Available online at www.sciencedirect.com
SCIENCE DIRECT®
Pharmacology, Biochemistry and Behavior 77 (2004) 667–674
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
www.elsevier.com/locate/pharmbiochembeh

Interaction between supraoptic nucleus and septal area in the control of water, sodium intake and arterial blood pressure induced by injection of angiotensin II

Wilson Abrão Saad[a,b,c,d,*], Luis Antonio de Arruda Camargo[b], Ismael Francisco Motta Siqueira Guarda[e], Talmir Augusto Faria Brisola dos Santos[a], Renata Saad Guarda[b], William Abrão Saad[f], Sylvio Simões[a], José Antunes Rodrigues[g]

[a]Department of Dentistry, UNITAU, Taubaté, São Paulo, Brazil
[b]Department of Physiology and Pathology, School of Dentistry, Paulista State University, UNESP, UNIARA, Araraquara, São Paulo, Brazil
[c]Department of Exacts and Naturals Sciences, UNIARA, Araraquara, São Paulo, Brazil
[d]Department of Physiological Science, UFSc-São Carlos, São Carlos, São Paulo, Brazil
[e]Department of Anesthesiology, 9 de Julho Medical Hospital, São Paulo, Brazil
[f]Department of Surgery, School of Medicine, University of São Paulo, São Paulo, Brazil
[g]Department of Physiology, School of Medicine Ribeirão Preto, University of São Paulo, São Paulo, Brazil

Received 17 September 2003; received in revised form 5 December 2003; accepted 8 January 2004

Abstract

We investigated the effects of injection into the supraoptic nucleus (SON) of losartanand PD 123319 (nonpeptide AT_1 and AT_2-angiotensin II [ANG II] receptor antagonists, respectively); $d(CH_2)_5$-Tyr(Me)-AVP (AVPA; an arginine–vasopressin [AVP] V_1 receptor antagonist), FK 409 (a nitric oxide [NO] donor), and N^W-nitro-L-arginine methyl ester (L-NAME; an NO synthase inhibitor) on water intake, sodium chloride 3% (NaCl) intake and arterial blood pressure induced by injection of ANG II into the lateral septal area (LSA). Male Holtzman rats (250–300 g) were implanted with cannulae into SON and LSA unilaterally. The drugs were injected in 0.5 μl over 30–60 s. Controls were injected with a similar volume of 0.15 M NaCl. ANG II was injected at a dose of 10 pmol. ANG II antagonists and AVPA were injected at doses of 80 nmol. FK 409 and L-NAME were injected at doses of 20 and 40 μg, respectively. Water and NaCl intake was measured over a 2-h period. Prior administration of losartan into the SON decreased water and NaCl intake induced by injection of ANG II. While there was a decrease in water intake, ANG II-induced NaCl intake was significantly increased following injection of AVPA. FK 409 injection decreased water intake and sodium intake induced by ANG II. L-NAME alone increased water and sodium intake and induced a pressor effect. L-NAME-potentiated water and sodium intake induced by ANG II. PD 123319 produced no changes in water or sodium intake induced by ANG II. The prior administration of losartan or AVPA decreased mean arterial pressure (MAP) induced by ANG II. PD 123319 decreased the pressor effect of ANG II to a lesser degree than losartan. FK 409 decreased the pressor effect of ANG II while L-NAME potentiated it. These results suggest that both ANG II AT_1 and AVP V_1 receptors and NO within the SON may be involved in water intake, NaCl intake and the pressor response were induced by activation of ANG II receptors within the LSA. These results do not support the involvement of LSA AT_2 receptors in the mediation of water and NaCl intake responses induced by ANG II, but influence the pressor response.

Keywords: Angiotensin II AT_1, AT_2 receptors; Arginine vasopressin V_1 receptors; Nitric oxide CNS; Electrolytic; Cardiovascular balance

1. Introduction

Evidence for connections between septal neurons and the supraoptic nucleus (SON) of the hypothalamus has been demonstrated by electrophysiological studies (Poulain et al., 1981). Neurons of the septal and paraventricular nucleus are sensitive to angiotensin (Camargo and Saad, 1999; Simon-

* Corresponding author. Department of Physiology and Pathology, School of Dentistry, Paulista State University, UNESP, 1680 Humaitá Street, Araraquara, SP 14801-903, Brazil. Tel./fax: +55-16-201-6488.
E-mail address: saad@foar.unesp.br (W.A. Saad).

0091-3057/$ – see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2004.01.013

net et al., 1980). Central injection of angiotensin II (ANG II) elicits prompt and pronounced responses, such as increased blood pressure, thirst, sodium appetite, and the release of vasopressin (Reid, 1988). Electrical stimulation of the basal forebrain causes the release of arginine–vasopressin (AVP) and prolonged thirst (Szczeparska-Sadowska et al., 1982). This effect seems to be produced by the activation of functional ANG II receptors within the SON because it is reversibly blocked by the angiotensin peptide antagonist salarasin (Jhamandas et al., 1989). Application of the non-peptide Type 1 angiotensin antagonist DuP753 blocks ANG II-induced depolarization in the SON. In contrast, application of the Type 2 antagonist PD 123177 was ineffective in blocking this response (Yang et al., 1992).

