water intake induced by water deprivation and enhanced by AVP [F (3,180)≡81.39, p≡0.001] (Fig. 2). While MSA injections of 160 nmol of A_1AVP elicited barrel rotation in seven of the twenty-four rats during the first 10–15 min of the test, lowers doses of the V_1 antagonist had no adverse effect on rats' motor function.

Further comparisons showed that MSA injections of the two AVP antagonists injected together, prior to the AVP, had no significant effect on water intake compared with injection of vehicle alone [F (1.90)≡2.35, p≡0.13] in dehydrated rats. The analysis comparing water intake after injections of AVP alone and of both AVP antagonists injected prior to AVP revealed a significant reduction in water intake in the latter case [F (1.80)≡4.71≡, p≡0.033] (Fig. 2).

Treatment with 10, 20, 40, 80 and 160 nmol doses of losartan or CGP42112A and both antagonists together, before AVP, induced a decrease in water ingestion compared to that in response to AVP alone. However, the decrease in water intake was enhanced when the two ANG II antagonists were injected together [F (4.235)≡73.92, p≡0.001] (Fig. 3).

To observe the effects of water dehydration on 0.3 M NaCl intake, one group of rats had one bottle containing water and another containing 0.3 NaCl in their cages. Control injections of

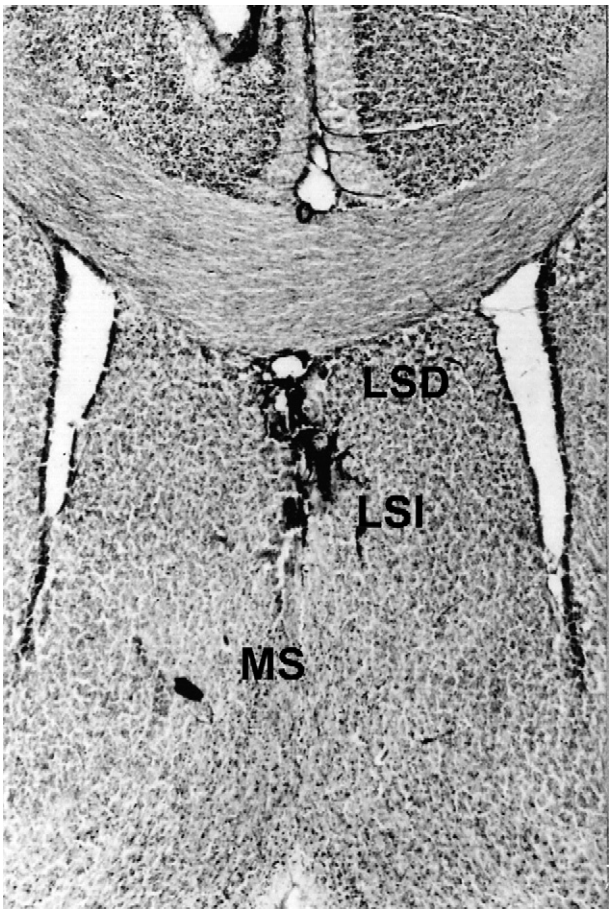

Fig. 1. Photomicrograph showing injection site into medial septal area (MSA). Abbreviations: MS: medial septal nucleus, LSI: lateral septal nucleus intermediate; LSD: lateral septal nucleus, dorsal (magnification ×36).

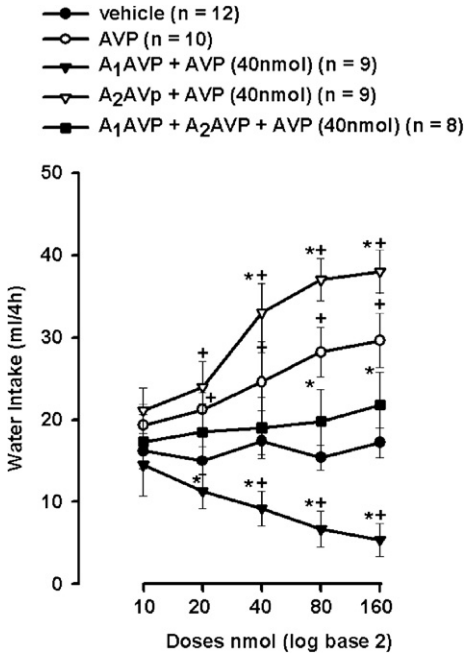

Fig. 2. Effects of A_1AVP and A_2AVP on water intake induced by AVP. Data were analyzed by Student–Newman–Keuls post hoc test (+$p<0.05$ versus vehicle, *$p<0.05$ versus AVP); n, number of rats.

