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A PREVIOUS HISTORY OF REPEATED AMPHETAMINE EXPOSURE MODIFIES BRAIN ANGIOTENSIN II AT_1 RECEPTOR FUNCTIONALITY

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Abstract—Previous results from our laboratory showed that angiotensin II AT_1 receptors (AT_1-R) are involved in the neuroadaptative changes induced by amphetamine. The aim of the present work was to study functional and neurochemical responses to angiotensin II (ANG II) mediated by AT_1-R activation in animals previously exposed to amphetamine. For this purpose male Wistar rats (250–320 g) were treated with amphetamine (2.5 mg/kg/day intraperitoneal) or saline for 5 days and implanted with intracerebroventricular (i.c.v.) cannulae. Seven days after the last amphetamine administration the animals received ANG II (400 pmol) i.c.v. One group was tested in a free choice paradigm for sodium (2% NaCl) and water intake and sacrificed for Fos immunoreactivity (Fos-IR) determinations. In a second group of rats, urine and plasma samples were collected for electrolytes and plasma renin activity determination and then they were sacrificed for Fos-IR determination in Oxytocinergic neurons (Fos-OT-IR). *Results:* Repeated amphetamine exposure (a) prevented the increase in sodium intake and Fos-IR cells in caudate-putamen and accumbens nucleus induced by ANG II i.c.v. (b) potentiated urinary sodium excretion and Fos-OT-IR in hypothalamus and (c) increased the inhibitory response in plasma renin activity, in response to ANG II i.c.v. Our results indicate a possible functional desensitisation of AT_1-R in response to ANG II, induced by repeated amphetamine exposure. This functional AT_1-R desensitisation allows to unmask the effects of ANG II i.c.v. mediated by oxytocin. We conclude that the long lasting changes in brain AT_1-R functionality should be considered among the psychostimulant-induced neuroadaptations. Published by Elsevier Ltd. on behalf of IBRO.

Key words: AT_1 receptors, angiotensin II, amphetamine, sodium intake, natriuresis, oxytocin.

INTRODUCTION

The renin angiotensin system (RAS) in the brain is involved in systemic blood pressure control, regulation of cerebral blood flow, body fluids and mineral balance, osmoregulatory homeostasis-associated behaviors such as thirst and sodium intake (Blair-West et al., 1997; Fitzsimons, 1998; Alova et al., 1999; de Gasparo et al., 2000). Angiotensin II (ANG II) is a pleiotropic neuropeptide that activates AT_1 receptors (AT_1-R) and plays a key role in mediating stress-induced responses including regulation of sympathetic and neuroendocrine systems (Saavedra et al., 2005). Moreover, there is a large body of evidence to support the concept of a relationship between brain ANG II and catecholamine systems (Georgiev et al., 1985; Paz et al., 2013). ANG II AT_1-R are located in dopamine (DA)-rich brain areas (Tchekalarova and Georgiev, 1998; Daubert et al., 1999), such as the nucleus accumbens (NAc) and caudate putamen (CPu), which are strongly related to self-administration and sensitisation to drugs of abuse (White and Kalivas, 1998). Within dopaminergic neurons, ANG II receptors are found on the soma and it has been shown that AT_1-R activation by ANG II facilitates the release of DA in the rat striatum in vitro as well as in vivo (Brown et al., 1996). In addition, intracerebroventricular (i.c.v.) ANG II administration increases extracellular DA in the NAc which is related to ANG II-induced drinking (Hoebel et al., 1994). Furthermore, studies in mammals have demonstrated that i.c.v. ANG II administration enhanced renal sodium excretion, water and sodium intake (Fluharty and Manaker, 1983; Unger et al., 1989; Ferguson et al., 2001), increased vasopressin and oxytocin secretion and decreased plasma renin activity (Weekley, 1992; Ferguson et al., 2001).

Psychostimulants produce persistent changes in cells and neural circuits of reward, leading to long-term

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Abbreviations: AT_1-R, angiotensin II AT_1 receptors; ANG II, angiotensin II; Fos-IR, Fos immunoreactivity; Fos-OT-IR, Fos-IR determination in Oxytocinergic neurons; RAS, renin angiotensin system; NAc, nucleus accumbens; CPu, caudate putamen; PVN, paraventricular nucleus; SON, supraoptic nucleus; SFO, subfornical nucleus; PB, phosphate buffer; NHS, normal horse serum; RSNA, renal sympathetic neural activity; ANP, atrial natriuretic peptide.

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hypersensitivity of those systems which can be revealed by the re-exposure to the same substance or to others, as well as to stress (Robinson and Kolb, 2004; Kalivas, 2007). Moreover, repeated sodium depletion in rats, stimulates cerebral and peripheral RAS, induces cross-sensitisation to amphetamine, promotes sodium intake and increases the dendritic branches and spines of medium spiny neurons within the shell of the NAc (Roitman et al., 2002; Clark and Bernstein, 2004). Previous results from our laboratory showed that AT_1-R are involved in the neuroadaptative changes induced by a single exposure to amphetamine; such changes are related to the development of behavioral and neurochemical sensitisation (Paz et al., 2011, 2013).

The induction of immediately early gene *c-fos* plays an important role in transducing extracellular stimuli into altered patterns of cellular gene expression and, therefore, into long-term changes in cellular functioning. Furthermore, it is a well-accepted marker of neuronal activation, and this approach has been used to define areas involved in the actions induced by amphetamine since enhanced Fos expression in the CPu and NAc was found after amphetamine administration (Rotllant et al., 2010; Paz et al., 2013). In addition, Fos immunoreactivity (Fos-IR) data suggest that there might be a shared neural circuitry among response systems implicated in feeding, drugs of abuse and sodium appetite (Clark and Bernstein, 2004). Since, i.c.v. ANG II induced early gene-encoded protein synthesis, such as Fos in the median preoptic area and in the paraventricular nucleus (PVN), and supraoptic nucleus (SON) of the hypothalamus (Lebrun et al., 1995). Furthermore, the AT_1-R antagonist, losartan i.c.v. prevented the ANG II-induced immediately early gene protein expression in PVN and SON (Lebrun et al., 1995).These regions are known to be involved in the central osmoregulatory and neuroendocrine actions of ANG II.

Considering the described effects associated with central administered ANG II, the aim of the present study was to evaluate the possible alterations induced by repeated amphetamine exposure in the responses to i.c.v. ANG II mediated by AT_1-R activation. The parameters analyzed were: water and sodium intake, plasma renin activity, sodium excretion, Fos-IR in CPu, NAc, subfornical nucleus (SFO) and Fos and oxytocin immunoreactivity in oxytocinergic neurons (Fos-OT-IR) in SON and PVN.

