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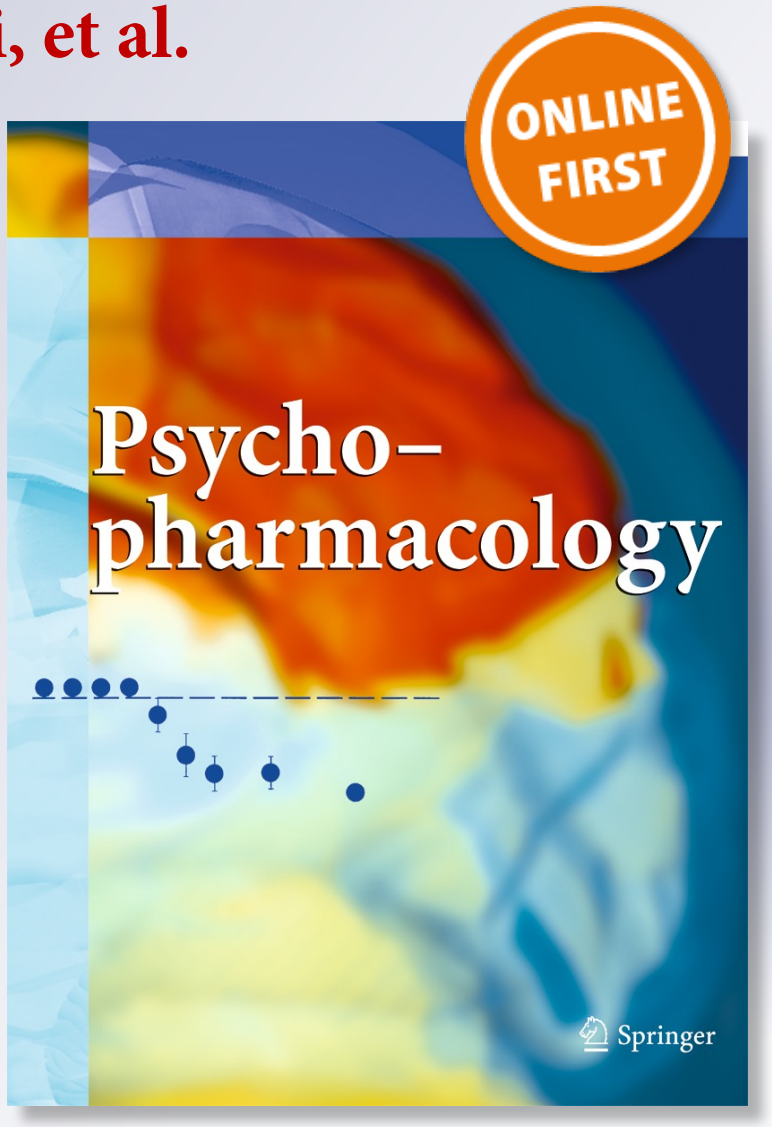

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ORIGINAL INVESTIGATION

Brain Angiotensin II AT_1 receptors are involved in the acute and long-term amphetamine-induced neurocognitive alterations

Natalia Andrea Marchese[1] · Emilce Artur de laVillarmois[1] · Osvaldo Martin Basmadjian[1] · Mariela Fernanda Perez[1] · Gustavo Baiardi[2] · Claudia Bregonzio[1]

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Abstract
Rationale Angiotensin II, by activation of its brain AT_1-receptors, plays an active role as neuromodulator in dopaminergic transmission. These receptors participate in the development of amphetamine-induced behavioral and dopamine release sensitization. Dopamine is involved in cognitive processes and provides connectivity between brain areas related to these processes. Amphetamine by its mimetic activity over dopamine neurotransmission elicits differential responses after acute administration or after re-exposure following long-term withdrawal periods in different cognitive processes.
Objective The purpose of this study is to evaluate the AT_1-receptor involvement in the acute and long-term amphetamine-induced alterations in long-term memory and in cellular-related events.
Methods Male Wistar rats (250–300 g) were used in this study. Acute effects: Amphetamine (0.5/2.5 mg/kg i.p.) was administered after post-training in the inhibitory avoidance (IA) response. The AT_1-receptor blocker Losartan was administered i.c.v. before a single dose of amphetamine (0.5 mg/kg i.p.). Long-term effects: The AT_1-receptors blocker Candesartan (3 mg/kg p.o.) was administered for 5 days followed by 5 consecutive days of amphetamine (2.5 mg/kg/day, i.p.). The neuroadaptive changes were evidenced after 1 week of withdrawal by an amphetamine challenge (0.5 mg/kg i.p.). The IA response, the neuronal activation pattern, and the hippocampal synaptic transmission were evaluated.
Results The impairing effect in the IA response of post-training acute amphetamine was partially prevented by Losartan. The long-term changes induced by repeated amphetamine (resistance to acute amphetamine interference in the IA response, neurochemical altered response, and increased hippocampal synaptic transmission) were prevented by AT_1-receptors blockade.
Conclusions AT_1-receptors are involved in the acute alterations and in the neuroadaptations induced by repeated amphetamine associated with neurocognitive processes.

Keywords Angiotensin II · Amphetamine · AT_1 receptors · Long-term memory · Long-term potentiation · Hippocampus · Inhibitory avoidance · FOS · Losartan · Candesartan

Introduction

The role of brain renin-angiotensin system (RAS) is complex, and its main active peptide, angiotensin II (Ang II), was initially described as a modulator of autonomic and hormonal systems, sensorial and cognitive processes, and it also participates in the regulation of cerebral blood flow. Ang II exerts its known actions principally by activation of the angiotensin receptors type 1 (AT_1-R) (Saavedra 1992; Saavedra et al. 2005). Locally produced brain Ang II plays an important role in the modulation of central dopaminergic neurotransmission. Dopamine (DA) innervated areas such as caudate putamen

Natalia Andrea Marchese and Emilce Artur de laVillarmois contributed equally to this work.