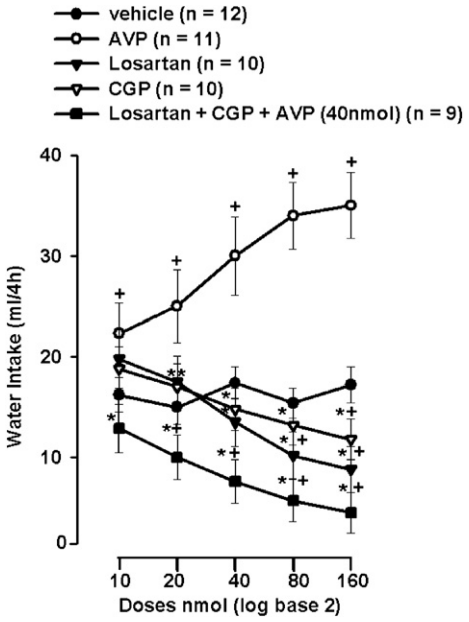

Fig. 3. Effects of losartan, CGP42112A and losartan+CGP42112A on water intake induced by AVP. Data were analyzed by Student–Newman–Keuls post hoc test (+$p<0.05$ versus vehicle, * $p<0.05$ versus AVP); n, number of rats.

the saline vehicle into the MSA had no effect on sodium ingestion (0.4±0.2 ml in 4 h, $n=9$ rats).

There were no differences among responses to saline (vehicle) and various doses of the vasopressin antagonists injected alone [F (2.125)≡0.92, $p\equiv0.40$] in the dehydrated rats. No distinct effects were observed when saline was compared with the doses of the AT_1 and AT_2 antagonists [F (2.120)v0.68, $p\equiv0.51$] in the rats deprived of water. Therefore the effects of the antagonists injected alone are not secondary responses to dehydration.

3.2. Effects of A_1AVP, A_2AVP, Losartan or CGP42112A on 0.3 M NaCl intake induced by AVP in deprived rats

AVP injections into the MSA caused a significant increase in NaCl intake following sodium depletion. Injection of A_1AVP before AVP into the MSA produced a significant relative decrease in sodium intake, whereas pretreatment with A_2AVP increased the sodium intake induced by 40 nmol AVP [F (3.180)≡=50.29, $p\equiv0.001$] (Fig. 4).

Injections of 160 nmol AVP elicited mild barrel rotation in nine out of twenty rats, which abated after 10–15 min. MSA injections of V_1 receptor antagonist had no adverse effect on the rats' motor function.

Simultaneous injections of V_1 and V_2 antagonists before AVP led to a decrease in sodium intake, compared to the effects of injecting vehicle alone, in sodium-deficient rats [F (1.90)≡8.87, $p\equiv0.004$]. However, this decrease after the V_1 and V_2 antagonists were injected together prior to AVP was not as marked as that produced by the injection of the V_1 antagonist alone prior to AVP [F (1.30)≡21.31, $p\equiv0.001$] (Fig. 4).

A significant decrease in sodium intake was observed after losartan or CGP42112A pretreatment, followed by 40 nmol of AVP, compared to the results obtained with various doses of AVP. As observed with water intake, the combined injection of both ANGII antagonists prior to 40nmol of AVP produced a more pronounced reduction in sodium intake than with the AT_1 and AT_2 antagonists injected alone [F (4.220)≡38.49, $p\equiv0.001$] (Fig. 5).

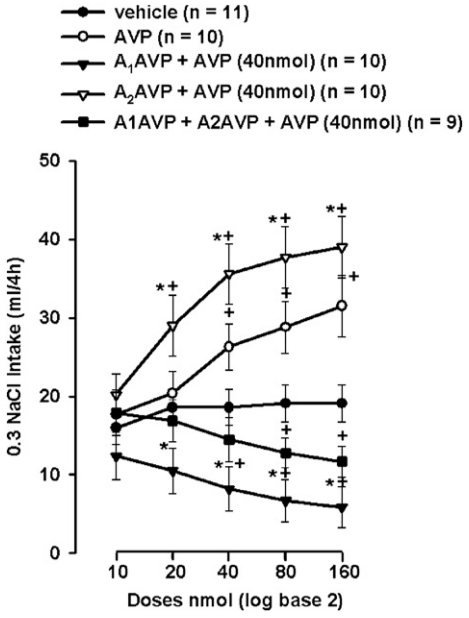

Fig. 4. Effects of A_1AVP and A_2AVP on 0.3 M NaCl intake induced by AVP. Data were analyzed by Student–Newman–Keuls post hoc test (+$p<0.05$ versus vehicle., *$p<0.05$ versus AVP); n, number of rats.