Nitric oxide (NO) synthase inhibitors have been used widely to determine the role of endogenous NO. N^{W}-nitro-L-arginine methyl ester (L-NAME) reduces renal blood flow, urine flow rate, and urinary sodium excretion (Naes et al., 1992). Several studies have shown that NO may function as a neurotransmitter or a neuromodulator. Recognition of the role of NO in cell-to-cell communication has changed the concept of traditional neurotransmission. *N*-methyl-D-aspartate receptors mediate the dipsogenic response and c-*fos* expression induced by intracerebroventricular infusion of ANG II (Zhu and Herbert, 1997). It has been demonstrated that NO may facilitate the release of excitatory transmitters, possibly through a presynaptic cyclic GMP-dependent mechanism (Wu et al., 1997). The influence of NO on angiotensin effects have been demonstrated (Saad et al., 2002a). Moreover, these effects implicated the participation of the septal area (Saad et al., 2002b,c). Treatment with L-NAME increases blood pressure that is at least in part, salt sensitive (Hodge et al., 2002). NO is involved in the regulation of drinking behavior induced by central administration of ANG II and cellular dehydration, and NO of the subfornical organ (SFO) plays an important role in this regulation (Saad et al., 1999).

The systemic application of ibersartan and losartan abolished ANG II central physiologic responses (water intake, sodium intake, and increased arterial pressure; Camargo and Saad, 1999). The role of the renin–angiotensin system in the control of arterial blood pressure and salt appetite in rats has been demonstrated (Thunhorst and Johnson, 1994). Treatment with losartan reversed the blood pressure increase. Central ANG II AT_1 and AT_2 receptors mediated chronic intracerebroventricular. ANG II-induced drinking in rats fed a high sodium chloride diet from weaning (Camara and Osborn, 2001).

Because the septum is known to send efferents to the SON (Poulain et al., 1981), and that both structures are involved in the control of hydromineal and cardiovascular balance, we investigated whether the dipsogenic, natriorhexigenic, water excretory, and pressor response induced by injection of ANG II into the lateral septal area (LSA) could be mediated by angiotensin, vasopressin receptors, and NO within the SON.

2. Materials and methods

2.1. Subjects

The animals were housed in individual metabolic cages. Food (Purina Rat Chow) and tap water were available ad libitum for the duration of the experiments. The temperature was maintained at 22 ± 2 °C. The light cycle was held at 12:12 with lights on at 0600 h. All experiments were conducted during the light period, between 0900 and 1500 h.

2.2. Surgical procedures

2.2.1. Cerebral cannula

Male Holtzman rats weighing 250–300 g were anesthetized with tribromoethanol (20 mg/100 g body weight) intraperitoneally, and implanted with 10- and 12-mm long and 0.7-mm OD stainless steel cannulae into the LSA and SON, according to the coordinates of the Paxinos and Watson (1986) rat brain atlas. For SON, the coordinates were as follows: AP = 1.3–2.2 mm posterior to the bregma; L = 1.8–2.0 mm lateral to the middle line; V = 9.4 mm below dura. For LSA, the coordinates were as follows: AP = 1.0–1.5 mm anterior to the bregma; L = 0.4–0.6 mm lateral to the middle line; V = 5.8 mm below the dura. The cannulae were fixed to the skull with the aid of jeweler screws and dental acrylic resin and protected with a stylet.

2.2.2. Vascular catheter

After the animals recovered from brain surgery (5 days), PE-10 polyethylene tubing connected to PE-50 tubing was inserted into the abdominal aorta through the femoral artery under 2,2,2-tribromoethanol anesthesia (20 mg/100 g body weight). The polyethylene tube was tunneled subcutaneously to the back of the rat and externalized at the dorsal cervical region. Catheters were filled with heparinized saline and plugged with 23-gauge obturators. Rats recovered from surgery (vascular catheter) for a minimum of 24 h before the beginning of testing.

2.3. Central drugs injections

ANG II was purchased from Sigma (St. Louis, MO) and dissolved in saline (0.15 M NaCl) at 10 pmol/0.5 μl. PD 123319 and losartan were purchased from DuPont Merck (Wilmington, DE) and dissolved in saline (0.15 M NaCl) at 80 nmol/0.5 μl. $d(CH_2)_5$-Tyr(Me)-AVP (AVPA) was purchased from Bachem (Torrance, CA) and dissolved in saline (0.15 M NaCl) at 80 nmol/0.5 μl. FK 409 was purchased from Joseph Leidy Laboratories (Philadelphia, PA) and dissolved in saline (0.15 M NaCl) at 20 μg/0.5 μl. N^{G}-nitro-L-arginine methyl ester (L-NAME) was purchased from Sigma and dissolved in saline (0.15 M NaCl) at 40 μg/0.5 μl.

2.4. Water and NaCl intake

ANG II (10 pmol/0.5 μl) or vehicle was injected into the LSA, and water and 3% NaCl were offered. Losartan, PD 123319, and AVPA were injected into the SON at the dose of 80 nmol/0.5 μl, 15 min before water, or 3% NaCl were offered. The antagonists were injected into the SON 15 min before ANG II was injected into the LSA.

FK 409 (20 μg/0.5 μl) or L-NAME (40 μg/0.5 μl) was injected into the SON 15 min prior to ANG II injection into the LSA. Water and NaCl intake were recorded every 30 min over a 2-h period using individual metabolic cages. Most of the water and sodium drinking occurred within 15–30 min that we observed for a 2-h period.