EXPERIMENTAL PROCEDURES

Animals

Adult male Wistar rats (250–320 g) from our own colony (Facultad de Ciencias Químicas, Universidad Católica de Córdoba, Argentina) were employed. The rats were maintained under controlled temperature (21 ± 1 °C) and under 12-h light–dark cycle conditions (lights from 8:00 a.m. to 8:00 p.m.) with free access to tap water and standard laboratory rodent chow (GEPSA rat chow: Na+ content: 0.35%; K+ content: 0.96%). Rats were housed in groups of five per cage. Seven days before experimental tests, they were housed in individual cages until the day of the test. All procedures were approved by the Animal Care and Use Committee of the Facultad de Ciencias Químicas, Universidad Católica de Córdoba, Argentina, in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals, 1996.

Drugs

D-amphetamine sulfate (Amphetamine, Sigma Chemical Co., Saint Louis, MO, USA) and angiotensin II (ANG II, Sigma Chemical Co.) were dissolved in 0.9% saline (NaCl) immediately before use.

Experimental design

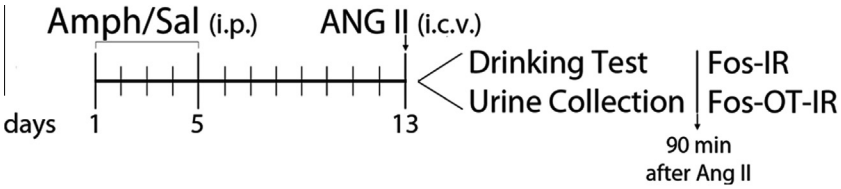
All experiments were performed 7 days after the last amphetamine administration because the neuroadaptative responses induced by the psychostimulant became evident after this drug free period. A total of 77 animals were randomly assigned to saline or amphetamine treatments. Rats received D-amphetamine 2.5 mg/kg/day or saline intraperitoneal (i.p.) for 5 days. On the last day of amphetamine administration, all animals were implanted with cannulae i.c.v. by stereotaxic surgery and they were left undisturbed (drug free period) in their home cages for 7 days. On the day after (day 13 Scheme A) animals received ANG II (400 pmol) i.c.v. and were randomly divided into two groups for: (a) *Drinking test* and (b) *Urine collection* (Scheme A).

Stereotaxic surgery

The animals were anesthetized with an i.p. injection of ketamine/xylazine (75/5 mg/kg body weight) and after loss of corneal and pedal reflexes; they were positioned on a stereotaxic apparatus. The guide cannulae (made from BD Precision Glide Needles, 23 gauge, 11 mm in length), were stereotaxically implanted bilaterally into the cerebral ventricles according to the Paxinos and Watson Atlas (Paxinos and Watson, 2009). Coordinates for cannulae implantation were anteroposterior: 1.0 mm from the bregma, lateral: 1.7 mm from the bregma and vertical: 3.5 mm from the bregma (Paxinos and Watson, 2009) and they were fixed to the skull with acrylic cement and stainless screws. Stainless steel stylets (made from Dental Cartridge Needles, 30 gauge, 11 mm in length) were inserted into the guide cannulae to prevent obstruction. After surgery, the rats were housed individually and maintained undisturbed for recovery for 7 days. Upon completion of each experiment all rats were sacrificed and the sites of injections were verified microscopically. Only the animals with right cannula position were considered for analysis.

Cerebral microinjection of ANG II

The rats were placed in the testing room, for habituation, 1 h before the beginning of the behavioral test. They were gently wrapped in a cloth and manually restrained and injected bilaterally into the lateral cerebral ventricles using a 30-gauge stainless steel injection needle attached to a 25-μl microsyringe (Hamilton Company,



Scheme A. Experimental design. Amph: amphetamine, Sal: saline, ANG II: angiotensin II, i.p.: intraperitoneal, i.c.v.: intracerebroventricular, Fos-IR: Fos immunoreactivity, Fos-OT-IR: Fos-Oxytocin immunoreactivity.

Reno, Nev, USA) by polyethylene tubing P20, inserted into the guide cannulae (1.1 mm below the tip of the guide cannulae). The animals received ANG II (400 pmol) i.c.v. and immediately after they were tested for sodium intake – Drinking test – (a) or placed in metabolic cages for urine collection (b). The microinjections were administered in a total volume of 4 μl/rat (2 μl in each side were gradually injected for a period of 1 min) into the lateral cerebral ventricles. The injection needles were left in place for additional 20s to allow diffusion. The dose was selected on the basis of preliminary reports (Vento and Daniels, 2010; Zapparoli et al., 2011).

(a) Drinking test

The basal water and sodium intake were determined in all animals after an i.c.v. injection of saline solution 1 day before the test. Twenty-four hours later, the animals received a microinjection of 4-μl ANG II i.c.v. Access to two burets, one filled with water and the other filled with 2% NaCl solution were left available on the test cages. The volume of water or 2% NaCl solution consumed was measured at 10, 20, 30, 40, 50 and 60 min after i.c.v. injections. Ninety minutes after the ANG II microinjection, the animals were prepared for brain fixation for Fos immunohistochemical detection (Scheme A).

(b) Urine collection

The rats received i.c.v. 4 μl ANG II (400 pmol) and they were housed individually in metabolic cages with free access to tap water without food. The urine was collected in centrifuge tubes 2 h after the ANG II i.c.v. At the end of the test, plasma samples were collected for analysis and then animals were prepared for brain fixation for Fos and oxytocin (OT) immunohistochemical detection (Fos-OT-IR) (Scheme A).

Biochemical determinations in urine and plasma

Electrolytes were measured by selective ion method, albumin by the bromocresol green colorimetric method, total proteins by kinetic assay, creatinine by the Jaffé method, urea by kinetic-UV assay and glucose levels by using the enzymatic method with a hexokinase. All these parameters were determined using an Automatic Analizator Roche-Hitachi, Cobas c311. Plasma renin activity was measured by Radioimmunoassay, using a Gamma Coat Plasma Renin Activity ^{125}I RIA Kit, DiaSorin.

Staining procedure for Fos and Fos and oxytocin immunohistochemistry

Ninety minutes after the ANG II microinjection (immediately after the test), animals were anesthetized with an i.p. injection of pentobarbital (50 mg/kg body weight) and after loss of corneal and pedal reflexes they were prepared for brain fixation for Fos or Fos-OT immunohistochemical detection.