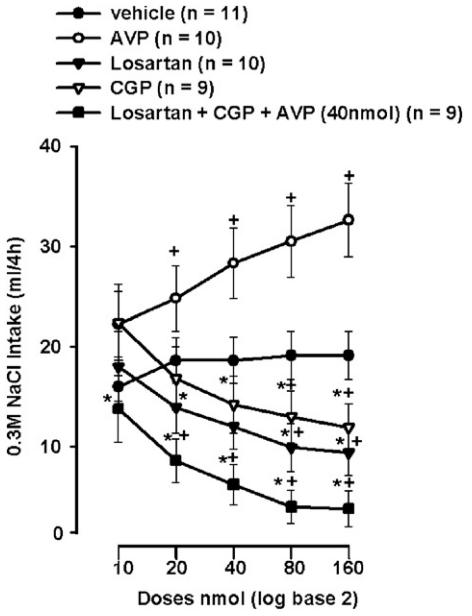

Fig. 5. Effects of losartan, CGP42112A and losartan+CGP42112A on 0.3 M NaCl intake induced by AVP. Data were analyzed by Student–Newman–Keuls post hoc test (+$p<0.05$ versus vehicle, * $p<0.05$ versus AVP); n, number of rats.

In tests where water and 0.3 M NaCl solution were available for drinking, vehicle injections produced no significant change in water intake in sodium-deprived rats (1.2±0.5 ml in 4 h, $n=10$ rats).

In the sodium intake experiments in rats treated with furosemide, the effects of either the V_1 or the V_2 antagonist were never significantly higher or lower than those of the vehicle [F (2.125)≡0.39, $p\equiv0.68$]. Furthermore, neither the AT_1 nor the AT_2 antagonist altered the baseline (vehicle) in the sodium intake [F (2.125)≡2.85, $p\equiv0.06$] in rats deprived of sodium. Therefore, the effects of the antagonists are not a secondary response to the deprivation.

4. Discussion

Systemic osmotic stimulus and hypovolemic increase the circulating AVP levels and also cause the liberation of AVP in the septum and in the lateral ventricles (Demotes-Mainard et al., 1986). Manipulations that facilitate sodium ingestion can also stimulate systemic liberation of AVP. The administration of furosemide raises plasma levels of AVP (Thunhorst et al., 1994). When a sodium deficiency exists, central AVP increases sodium ingestion (Richter, 1956). The role of central AVP is to maintain the fluid balance, especially by regulating the extracellular fluid volume. Extracellular dehydration is an issue in sodium deficiency, and the volume reduction is corrected by behavior and endocrine processes. A central action of AVP is to stimulate water ingestion (Szczepanska-Sadowska et al., 1982) and plasmatic AVP reduces the loss of urine. Another central action of AVP is to stimulate the ingestion of salt raising the extracellular sodium level. As a consequence, intracellular water shifts to the extracellular space (Fitzsimons, 1990), avoiding the dilution that may, otherwise, result from ingestion of water alone. (Stricker and Verbalis, 1988).

In the third periventricular area (A3pV), neurons respond to both ANGII and AVP. The combined action of these two hormones may be subtractive, additive or even multiplicative, depending on conditions. It seems that, in addition to responding to hydromineral imbalances, both hormones can co-modulate their responsiveness (Nicolaidis and Jeulin, 1984). Several results suggest that physiological adaptation to restraint is associated with specific changes in V_1, AT_1 and AT_2 receptor densities within the brain nuclei and kidneys (McDougall et al., 2001). The increased secretion of AVP, in response to central ANGII production might be induced by the stimulation of ANGII (receptors) in the medial septum, as receptor studies and electrophysiological work have shown (Simonnet et al., 1980; Sirett et al., 1977).

The present results show that AVP injected into the MSA increased the water intake induced by 24 h of water deprivation in a dose-dependent manner. In sodium-depleted rats, the administration of AVP into the same area increased sodium intake, also in a dose-dependent way. These effects were compared with the water and sodium intakes under basal conditions of dehydration and sodium deficiency. Previous treatment by injection of V_1 and V_1/V_2 receptor antagonists suppressed water and sodium intake without causing motor disturbances, suggesting that endogenous AVP actually stimulates water and sodium appetite by activating V_1 receptors. Various doses of the V_2 antagonist injected into the MSA, increased AVP-induced water and sodium intake.