2.5. Arterial blood pressure recordings

Direct mean arterial blood pressure (MAP) was recorded in unanesthetized and unrestrained rats. The animal was removed from the home cage and placed in a test cage, without access to food or water. The previously implanted catheter was connected to a Statham (P23 Db) pressure transducer (Statham-Gould, Valley View, OH) coupled to a multichannel recorder (Dataq Multirecord, USA). This program permits the acquisition of cardiovascular data by computer.

2.6. Experimental procedures

2.6.1. Effects of losartan, PD 123319, AVPA, FK 409, and L-NAME injected into the SON on water and 3% NaCl intake after ANG II injection into the LSA

Following a recovery period of at least 5 days, Holtzman rats with cannulae implanted into the SON and LSA unilaterally were randomly assigned to one of eight treatment conditions: vehicle + vehicle ($n=10$), vehicle + ANG II ($n=10$), losartan + ANG II ($n=8$), AVPA + ANG II ($n=8$), PD 123319 + ANG II ($n=8$), FK 409 + ANG II ($n=8$), L-NAME + ANG II ($n=8$), or losartan + FK409 + ANG II ($n=8$). Antagonists or vehicle pretreatment were administered into the SON. Fifteen minutes following the drug injections, ANG II (10 pmol/0.5 μl) was administered into the LSA. Water and NaCl 3% intake (ml) was recorded at every 15 min for 120 min following ANG II administration. Vehicle was injected in SON and LSA.

2.6.2. Effects of losartan, PD 123319, AVPA, FK 409, and L-NAME injected into SON on the increase in MAP after ANG II injection into the LSA

Holtzman rats were implanted with cannulae into the SON and LSA. Following a recovery period of at least 5 days, animals were randomly assigned to one of eight treatment conditions: vehicle + vehicle ($n=10$), vehicle + ANG II ($n=10$), losartan + ANG II ($n=9$), AVPA + ANG II ($n=9$), PD 123319 + ANG II ($n=8$), FK 409 + ANG II ($n=8$), L-NAME + ANG II ($n=8$), or losartan + FK 409 + ANG II ($n=8$). Antagonists or vehicle pretreatment were administered into the SON. Fifteen minutes following the drug injections, ANG II (10 pmol/0.5 μl) was administered into the LSA. MAP (mm Hg), the peak response, was recorded every 5 min for 120 min following ANG II administration.

2.7. Histology

At the end of the experiments, the rats were anesthetized with ether and injected with 0.5 μl of fast green dye via the intracranial cannula, followed by perfusion with saline and buffered formalin. The brains were removed, fixed in 10% formalin, frozen at −25 °C, and cut into 20- to 30-μm coronal sections. Only animals in which the injection was placed in the intermediate and caudal areas of the lateral septum unilaterally were used in this study (Fig. 1). The SON parameters studied were observed in subjects that had the injection placed in the lateral medial portion of this nucleus unilaterally (Fig. 2).

2.8. Data analysis

Results are reported as means ± S.E.M. for the indicated experiments. Statistical analysis was subjected to two-way

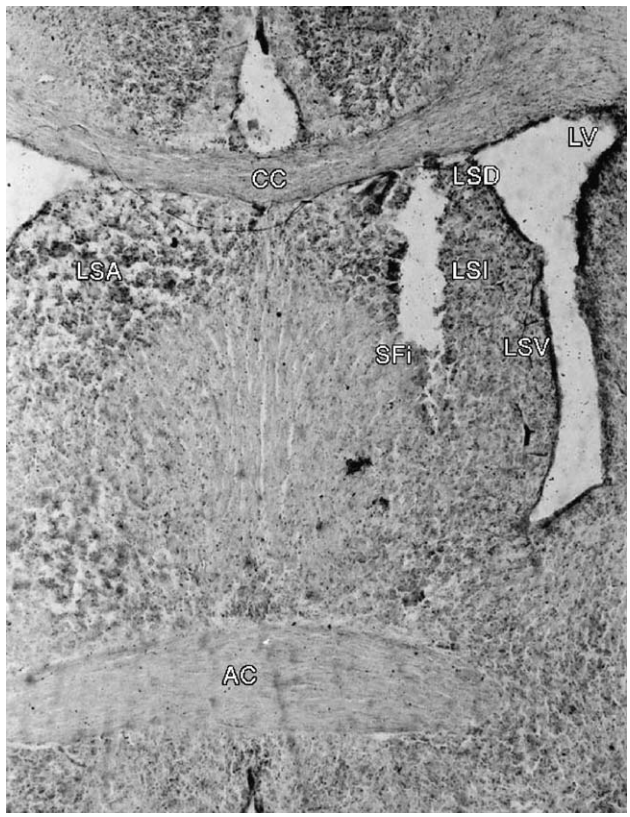

Fig. 1. Photomicrograph of a hematoxylin-stained transverse section of the rat brain showing the site of injection into the LSA. LSD, dorsal part; LSI, intermediate part; LSV, ventral part; Sfi, septofimbrial nucleus. (Magnification ×36).