Fos-IR assay was performed in CPu, NAc core and SFO, and Fos-IR-OT in PVN and SON. This approach was selected because the increased Fos protein synthesis, 1–2 h post-stimulation, is correlated with increased neural activity in a wide range of neural systems (Morgan and Curran, 1989; Nordquist et al., 2008). The animals were anesthetized with pentobarbital and perfused transcardially with 250 ml of normal saline and heparin (200 μl/L) followed by 400 ml of 4% paraformaldehyde in 0.1 M phosphate buffer (PB, pH 7.4). The brains were removed, fixed in the same solution overnight and then stored at 4 °C in PB containing 30% sucrose. Coronal sections of 40 μm were obtained using a freezing microtome (Leica CM15105) and collected in PB 0.01 M. They were placed in a mixture of 10% H_2O_2 and 10% methanol for 2 h. The free-floating sections were incubated in 10% normal horse serum (NHS) (GIBCO, Auckland, NZ, USA) in PB for 2 h to block non specific binding sites. In all animals, free-floating sections were first processed for Fos-IR using an avidin biotin-peroxidase procedure. The staining procedures following the double-labeling procedures were previously described in Franchini and Vivas (1999), Franchini et al. (2002)). In brief, the free-floating sections were incubated overnight at room temperature in a rabbit anti-Fos antibody (produced in rabbits against a synthetic 14-amino acid sequence, corresponding to residues 4–17 of human Fos) (Ab-5; Oncogene Science, Manhasset, NY, USA), diluted 1:10,000 in PB containing 2% NHS and 0.3% Triton X-100 (Flucka, BioChemika, Sigma–Aldrich, Steinheim, Switzerland). The sections were then rinsed with PB 0.01 M and incubated with biotin-labeled universal secondary antibody (diluted 1:500 in 2% NHS-PB), and avidin–biotin-peroxidase complex (Vector Laboratories, Burlingame, CA, USA; diluted 1:200 in 2% NHS-PB) for 2 h each at room temperature. The peroxidase label was detected with diaminobenzidine hydrochloride (Sigma Chemical Co.); the solution was intensified with 1% cobalt chloride and 1% nickel ammonium sulfate. This method produces a violet nuclear reaction product. The series of Fos-labeled sections, also processed for OT immunohistochemical localization, were incubated for 72 h at 4 °C

with polyclonal rabbit anti-OT antibody (Peninsula Laboratories, San Carlos, CA, USA; 1:1000). After incubation, the sections were rinsed and incubated with biotin-labeled anti-rabbit immunoglobulin and the avidin–biotinperoxidase complex for 1 h at room temperature. Cytoplasmic oxytocin immunoreactivity (OT-IR) was detected with unintensified diaminobenzidine hydrochloride which produces a brown reaction product. Finally, the free-floating sections were mounted on gelatinized slides, air dried overnight, dehydrated, cleared in xylene and placed under a coverslip with DPX mountant for histology (Flucka, BioChemika, Sigma–Aldrich, Steinheim, Switzerland).

Cytoarchitectural and quantitative analysis

Images containing Fos-IR nuclei and Fos-OT-IR were obtained using a computerized system that included a Leica DM 4000B microscope equipped with a DFC Leica digital camera attached to a contrast enhancement device. The brain nuclei evidencing Fos-IR were identified and delimited according to atlas of Paxinos and Watson (Pelisch et al., 2011). The numbers of Fos-IR nuclear profiles in the sections were counted at one level; the distance from the bregma of the corresponding plates is as follows: for dorsomedial region of CPu = 1.6 mm and for NAc core = 1.6 mm.

The number of Fos-OT-IR-positive neurons were counted in different PVN subnuclei, i.e., periventricular magnocellular (PeM), anterior magnocellular (PaAM), medial magnocellular (PaMM), the dorsomedial cap (PaDC), lateral magnocellular (PaLM), and parvocellular posterior (PaPo) (corresponding to plates with a distance of −0.92 mm to −2.12 mm from bregma) and for SON = -1.3 mm.

The brain sections were processed concurrently for subjects across all groups. Images were standardized using Adobe Photoshop image analysis program (version 5.5). Counting of Fos-IR and Fos-OT-IR was accomplished using IMAGE J software from the National Institutes of Health (NIH). Threshold was fixed between intervals of 0–150 in black and white conditions; all higher values were considered background. Fos-IR neurons were identified by dense black staining of the nucleus and counted by setting a size range for cellular nuclei (8 to 12 μm of diameter) and IR-OT neurons were identified by dense brown staining of cytoplasm. To count double-immuno labeled cells Fos-OT-IR we took into account the presence of both stains simultaneously.

The measurement for each brain area was done bilaterally in two sections. The value obtained was the average of the four counts. The counting was made on a 0.37 mm^2 area (corresponding to 200× magnification). Since the size and section thickness of nuclei did not change between experimental and control groups, any systematic error could be identical for all groups. The counting was made by two operators, on each section analyzed, to ensure that the number of profiles obtained was similar, but only one counting was used. Counting of Fos-IR and Fos-OT-IR cells was performed blinded to the observer.

Statistical analysis

The results are expressed as mean ± SEM, for groups of animals measured individually. The *t* Test analysis was used to assess the significance of differences, $p < 0.05$ was considered as statistically significant. All statistics were performed with the use of Prism 6.0 software (GraphPad Software for Science, San Diego, CA, USA).

RESULTS

Effect of ANG II i.c.v. on water and sodium intake, natriuresis, plasma renin activity and Fos pattern in the NAc core and CPu

The present report confirmed that ANG II (400 pmol) injected into the lateral ventricle of conscious rats, induces a significant increase in water and sodium chloride intake, and natriuresis and decreases plasma renin activity. These effects were described by many researchers (Fluharty and Manaker, 1983; Unger et al., 1989; Weekley, 1992; Fitzsimons, 1998; Ferguson et al., 2001; Geerling and Loewy, 2008). In addition, in the present work it was found that ANG II i.c.v. increase Fos-IR in NAc core: 87.3 ± 10.7 vs. 26.5 ± 4.1 in control animals ($t = 4.43$ $p < 0.01$, $n = 6$–4) and in CPu: 67.2 ± 5.7 vs. 18.1 ± 2.6 in control animals ($t = 6.6$ $p < 0.01$, $n = 6$–4).

Effect of previous amphetamine exposure on ANG II i.c.v.-induced water and sodium intake, plasma renin activity and natriuresis

Effect of previous amphetamine exposure on ANG II i.c.v.-induced water and sodium intake

The ANG II i.c.v. induced a similar increase in water intake in all studied groups, 7 days after repeated treatment, since no differences were found between the amphetamine and saline groups (saline 9.49 ± 1.79 $n = 10$ vs. amphetamine 10.83 ± 1.92 $n = 12$; *t* Test: $t = 0.5041$ $p > 0.05$).

Seven days after repeated amphetamine, the sodium intake induced by ANG II was significantly lower than in control group (saline) (Fig. 1A). (*t* Test: $t = 3.006$ $p < 0.01$).

Effect of previous amphetamine exposure on ANG II i.c.v.-induced plasma renin activity

Repeated amphetamine exposure significantly decreased plasma renin activity compared to control group when analyzed 7 days after the last administration (Fig. 1B). (*t* Test: $t = 4.265$ $p < 0.001$).

Effect of previous amphetamine exposure on ANG II i.c.v.-induced natriuresis

Seven days after repeated amphetamine administration, the natriuresis (2 h urine collection) induced by ANG II i.c.v. was significantly higher in amphetamine than in control (Fig. 1C). (*t* Test: $t = 2.102$ $p < 0.05$).