The effects of central AVP on water and sodium intakes are conflicting. High doses of V_1 antagonist injected centrally did not spontaneously change or inhibit water intake (Fitzsimons, 1979). AVP injection into the third ventricle caused a significant increase in water intake (Szczepanska-Sadowska et al., 1982). The same effect on water intake was observed with AVP activation in the lateral septal area (LSA) (de Arruda Camargo et al., 2003; Mima et al., 2004). The structures that surround the third ventricle, like the subfornical organ (SFO) and organum vasculosum of the lamina terminalis (OVLT), play an important role in the control of body fluid osmolarity (Johnson, 1985), and V_1 receptors are present in both structures (Jurzak et al., 1995; Sofroniew and Schrell, 1981). Regardless of the central site of action, Flynn et al. (2002) suggest that the sodium appetite aroused by injections of DOCA and furosemide involves brain AVP acting at V_1 receptors. On the other hand, AVP administration into the ventral region of the third ventricle, the preoptic area and into the LSA led to a reduction in sodium ingestion (Sato et al., 1997; Mima et al., 2004). The discrepancy between the present results, which showed an increase in salt intake induced by AVP administered into the MSA, and the fall in salt intake observed by Mima et al. (2004) when they induced vasopressinergic activation of the LSA, is probably due to the difficulty in defining the chemical character of most of pathways involved and to establish at high resolution of the relation of the supraoptic nucleus (SON) to the cells or afferent and efferent projections in different parts of the septal complex (Swanson and Cowan, 1979). It was also found that a subpopulation of lateral septal neurons bear oxytocin receptors (Raggenbass et al., 1988) and it was demonstrated that central oxytocin pathways mediate an inhibitory effect that limits

salt ingestion (Blackburn et al., 1992). It has also been suggested that a portion of AVP binding sites in the lateral septum may be localized presynaptically on the terminals of noradrenergic neurons (Ishizawa et al., 1990). Saline intake is also inhibited or activated in the CNS by noradrenaline (Camargo and Saad, 2001).

Most of the known effects of ANG II are mediated through the AT_1 receptors, e.g., vasoconstriction, aldosterone and AVP release, salt and water retention, and sympathetic activation. The function of the AT_2 receptor has begun to be unraveled over the last few years, owing to various approaches including gene transfection and deletion. Various published data suggest that the AT_2 receptor counterbalances the effects of the AT_1 receptor in vitro as well as in vivo (de Gasparo et al., 2000).

Another aim of this study was to determine the contribution of MSA AT_1 and AT_2 receptors in water and sodium intake induced by AVP in water-deprived and sodium-depleted rats. The results demonstrate that the AT_1 receptor antagonist abolished water and sodium intake induced by AVP, whereas the, AT_2 receptor antagonist only impaired these effects of AVP. Concomitant administration of losartan and CGP4212A promoted greater decreases in water and sodium ingestion than either antagonist injected alone.

The interaction between the central ANG II and AVP systems is well established (Keil et al., 1975; Mouw et al., 1971). ANG II activates AVP neurons, as demonstrated by in vivo studies using c-Fos and AVP mRNA expression and AVP secretion (Dawson et al., 1998; Hogarty et al., 1992; Lu et al., 1995; Phillips et al., 1996). Moreover, disturbances of the hydromineral balance, such as dehydration or osmotic stimuli, have been shown to increase ANG II receptor density, AT_1 receptor mRNA, and AVP mRNA in the CNS (Nazarali et al., 1987; Sanvitto et al., 1997). The results obtained by Antunes et al. (1998) demonstrated that both AT_1 and V_1 receptors within the SON might be involved in the water and sodium intake induced by the activation of ANG II receptors in the MSA. Although the physiological role of the AT_2 receptors in the CNS is unclear, some of the AT_1-mediated effects may be enhanced by blockade of AT_2 receptors in the brain, suggesting that the central AT_2 receptor may exert an inhibitory control on AT_1 receptor-mediated actions in the brain (Hohle et al., 1995).

The present study shows that V_1 antagonist injection into the MSA of water-deprived and sodium-depleted rats decreased water and sodium intake responses produced by AVP activation. Conversely, pretreatment with V_2 antagonist increased water and sodium ingestion induced by AVP injected into the same area, suggesting that the AVP role in the increase of water and sodium intake is mediated by V_1-like receptors in the MSA. This paper also shows that losartan and CGP42112A, when injected into the MSA before AVP, decreases the water and sodium intake induced by AVP. Blockage of AT_1 receptors in the MSA lead a greater effect on this behavior than did the blockage of AT_2 receptors. This fact indicates that MSA AT_1 receptors are primarily responsible for water and sodium intake induced by AVP in water-deprived and sodium-depleted rats. Losartan prevented the effects mentioned above more effectively when combined with CGP42112A.

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