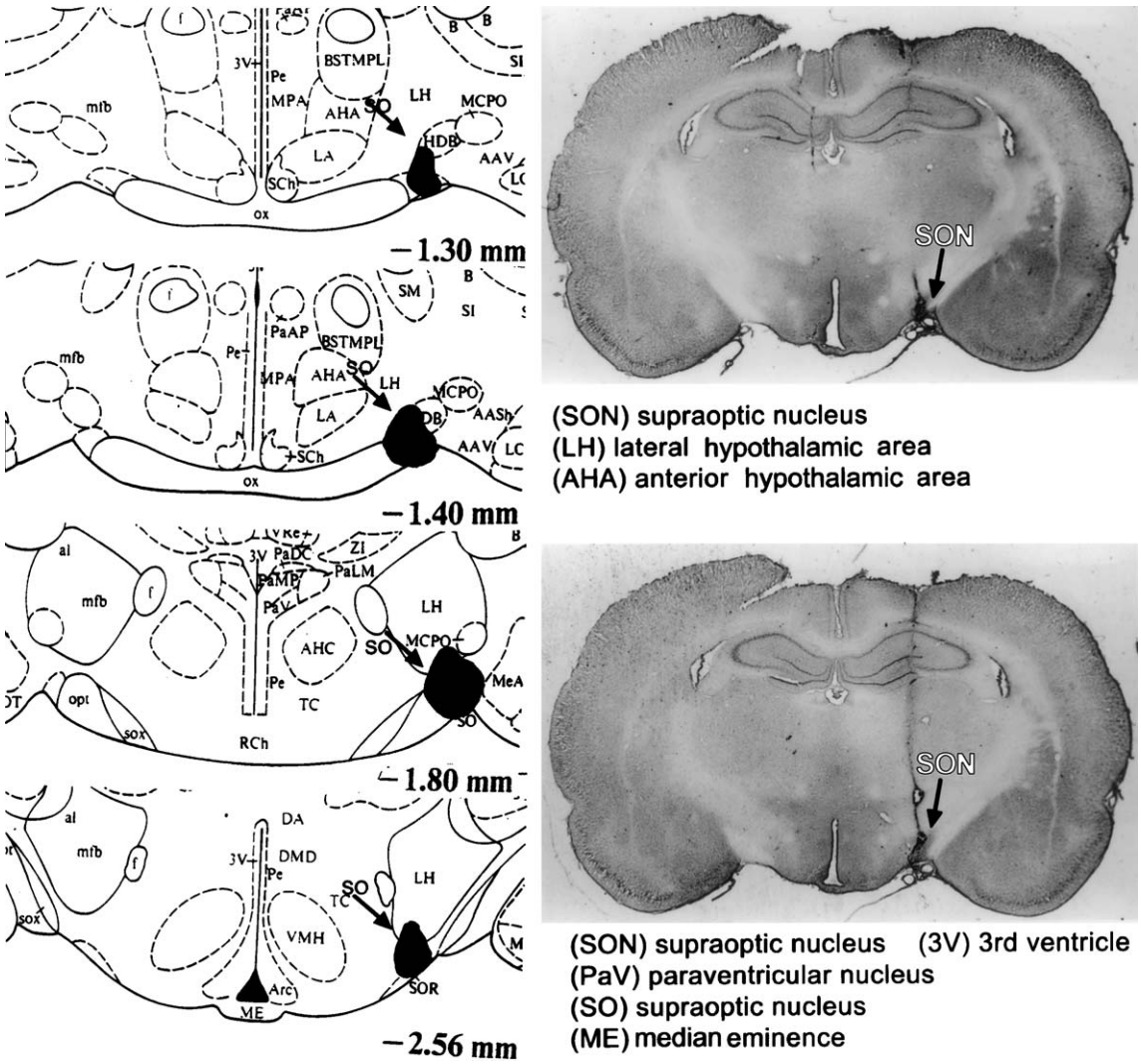

Fig. 2. Photomicrograph of a hematoxylin-stained transverse section showing the site of injection into the SON (arrows).

analysis of variance (ANOVA) followed by the Neuman–Keuls post hoc test. Differences were considered significant at $P < .05$.

3. Results

3.1. Effects of losartan, PD 123319, AVPA, FK 409, and L-NAME injected into the SON on water and 3% NaCl after ANG II injection into the LSA

Water intake after injection of 0.15 M NaCl into the LSA/SON was 0.30 ± 0.1 ml/2 h. Injection of ANG II into the LSA increased water intake. Losartan injected into the SON before ANG II injection into the LSA decreased water intake. AVPA injected into the SON decreased water intake induced by ANG II injection into the LSA. FK 409 injected into the SON prior to ANG II injected into the LSA decreased water intake. L-NAME alone injected into these sites caused increased water consumption. L-NAME potentiated the effect of ANG II on these responses. PD 123319 injected into the SON prior to ANG II injection produced no changes in water intake. Losartan + FK 409 injected into the SON prior to ANG II injected into the LSA abolished the dipsogenic effect of ANG II (Fig. 3).

NaCl intake after injection of 0.15 M NaCl into the LSA/SON was 0.1 ± 0.01 ml/2 h. ANG II injected into the LSA increased NaCl intake. Losartan injected into the SON prior to ANG II injection into the LSA decreased NaCl intake. AVPA injected into the SON increased NaCl ingestion induced by ANG II injected into the LSA. NaCl intake induced by injection of ANG II into the LSA was reduced by prior injection of FK 409 into the SON. L-NAME alone produced an increase in 3% NaCl intake (2.6 ± 0.3 ml/2 h). The natriorhexigenic effect of ANG II was potentiated by prior injection of L-NAME into the SON. PD 123319 produced no effect on NaCl