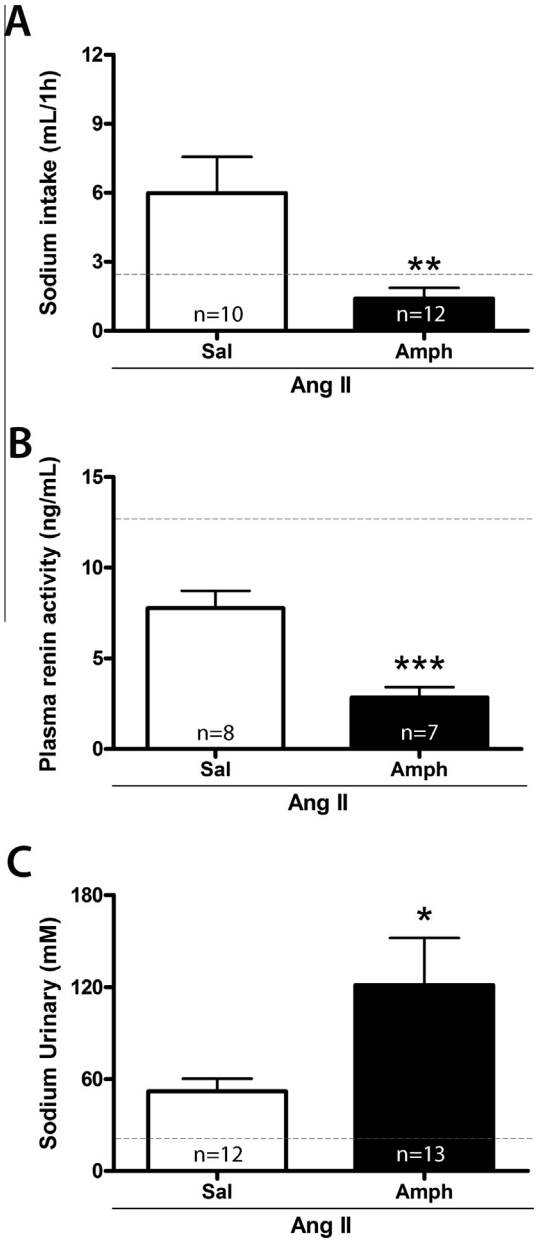


Fig. 1. Sodium intake (A), plasma renin activity (B) and natriuresis (C) induced by ANG II i.c.v. (400 pmol/4 μl) (n = 11–13), 7 days after amphetamine administration. The dotted line on the graph represents the mean of the basal group with saline i.c.v. Values are mean ± SEM: $^{*}p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$ significantly different from saline group.

Effect of previous amphetamine exposure on ANG II i.c.v.-induced Fos pattern in the dorsomedial region of CPu, NAc core and SFO

The ANG II i.c.v. induced a similar increase in Fos-IR cells in SFO in all groups studied, 7 days after repeated amphetamine or saline administration, since no differences were found between groups (saline 63.08 ± 11.37 n = 6 vs. amphetamine 65.43 ± 11.09 n = 7, t Test: t = 0.1471 $p > 0.05$).

CPu: Repeated amphetamine exposure decreased the number of Fos-IR cells compared to control group (saline) in response to ANG II i.c.v. when analyzed 7 days after the last administration, in CPu (Fig. 2) (t Test: t = 2.830 $p < 0.05$). Representative microphotographs are shown in Fig. 2.

NAc core: Seven days after amphetamine exposure, a significant decrease was found in the number of Fos-IR cells compared to control group in NAc core in response to ANG II i.c.v (Fig. 3) (t Test: t = 2.563 $p < 0.05$). Representative microphotographs are shown in Fig. 3.

Effect of previous amphetamine exposure on ANG II i.c.v.-induced double-immuno labeled cells Fos-OT in the SON and PVN

SON: Seven days after repeated amphetamine exposure, a significant increase in the number of Fos-OT-IR-positive neurons was observed compared to the control group in response to ANG II i.c.v (Fig. 4) (t Test: t = 3.976 $p < 0.01$). Representative microphotographs are shown in Fig. 4.

PVN: Repeated amphetamine exposure increased the number of Fos-OT-IR-positive neurons compared to the control group, in response to ANG II i.c.v when analyzed 7 days after the last amphetamine administration in the PaMM (Fig. 5) (t Test: t = 4.895 $p < 0.001$) and other subnuclei of PVN. Representative microphotographs are shown in Fig. 5.

Urinary and serum parameters

No significant differences among groups (saline or amphetamine) were found in creatinine, urea, chloride and potassium in urine and albumin, total proteins, creatinine, urea, chloride, potassium, sodium and glucose in serum in response to ANG II i.c.v. 7 days after amphetamine administration. No differences were found in urine volume after ANG II i.c.v. or body weight between groups (Table 1).

DISCUSSION

The main finding of the present work is that a previous history of repeated amphetamine exposure is able to modify the brain RAS responses in a long-lasting manner. These alterations revealed by intracerebral ANG II administration seem to involve the AT_1-R functionality.

It is known that brain ANG II regulates some responses induced by drugs of abuse such as cocaine and amphetamine (Hosseini et al., 2007; Watanabe et al., 2010; Paz et al., 2011, 2013). It has been described that ANG II can markedly potentiate DA release in CPu projecting dopaminergic neurons involving pre- and post-synaptic mechanisms (Mendelsohn et al., 1993; Brown et al., 1996) and in NAc (Hoebel et al., 1994). The AT_1-R are located in these DA-innervated brain areas (Daubert et al., 1999) and mediate the DA release induced by ANG II (Georgiev et al., 1985; Brown et al., 1996). The brain areas Cpu and NAc are strongly related to self-administration, motivation, reward and behavioral responses to drugs of abuse (White and Kalivas, 1998).

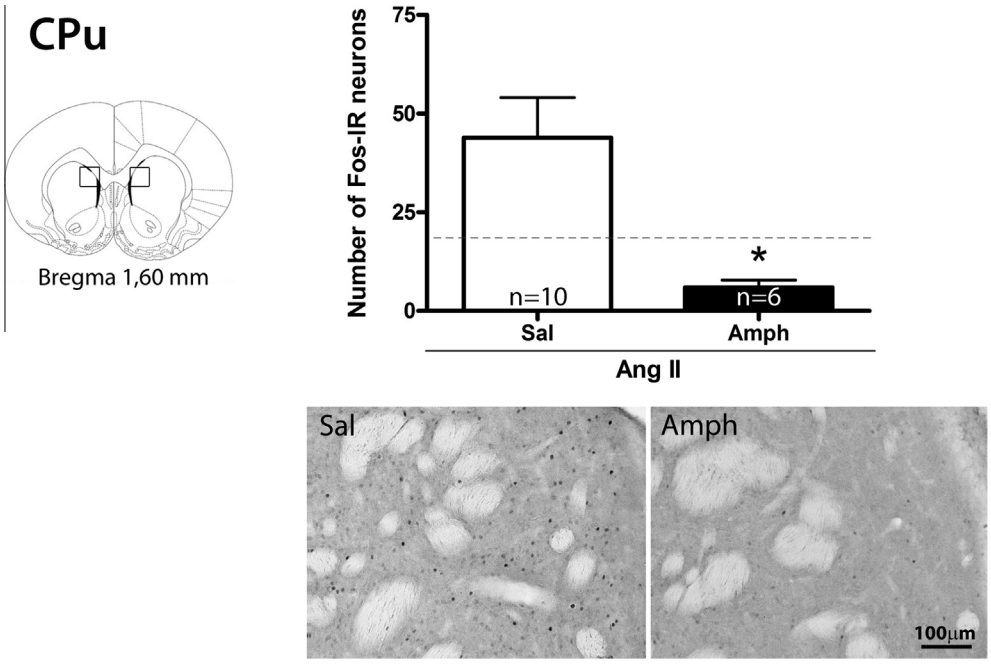


Fig. 2. Average number of Fos-IR neurons in dorsomedial region of CPu, in response to ANG II i.c.v. (n = 5–10), 7 days after amphetamine exposure. The dotted line on the graph represents the mean of the basal group with saline i.c.v. Values are mean ± SEM: $^{*}p < 0.05$ significantly different from saline group. Schematic coronal slices indicating the region where the counting was done in CPu. Photomicrographs 200× magnification showing the pattern of Fos-IR neurons after ANG II i.c.v. in CPu. Scale bar = 100 μm.

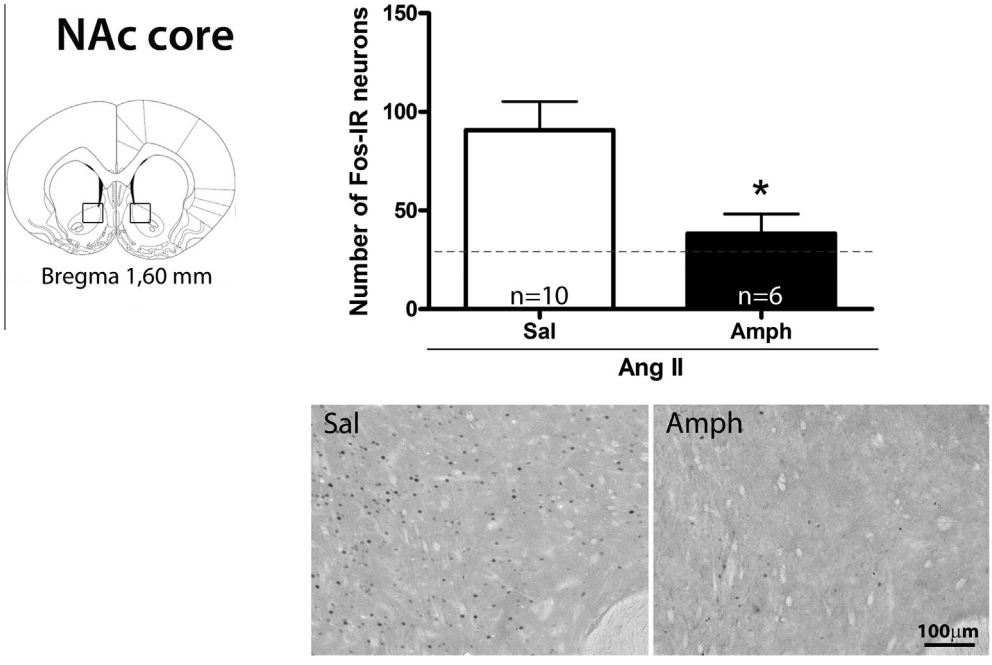


Fig. 3. Average number of Fos-IR neurons in NAc core in response to ANG II i.c.v. (n = 5–10), 7 days after amphetamine exposure. The dotted line on the graph represents the mean of the basal group with saline i.c.v. Values are mean ± SEM: $^{*}p < 0.05$ significantly different from saline group. Schematic coronal slices indicating the region where the counting was done in NAc core. Photomicrographs 200× magnification showing the pattern of Fos-IR neurons after ANG II i.c.v. in NAc core. Scale bar = 100 μm.

There is evidence showing a cross-sensitisation between sodium depletion (manipulation that strongly activate RAS) and amphetamine or cocaine exposure, since one treatment enhances the response to the other (Clark and Bernstein, 2004; Acerbo and Johnson, 2011). This cross-sensitisation suggests that a common neural substrate is involved in the two experiences. This neural substrate is the mesolimbic dopaminergic system, involved in mediating motivation and reward responses to drug abuse and natural rewards (Stewart and Badiani,