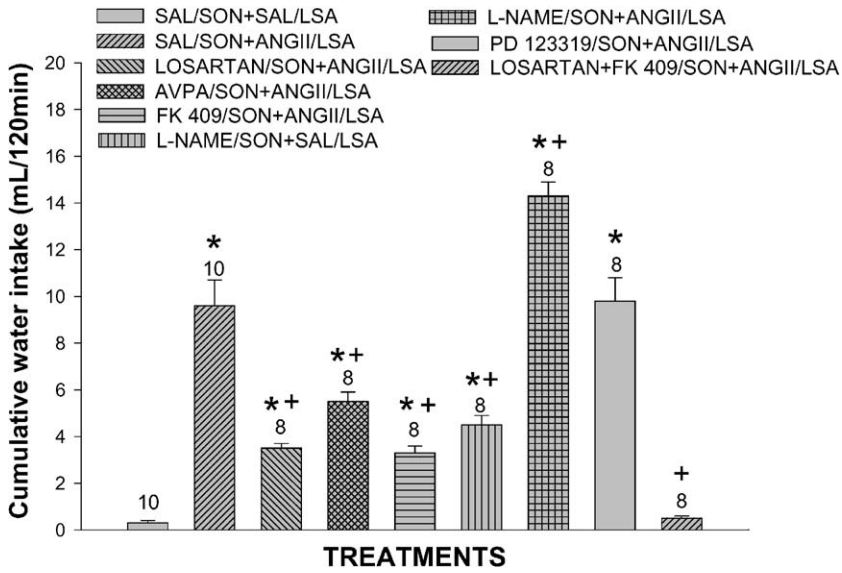

Fig. 3. Effect of pretreatment with losartan, PD 123319, d$(CH_2)_5$-Tyr(Me)-AVP (Ant.-AVP), FK 409, L-NAME, and losartan + FK 409 or vehicle (saline) into the SON on water intake evoked by injection of ANG II into the LSA. Data are reported as mean ± S.E.M. * $P < .05$ compared to the saline group; $^{+}P < .05$ compared to the ANG II group (Neuman–Keuls post hoc test). Numbers above the bars indicate number of animals per group.

intake induced by ANG II. Losartan in association with FK 409 abolished NaCl ingestion induced by ANG II (Fig. 4).

3.2. Effects of losartan, PD 123319, AVPA, FK 409, and L-NAME injected into the SON on the increase in MAP after ANG II injection into the LSA

The MAP peak response, after injection of 0.15 M NaCl into the LSA/SON, was 3 ± 1 mm Hg. ANG II injected into the LSA increased MAP. Losartan injected prior to ANG II into the SON decreased the pressor effect of ANG II. AVPA injected into the SON prior to ANG II into the LSA decreased MAP. PD 123319 injected into the SON prior to ANG II injection into the LSA reduced the pressor effect of ANG II. FK 409 reduced the pressor effect of ANG II. L-NAME injected alone produced an increase in MAP. L-NAME injected into the SON prior to ANG II injection into the LSA potentiated the pressor effect of ANG II injected into

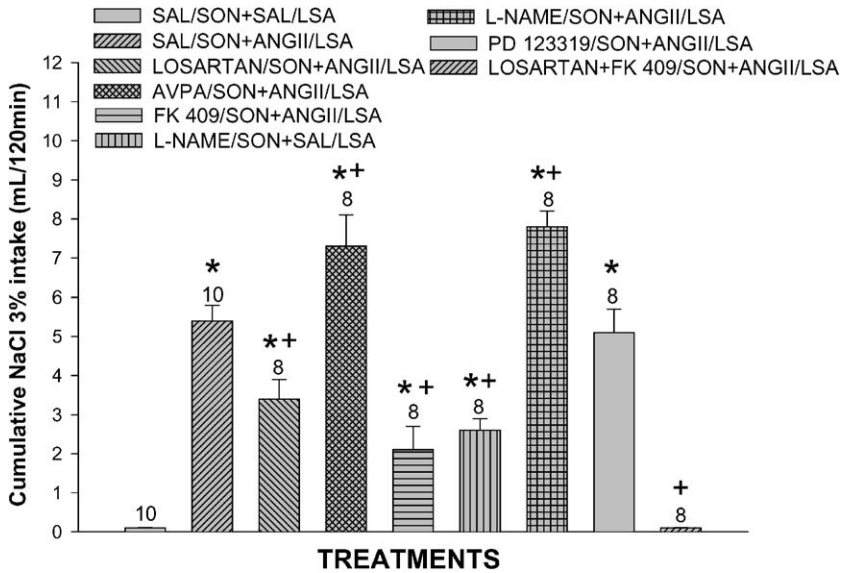

Fig. 4. Effect of pretreatment with losartan, PD 123319, d$(CH_2)_5$-Tyr(Me)-AVP (Ant.-AVP), FK 409, L-NAME, and losartan + FK 409 or vehicle (saline) into the SON on 3% NaCl intake evoked by injection of ANG II into the LSA. Data are reported as mean ± S.E.M. * $P < .05$ compared to the saline group; $^{+}P < .05$ compared to the ANG II group (Neuman–Keuls post hoc test). Numbers above the bars indicate number of animals per group.

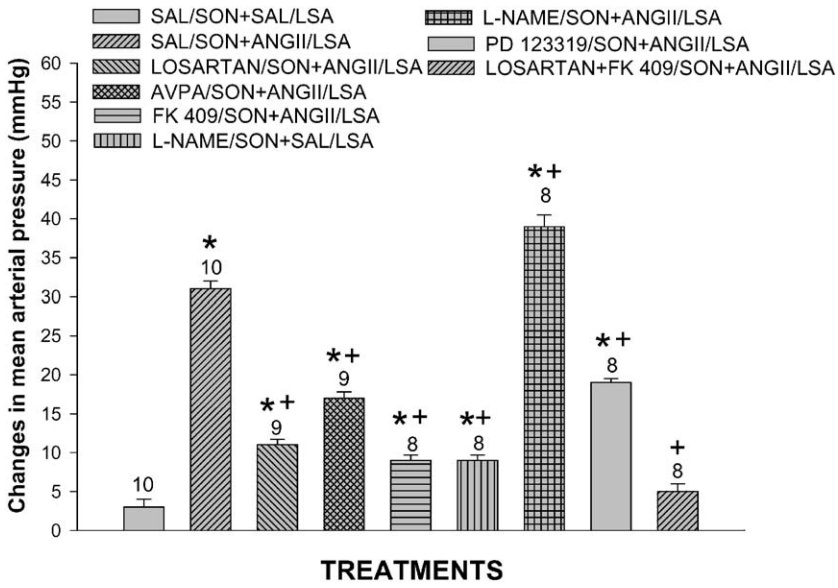

Fig. 5. Effect of pretreatment with losartan, PD 123319, d$(CH_2)_5$-Tyr(Me)-AVP (Ant.-AVP), FK 409, L-NAME, and losartan + FK 409 or vehicle (saline) into the SON on the increase in MAP evoked by injection of ANG II into the LSA. Data are reported as mean ± S.E.M. * $P < .05$ compared to the saline group; $^{+}P < .05$ compared to the ANG II group (Neuman–Keuls post hoc test). Numbers above the bars indicate number of animals per group.

the LSA. Losartan + FK 409 injected into the SON prior to ANG II abolished the pressor effect of ANG II (Fig. 5).

4. Discussion

The present results show that injection of the selective ANG II AT_1 antagonist losartan into the SON reduced water intake, NaCl intake and the increase in MAP induced by angiotensinergic activation of the LSA, whereas injection of the AT_2 selective antagonist PD 123319 for receptors had no effect on water and NaCl intake but reduced the pressor effect of ANG II. Prior injection of AVPA, an AVP V_1 receptor antagonist, into the SON decreased ANG II-induced water and sodium intake, and decreased MAP. Only animals in which the injection was placed in the intermediate and caudal areas of the lateral septum unilaterally were used in this study. Vehicle was used as the control and there were no control tissues. These effects may be due to inhibitory and excitatory regulatory mechanisms that involve V_1 receptors. An interaction of a vasopressin antagonist with vasopressin receptors in the septum has been demonstrated (Dorsa et al., 1988).

The results indicated that water and 3% NaCl intake induced by ANG II involves vasopressin V_1 vasopressin receptors. The present results also indicate that the pressor effect of ANG II involves the central angiotensin system and AT_1 receptor activation and the AT_2 receptor influences the pressor effect of ANG II with less intensity.

Quantitative autoradiography with selective ANG II-receptor antagonists revealed that the SON of the rat contains AT_1 receptors (Tsutsumi and Saavedra, 1991). Furthermore, it has been reported that water and salt appetite can be triggered by iontophoretically applied ANG II into the anteromedian septum (Mousseau et al., 1996). The vasopressin V_1 receptor is also found in the LSA (Poulin et al., 1988), and treatment with V_1 receptor antagonist caused a marked decrease in receptor affinity for AVP (Swank and Dorsa, 1991).

An endogenous origin for ANG II is suggested by various reports of angiotensin-like immunoreactivity in magnocellular neurons of the SON (Renaud and Bourque, 1991). It is thus possible that ANG II is released locally from axon collaterals or somatodendritic sites in a manner similar to that proposed for oxytocin or vasopressin (Richard et al., 1991). The septal influences on the control of AVP and ANG II secretion is presumably mediated by cells projecting from this area to the vasopressin-containing magnocellular neurons of the SON (Ferguson et al., 1985).

It has been postulated that ANG II-induced water intake can be explained at least in part by the increase in AVP content and presumed release from the SON. The increased release of AVP from axons, of neurons terminating on the effector neurons of the drinking response, would inhibit the stimulatory response evoked by the action of ANG II on its receptors on these same effector neurons (De Angelis et al., 1996).

The present results show that L-NAME progressively reduced water intake induced by thirst stimuli. It has been demonstrated that intracerebroventricular injection of N^G-monomethyl-L-arginine (NMMA), a blocker of NO synthase, attenuates water intake (Kadekaro et al., 1994) and preferentially increases plasma concentrations of oxytocin and vasopressin in rats deprived of water for 24 h (Liu et al., 1998). Water intake increased after subcutaneous adminis-

tration of hypertonic saline, and L-NAME previously injected into the lateral ventricle progressively reduced this ingestion (Saad et al., 1999).

Another example of central interaction areas in the control of water ingestion has been demonstrated. For example, electrolytic lesions of the lateral preoptic area and SFO in the same animal abolished the daily water intake induced by hypertonic saline (Saad and Camargo, 1980).

Prior injection of L-NAME into the SFO produced a progressive reduction in water intake induced by ANG II. These results agree with those of Liu et al. (1998). Drinking behavior induced by subcutaneous injection of hypertonic saline or by ANG II injection into the lateral ventricle is attenuated by central inhibition of NO synthase with L-NAME and that the highest dose of L-NAME abolished water intake induced by cellular dehydration and by ANG II injected into the lateral ventricle (Saad et al., 1999, 2003). These results clearly demonstrate that NO influences the dipsogenic effect of ANG II, and that the SON is an important area for this behavior.