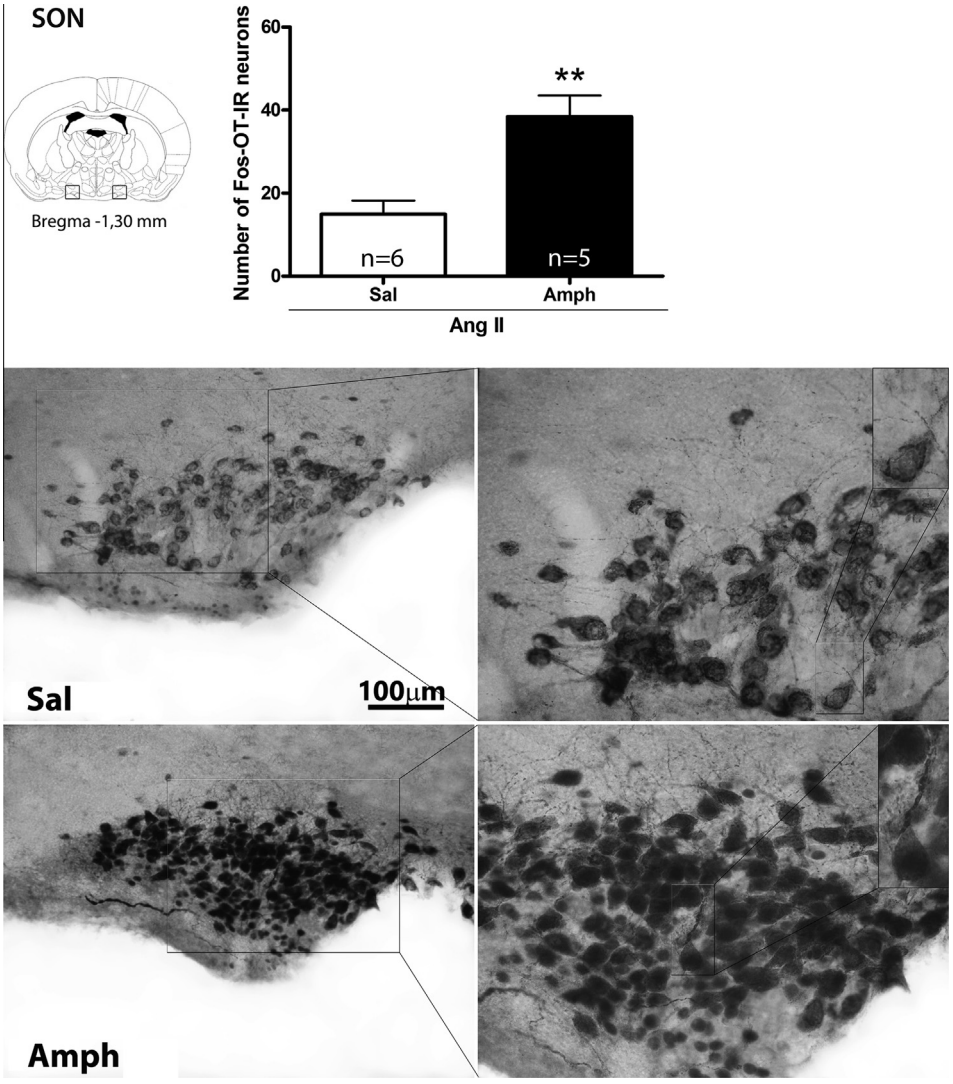


Fig. 4. Average number of Fos-OT-IR neurons in SON in response to ANG II i.c.v. (n = 5–6), 7 days after amphetamine exposure. Values are mean ± SEM: $^{**}p < 0.01$ significantly different from saline group. Schematic coronal slices indicating the region where the counting was done in SON. Photomicrographs 200× magnification showing the pattern of double immunoreactivity cells (Fos-OT) in the SON in response to ANG II i.c.v., 7 days after amphetamine exposure. The images on the right are higher magnifications (400×) of the areas indicated in the left images (200×) and images of the upper right boxes are higher magnifications (100×) of cells indicated in images 400×. Scale bar = 100 μm.

1993; Lucas et al., 2000; Kelley and Berridge, 2002; Roitman et al., 2002; Wise, 2002). Moreover, the sensitisation of sodium appetite and thirst has been associated with central actions of ANG II and Aldosterone (Moellenhoff et al., 2001). In addition, the Spontaneous Hypertensive Rats (SHR), in which the brain RAS components are augmented, have alterations in the dopaminergic neurotransmission (Hollister et al., 1974; McCarty et al., 1980; Hynes et al., 1985; van den Buuse and de Jong, 1989; Van den Buuse et al., 1992).

Circulating ANG II induces sodium retention by a direct renal action as well as through aldosterone release from the adrenal gland; meanwhile, intracerebrally administered ANG II enhances natriuresis (Fluharty and Manaker, 1983; Unger et al., 1989; Ferguson et al., 2001) together with an increased water and sodium intake (Fitzsimons, 1998; Geerling and Loewy, 2008). However, it has been described that ANG II has a dual effect through its AT_1-R: one is direct and stimulant on sodium intake (Buggy and Jonklaas, 1984; Moe et al., 1984), the other is indirect and inhibitor on sodium intake, mediated by central activation of oxytocinergic system (Fitts et al., 2005).

Water and sodium intake

In the present work, we first confirmed that ANG II (400 pmol) injected intracerebrally in conscious rats, produced a marked increase in water and sodium intake, as well as and increased natriuresis. All these effects have been previously described (Fluharty and Manaker, 1983; Unger et al., 1989; Fitzsimons, 1998; Ferguson et al., 2001; Geerling and Loewy, 2008); however, the results obtained in the present work show that previous