Other studies demonstrated that alpha-1 and beta-adrenoceptors of the lateral hypothalamus are possibly involved with the central mechanism that control water and sodium intake and is dependent on ANG II, the SFO, and the paraventricular nucleus (Camargo et al., 2000, 2003a).

These results show that the ANG II-induced pressor response was dependent on AT_1, AT_2, and V_1 receptors. NO also plays a role in this response. Treatment with ANG II AT_1 receptor antagonist losartan reversed the blood pressure increase. Treatment with L-NAME induces an increase in blood pressure that is at least in part, salt sensitive. Furthermore, the salt-sensitive component appears to be ANG II-dependent because it was associated with increasing plasma ANG II levels and could be reversed by treatment with an ANG II-receptor antagonist (Hodge et al., 2002). In the median preoptic nucleus, ANG II via AT_1 receptors mediates cardiovascular responses to an acute increase in cerebrospinal fluid sodium as well as the chronic pressor responses to high sodium intake in spontaneously hypertensive rats (Budzikowski and Leenen, 2001). These results are strongly supported by several studies of Camara and Osborn (2001), Camargo et al. (2002, 2003b), Welch and Wilcox (2002), Welch et al. (2003). The present results suggest that AT_1 receptors of the SON mediate water and NaCl ingestion induced by angiotensinergic activation of the LSA, whereas AVP V_1 AVPergic neurons activate water intake but inhibit sodium ingestion.

In summary, this study demonstrated that angiotensin (via AT_1 receptors), AVP and NO in the SON are involved in water and sodium intake and the pressor responses induced by administration of angiotensin into the LSA. The AT_2 receptor antagonist produced no effect on water and sodium intake but partially reduced the pressor effect of ANG II as occurred with the AVP V_1 receptor antagonist.

Acknowledgements

The authors greatly appreciate the technical assistance of Aparecida C. Luiz, Reginaldo C. Queiróz, Silas P. Barbosa, and Silvia Fóglia. They also thank Silvana A.D. Malavolta for preparation of the manuscript, and Ana V. Oliveira and Fernando L. Capelli for animal care. Research was supported by CNPq (520408/96.9), FAPESP (99/06582-2 and 02/03806-1) and FUNDUNESP (01/06756-3) PRONEX and Alan N. Epstein grants.

References

Budzikowski AS, Leenen FH. ANG II in median preoptic nucleus and pressor responses to CSF sodium and high sodium intake in SHR. Am J Physiol 2001;281:H1210–6.

Camara AK, Osborn J. Central AT1 and AT2 receptors mediate chronic intracerebroventricular angiotensin II-induced drinking in rats fed high sodium chloride diet from weaning. Acta Physiol Scand 2001;171:195–201.

Camargo LAA, Saad WA. Renal effects of angiotensin II receptor subtype 1 and 2-selective ligands injected into the paraventricular nucleus of conscious rats. Regul Pept 1999;4:91–6.

Camargo LAA, Saad WA, Camargo GP. Effects of subtypes alpha- and beta-adrenoceptors of the lateral hypothalamus on the water and sodium intake induced by angiotensin II injected into the subfornical organ. Brain Res 2000;27:176–81.

Camargo LAA, Saad WA, Simões S, Santos TAFB, Saad WA. Interaction between paraventricular nucleus and septal area in the control of physiological responses induced by angiotensin II. Braz J Med Biol Res 2002;35:1017–23.

Camargo LAA, Saad WA, Cerri PS, Camargo GMPA. Effects of subtypes of adrenergic and angiotensinergic antagonists on the water and sodium intake induced by adrenaline injected into the paraventricular nucleus. Brain Res 2003a;994:234–42.

Camargo LAA, Saad WA, Cerri PS. Effects of V1 and angiotensin receptor subtypes of the paraventricular nucleus on the water intake induced by vasopressin injected into the lateral septal area. Brain Res Bull 2003b;61:481–7.

De Angelis PR, Antunes VR, Camargo GM, Saad WA, Renzi A, Camargo LAA. Central interaction between atrial natriuretic peptide and angiotensin II in the control of sodium intake and excretion in female rats. Braz J Med Biol Res 1996;29:1671–4.

Dorsa DM, Brot MD, Shewey LNM, Myers KM, Szot P, Miller MA. Interaction of a vasopressin antagonist with vasopressin receptors in the septum of the rat brain. Synapse 1988;2:205–11.

Ferguson AV, Bourque CW, Renaud LP. Subfornical organ and supraoptic nucleus connections with septalneurons in rats. Am J Physiol 1985;249:R214–8.

Hodge G, Ye VZ, Duggan KA. Salt-sensitive hypertension resulting from nitric oxide synthase inhibition is associated with loss of regulation of angiotensin II in the rat. Exp Physiol 2002;87:1–8.

Jhamandas JH, Lind RW, Renaud LP. Angiotensin II may mediate excitatory neurotransmission from the subfornical organ to the hypothalamic supraoptic nucleus: an anatomical and electrophysiological study in the rat. Brain Res 1989;487:52–61.

Kadekaro M, Terrel ML, Herman P, Summy-Long JY. Central inhibition of nitric oxide synthase attenuates water intake but does not alter enhanced glucose utilization in the hypothalamus–neurohypophysial system of dehydrated rat. Neurosci Lett 1994;173:115–8.