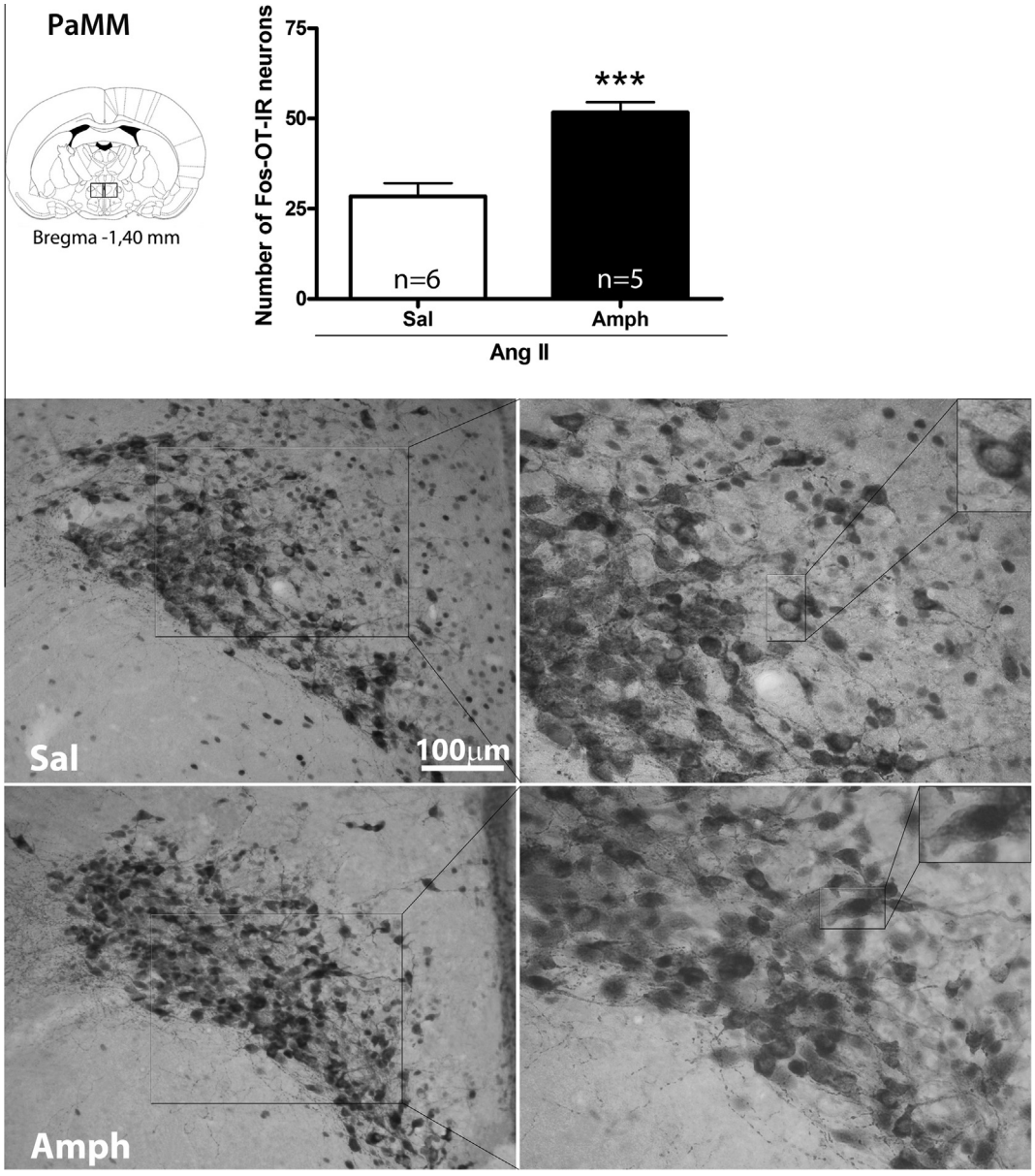


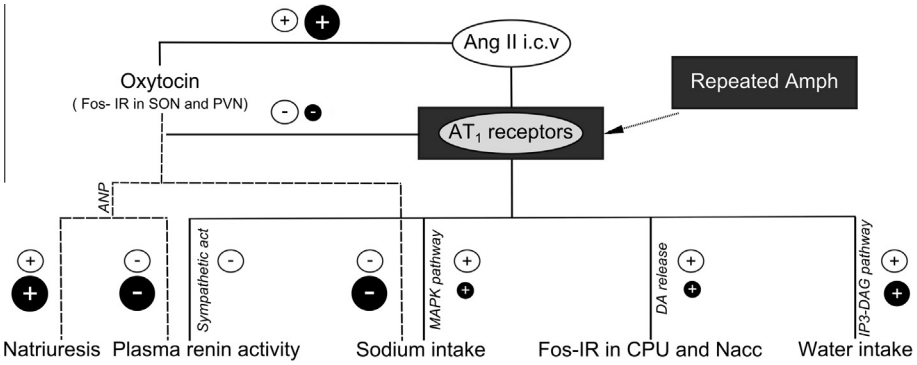
Fig. 5. Average number of Fos-OT-IR neurons in PaMM of PVN in response to ANG II i.c.v. (n = 5–6), 7 days after amphetamine exposure. Values are mean ± SEM: $^{***}p < 0.001$ significantly different from saline group. Schematic coronal slices indicating the region where the counting was done in PaMM. Photomicrographs 200× magnification showing the pattern of Fos-OT cells in the PaMM in response to ANG II i.c.v., 7 days after amphetamine exposure. The images on the right are higher magnifications (400×) of the areas indicated in the left images (200×) and images of the upper right boxes are higher magnifications (100×) of cells indicated in images 400×. Scale bar = 100 μm.

exposure to repeated amphetamine administration modified the effects of ANG II i.c.v. on these parameters in a long-term manner. A possible explanation for the altered responses obtained in amphetamine-exposed animals may involve the desensitisation of AT_1-R through internalization of these receptors (Hunyady et al., 2000). This is based on the evidence showing that ANG II i.c.v. induces internalization of AT_1-R (Sasamura et al., 1994). In this sense, after a persistent or repetitive stimulation of AT_1-R, a decrease in the response to ANG II (Tang et al., 1995) was found. Moreover, it was shown that the early inducible genes, *c-fos*, *c-jun* and *delta-fos* are involved in the control of expression of transcription factors that ultimately mediate the desensitisation to the ANG II signal (Moellenhoff et al., 2001).

In the present study, it was found that repeated amphetamine exposure markedly decreased the sodium intake induced by centrally administered ANG II meanwhile water intake was unaffected. Sodium intake behavior is likely to reflect the differential regulation of intracellular signaling pathways. In this sense, it has been hypothesized that differential AT_1-R signaling pathways play separable roles in water and saline intake stimulated by ANG II (Daniels et al., 2005, 2007).

Table 1. Urinary and serum parameters, 7 days post-amphetamine. Creatinine, urea, chloride and potassium at urinary level; albumin, totals proteins, creatinine, urea, chloride, potassium, sodium and glucose at serum; body weight and volume urinary. Parameters measured at 7 days post-amphetamine, in response at ANG II i.c.v. Groups: Saline and amphetamine (n = 15–21). Values are expressed as mean ± SEM

Groups	Body weight (g)	Samples	Vol. urine mL	Alb g/dL	Prot g/dL	Creat mg%	Urea mg%	Cl^- mM	K^+ mM	Na^+ mM	Gluc mg%
Sal	285.7 ± 2.7	Plasma	–	3.5 ± 0.1	6.6 ± 0.2	0.40 ± 0.02	47.4 ± 2.8	104.7 ± 1.9	5.47 ± 0.23	159.8 ± 4.7	180.8 ± 6.2
		Urine 2 h	5.6 ± 1.4	–	–	29.4 ± 6.9	1651 ± 409	105.7 ± 25.6	94,8 ± 21,3	Fig. 1C	–
Amph	286.8 ± 2.5	Plasma	–	3.6 ± 0.2	6.7 ± 0.3	0.39 ± 0.03	47.8 ± 2.6	105.7 ± 4.8	5.50 ± 0.19	162 ± 5.4	174.0 ± 20.6
		Urine 2 h	5.9 ± 1.2	–	–	24.3 ± 5.9	1332 ± 319	103.7 ± 36.3	98,10 ± 18,6	Fig. 1C	–



Scheme B. Effect of repeated amphetamine (Amph) exposure in the ANG II i.c.v. responses mediated by AT_1-R. The described ANG II i.c.v. responses were not observed and the effects of oxytocin in response to ANG II i.c.v. predominated. Open circles: described actions of Ang II i.c.v. Closed circles: actions of Ang II i.c.v. after repeated amphetamine exposure. The symbols' sizes indicate the influence of the condition (control/Amph) in each response.

There are results that support this hypothesis demonstrating that G protein-dependent pathways appear to be more important for water intake stimulated by ANG II, whereas G protein-independent pathways may be more relevant for ANG II-stimulated sodium intake (Daniels et al., 2009). In accordance to these results, repeated i.c.v. ANG II administration reduced the dipsogenic effect without affecting sodium intake (Vento and Daniels, 2010). Based on the above-mentioned findings, a possible explanation for our results could be that amphetamine exposure alters the intracellular signaling pathway involved in the effects of ANG II on sodium intake.

It has been shown that exogenous i.c.v. ANG II administration stimulates OT release from the pituitary gland (Lang et al., 1981; Ferguson and Kasting, 1988). Several treatments that chronically increase sodium intake (e.g., sodium deprivation, adrenalectomy, and de oxycorticosterone-DOCA-injections) decrease basal OT levels meanwhile treatments that stimulate OT secretion (e.g., hypertonic saline, lithium chloride, and copper sulfate) inhibit sodium intake in sodium-deprived rats (Stricker and Verbalis, 1987, 1996; Blackburn et al., 1992). Additionally, blockade of central OT-receptors before i.c.v. ANG II administration, resulted in a three to fourfold potentiation of ANG II-induced sodium intake. However, in the absence of exogenously administered ANG II, blockade of OT-receptors does not interfere with the dipsogenic properties of ANG II, nor stimulates sodium intake (Blackburn et al., 1992). Though, other researchers found a slight increase in water and sodium intake in rats induced by intracerebral administration of OT-receptor antagonist (Fitts et al., 2003). In addition, losartan, a selective AT_1-R antagonist, blunted sodium intake induced by the OT-receptor antagonist administration in rats (Fitts et al., 2005). This supports the idea of an inhibitory oxytocinergic tone involving the activation or disinhibition of AT_1-R (Fitts et al., 2005).