Liu H, Terrell ML, Bui V, Summy-Long JY, Kadekaro M. Nitric oxide control of drinking, vasopressin and oxytocin release and blood pressure in dehydrated rats. Physiol Behav 1998;63:763–9.

Mousseau MC, Thornton SN, Martial FP, Lienard F, Nicolaidis S. Neuronal responses to iontophoretically applied angiotensin II, losartan and aldosterone, as well as gustatory stimuli, in nonanesthetized control and desoxycorticosterone acetate-pretreated rats. Regul Pept 1996;66:51–4.

Naes PA, Kirkeboen KA, Christensen G, Kiil F. Inhibition of renal nitric oxide synthesis with N^G-monomethyl-L-arginine and N^G-nitro-L-arginine. Am J Physiol 1992;262:F939–42.

Paxinos G, Watson C. The rat brain in stereotaxic coordinates. San Diego: Academic Press; 1986.

Poulain DA, Lebrun CJ, Vincent JD. Electrophysiological evidence for connections between septal neurones and the supraoptic nucleus of the hypothalamus of the rat. Exp Brain Res 1981;42:260–8.

Poulin P, Lederis K, Pittman OJ. Subcellular localization and characterization of vasopressin binding sites in the ventral septal area, lateral septum, and hippocampus of the rat brain. J Neurochem 1988;50:889–98.

Reid IA. Actions of angiotensin II on the brain: mechanisms and physiologic role. Am J Physiol 1988;246:F533–43.

Renaud LP, Bourque CW. Neurophysiology and neuropharmacology of hypothalamic magnocellular neurons secreting vasopressin and oxytocin. Prog Neurobiol 1991;36:131–69.

Richard P, Moos F, Freund-Mercier MJ. Central effects of oxytocin. Physiol Rev 1991;71:331–70.

Saad WA, Camargo LAA. Interaction between the lateral preoptic area and the subfornical organ in the control of water ingestion caused by cellular dehydration, hypotension, hypovolemia, and deprivation. Behav Neural Biol 1980;28:138–49.

Saad WA, Camargo LAA, Saad R, Pereira AF, Simões S. Effect of injection of L-NAME on drinking response. Braz J Med Biol Res 1999;32:1413–6.

Saad WA, Guarda IFMS, Guarda RS, Camargo LAA, Santos TAFB, Saad WA, et al. Role of nitric oxide and beta-adrenoreceptors of the central nervous system on the salivary flow induced by pilocarpine injection into the lateral ventricle. Pharmacol Biochem Behav 2002a;72:229–35.

Saad WA, Guarda IF, Camargo LAA, Santos TAFB, Saad WA, Simões S, et al. Novel evidence that nirtric oxide of the medial septal area influences the salivary secretion induced by pilocarpine. Life Sci 2002b;70:2403–12.

Saad WA, Guarda IF, Camargo LAA, Santos TAFB, Simões S, Saad WA. Adrenoceptors of the medial septal area modulate water intake and renal excretory function induced by central administration of angiotensin II. Braz J Med Biol Res 2002c;35:951–9.

Saad WA, Guarda IMFS, Carmargo LAA, Santos TAFB, Guarda RS, Saad WA, et al. Role of nitric oxide of the median preoptic nucleus (MnPO) in the alterations of salivary flow, arterial pressure and heart rate induced by injection of pilocarpine into the MnPO and intraperitoneally. Braz J Med Biol Res 2003;36:897–905.

Simonnet G, Bioulac B, Rodriguez F, Vincent JD. Evidence of a direct action of angiotensin II on neurones in the septum and in the medial preoptic area. Pharmacol Biochem Behav 1980;13:359–63.

Swank MW, Dorsa DM. Chronic treatment with vasopressin analogues alters affinity of vasopressin receptors in the septum and amygdala of the rat brain. Brain Res 1991;544:342–4.

Szczeparska-Sadowska E, Sobocinska J, Sadowski B. Central dipsogenic effect of vasopressin. Am J Physiol 1982;242:R372–9.

Thunhorst RL, Johnson AK. Renin–angiotensin, arterial pressure, and salt appetite in rats. Am J Physiol 1994;266:R458–65.

Tsutsumi K, Saavedra JM. Characterization and development of angiotensin II receptor subtypes (AT1 and AT2) in rat brain. Am J Physiol 1991;261:R209–16.

Welch WJ, Wilcox CS. What is brain nitric oxide synthase doing in the kidney? Curr Opin Nephrol Hypertens 2002;11:109–15.

Welch WJ, Baumgartl H, Lubbers D, Wilcox CS. Renal oxygenation defects in the spontaneously hypertensive rat: role of AT1 receptors. Physiol Behav 2003;63:202–8.

Wu SY, Dun SL, Forstermann U, Dun NJ. Nitric oxide and excitatory postsynaptic currents in immature rat sympathetic preganglionic neurons in vitro. Neuroscience 1997;79:237–45.

Yang CR, Phillips MI, Renaud LP. Angiotensin II receptor activation depolarizes rat supraoptic neurons in vitro. Am J Physiol 1992; 263:R1333–8.

Zhu B, Herbert J. Angiotensin II interacts with nitric oxide cyclic Gmp pathway in the central control of drinking behaviour: mapping with c-*fos* and NADPH-diaphorase. Neuroscience 1997;79:543–53.