In the present work, the decreased sodium intake responses to ANG II i.c.v. found 7 days post-repeated amphetamine, reveals a long-lasting effect of amphetamine exposure. Based on the response outlined above, it is possible to suggest that the decreased response in sodium intake induced by ANG II i.c.v. in amphetamine-exposed animals could be attributed to an increased OT response to ANG II as a consequence of AT_1-R altered functionality. This hypothesis is supported by our results showing quantification of Fos-OT-positive neurons discussed below.

Expression of Fos and Fos-OT

Forebrain areas, such as the SFO and the PVN, are known to be involved in osmoregulation and

predominately express AT_1-R (Saavedra, 1992; Phillips et al., 1993). The experience with sodium depletion enhances sodium intake and Fos-IR in SFO, PVN and NAc (central structures implicated in sodium appetite and reward signaling) (Voorhies and Bernstein, 2006; Na et al., 2007). In our laboratory, we found that ANG II i.c.v. induced an increase of threefold in NAc and CPu of Fos-IR with respect to the control group. Furthermore, the AT_1-R may mediate the expression of Fos in SFO and PVN, after a single ANG II i.c.v. injection (Lebrun et al., 1995; Blume et al., 1997). In contrast, repeated ANG II i.c.v. administration (for 7 days) induced a decline of 50% in Fos expression in SFO and PVN and increased AT_1-R expression in these brain areas (Moellenhoff et al., 2001). This phenomenon could be explained by AT_1-R desensitisation caused by the sustained ANG II binding and the consequent reduction of the cell surface expression of AT_1-R. This specific reduction of AT_1-R expression could not be visualized by these authors, due to the methods used (immunohistochemistry or Western blot) without tracking of receptors' localization (Moellenhoff et al., 2001).

On the other hand, it has been described that amphetamine and cocaine induced an over expression of Fos-IR cells in CPu and NAc, as well as other alterations in cellular activity (Graybiel et al., 1990; Young et al., 1991; Vanderschuren et al., 2002; Nordquist et al., 2008; Larson et al., 2010; Rotllant et al., 2010; Paz et al., 2013). A single cocaine injection increased Fos-IR in NAc, however, a long-term reduction of the Fos signal was observed with chronic cocaine administration (Hope et al., 1992). In the present investigation, the neuronal activation, measured as Fos-IR in CPu and NAc core showed a decreased response to ANG II i.c.v. after repeated amphetamine exposure. This decreased response could evidence an AT_1-R desensitisation induced by repeated amphetamine administration. In this sense, a desensitisation reduced Fos expression has been described as a consequence of repetitive ANG II i.c.v. administration in different brain areas that co-expressed AT_1-R (Moellenhoff et al., 2001). Interestingly, these results are in agreement with those obtained with the decreased response in sodium intake to ANG II i.c.v. This supports the hypothesis that AT_1-R are involved in the long-lasting effects induced by amphetamine.

Contrarily, amphetamine exposure did not affect the number of Fos-IR neurons in SFO and also reduced sodium intake without altering water intake induced by central ANG II administration, suggesting that SFO is related to water intake rather than sodium intake, as it was reported by the work of Fitzsimons (Fitzsimons, 1998).

Most SON neurons produce either oxytocin or vasopressin and project to the neural lobe. Although vasopressinergic neurons slightly outnumber oxytocinergic neurons, the large size of the SON relative to the PVN makes it quantitatively the most important site for the production of both hormones (Gimpl and Fahrenholz, 2001). The PVN is cytoarchitectonically complex, but the majority of PVN neurons sending axons to the neural lobe of the pituitary lie in two contiguous groups: the PaMM contains mostly oxytocinergic neurons, the PaLM contains primarily vasopressinergic neurons (except for a ring of OT neurons that lies around the densely packed PaLM) (Gimpl and Fahrenholz, 2001).

It has been shown that ANG II i.c.v. activates OT neurons in PVN and SON (Lang et al., 1981; Ferguson and Kasting, 1988; Blackburn et al., 1992). In the present study, the repeated amphetamine administration potentiated the activation of OT neurons induced by ANG II i.c.v. in different oxytocinergic subnuclei of PVN and SON, possibly evidencing an increased OT response to ANG II as a consequence of the reduced AT_1-R functionality mentioned above.

Natriuresis and plasma renin activity

It has been described that central endogenous ANG II can activate AT_1-R located in brain areas involved in the regulation of peripheral sympathetic nerve activity. In this sense, losartan i.c.v. administration decreased basal renal sympathetic neural activity (RSNA) (DiBona, 2000).

The mechanisms by which ANG II i.c.v. induces natriuretic effects remains to be elucidated and several possibilities could be considered. First, the central nervous system may directly influence renal sodium excretion through neural routes because a decrease in RSNA induced by ANG II i.c.v. has been shown to be, mediated by the AT_1-R (Kannan et al., 1991; McKinley et al., 2001). Second, the natriuresis induced by ANG II i.c.v. could be mediated through brain oxytocin release (Verbalis et al., 1991); this increases the atrial natriuretic peptide (ANP) excretion from the heart (Haanwinckel et al., 1995; McCann et al., 2003). The ANP via renal-specific receptor increases urinary GMPc, the hydrostatic pressure in the glomerulus and promote sodium excretion (McCann et al., 2003). In the present study, amphetamine administration potentiated the ANG II i.c.v. natriuretic effect.

The ANG II i.c.v. activates AT_1-R and induces a decrease in plasma renin activity (Weekley, 1992; McKinley et al., 1994). In the present work, we observed that amphetamine-exposed rats presented a higher decrease in plasma renin activity in response to ANG II i.c.v. than in controls. Taken together our results suggest that the decreased response in plasma renin activity results from alterations in brain areas associated with RSNA which are controlled by endogenous ANG II. However, it has been also described that ANP decreases the plasma renin activity (Antunes-Rodrigues et al., 2004). Moreover, the increased natriuresis and decreased sodium intake induced by ANG II i.c.v. in amphetamine-exposed animals could be due to an increased OT response to ANG II as a consequence of altered AT_1-R functionality. ANG II i.c.v. is known to stimulate OT neurons through AT_1-R activation. In this sense, a dual effect has been described: whereas ANG II i.c.v. via AT_1-R stimulates sodium intake and also inhibits sodium intake and stimulates natriuresis via OT neurons activation.

Conclusions

The repeated amphetamine exposure could reduce AT_1-R functionality (desensitisation-like) evidenced as a potentiated oxytocinergic response to ANG II i.c.v. that elicits a decrease in sodium intake, increase natriuresis and decreased plasma renin activity. These results are also supported by the increased number of Fos-OT-IR neurons in PVN and SON in response to ANG II i.c.v. found in the amphetamine-exposed group (see Scheme B).

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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