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(CPu), nucleus accumbens (NAc), substancia nigra (SN), the hypothalamus, and ventral pallidum express high AT_1-R density (Zhuo et al. 1998; Daubert et al. 1999; Paz et al. 2014). Indeed, AT_1-R are located in the soma and terminal fields of dopaminergic neurons, and there is a cross regulation between DA and Ang II systems. Thereby, decreased levels of DA after chronic depletion with reserpine or 6-hydroxydopamine promotes an increase in AT_1-R expression in SN and CPu, which can be reversed by restatement of DA activity (Villar-Cheda et al. 2010; Labandeira-Garcia et al. 2011). Similarly, knockout mice for DA receptors (D1-R and D2-R type) have increased levels of AT_1-R, while transgenic mice overexpressing D2-R have reduced levels. Moreover, aged rats show decreased levels of DA receptors and increased expression of AT_1-R simultaneously, when compared to young animals (Villar-Cheda et al. 2014). On the other hand, acute or chronic manipulation of brain RAS with AT_1-R antagonists decreased D2-R and increased D1-R expression (Dominguez-Meijide et al. 2014). Functional evidences indicate that tonic and evoked DA synthesis and release are positively regulated by AT_1-R activation (Hoebel et al. 1994; Brown et al. 1996). Finally, recent evidences point out a direct interaction between AT_1-R and D2-R, as they shape functional heterodimers in cultured striatum cells (Martinez-Pinilla et al. 2015).

Amphetamine (Amph) is a drug of abuse, worldwide consumed for its stimulant properties over the central nervous system. It promotes mainly noradrenergic and dopaminergic neurotransmission and induces long-term changes in multiple neuronal circuits, modifying their future responses to pharmacological or non-pharmacological challenges (Pierce and Kalivas 1997; Vanderschuren and Kalivas 2000). The altered neuronal connectivity induced by Amph has long been studied in reward-processing brain areas (i.e., CPu and NAc) and in behavioral performance (i.e., locomotor activity); however, only few evidences have focused on the effects of Amph exposure over learning and memory processes. Depending on the type of memory evaluated, controversial results have been reported after Amph administration: an improving effect is observed with an acute administration in reward-associated memories (Nelson and Killcross 2006; Simon and Setlow 2006), while fear memories can be either improved or interfered. The DBA/2 mice (DBA inbred strain) display poor retention latencies in inhibitory avoidance (IA) responses when receiving Amph, stress, or DA agonist after the training session (Cestari et al. 1992; Cabib and Castellano 1997). Meanwhile, rodents under an Amph sensitization protocol show no altered performance after long periods of withdrawal (Eldred and Palmiter 2013).

The striatum, which comprises the CPu and NAc, receives inputs from all areas of the cortex as well as from the thalamus and limbic structures such as the hippocampus (HP) and amygdala (Parent 1990). Repeated Amph exposure results in altered interactions in the striatum and prefrontal cortex (PFC) between converging dopaminergic inputs from the ventral tegmental area and glutamatergic inputs from the amygdala and HP (Ito and Canseliet 2010). The HP has been implicated in spatial and context-dependent learnings, including those related to the development and persistent expression of addictive behaviors and drug sensitization (Wolf 2002; Robbins et al. 2008). A major form of synaptic plasticity in the HP is long-term potentiation (LTP) characterized by an enduring increase in the efficacy of synaptic transmission. This phenomenon is accepted as a molecular mechanism for learning and memory in the brain in which contextual cues are relevant (Phillips and LeDoux 1992; Martin et al. 2000). Psychostimulants such as cocaine are known to facilitate this phenomenon in the HP (Perez et al. 2010; Gabach et al. 2013).

Brain RAS is proposed as a neuromodulatory system involved in regulation of vascular, glial, and neuronal function. Previously, we have reported reciprocal interactions between brain Ang II and Amph effects in long-term modifications in the reward circuit and behavioral-related responses. We observed that AT_1-R are involved in the behavioral and neurochemical adaptive responses induced by Amph exposure (Paz et al. 2011; Paz et al. 2013). Moreover, Amph exposure induced long-term changes in AT_1-R density and in angiotensinogen mRNA in CPu, a rich DA area strongly related to drugs of abuse responses (Paz et al. 2014). Most of the studies employing repeated Amph administration investigated the effects on locomotor and/or stereotyped activities and attributed the enhanced locomotor activity induced by Amph to increases in striatal and cortical DA (Robinson and Kolb 1997; White and Kalivas 1998; Robinson and Kolb 2004). Only a few studies assessed possible alterations in learning and memory induced by Amph in rodents and primates (Ito and Canseliet 2010; Eldred and Palmiter 2013; Leri et al. 2013). Therefore, the aim of the current study is to evaluate the participation of RAS over alterations in learning and memory processes induced by Amph, in order to explore this system as a target for pharmacological intervention in treatment of disorders related to psychostimulant abuse. For this purpose, we used behavioral, neurochemical, and electrophysiological approaches in order to elucidate the role of AT_1-R in learning and memory alterations induced by Amph and the possible brain structures and mechanisms implicated in those alterations.

Materials and methods

Animals

A total of 213 adult male Wistar rats (250–330 g) from the Department of Pharmacology vivarium (Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Argentina) were used. Rats were maintained at 20–24 °C under a 12-h

light–dark cycle (lights on at 07 a.m.) with free access to food and water. Animals were randomly housed in groups of four per cage a week before the beginning of the treatment.

All procedures were handled in accordance with the NIH Guide for the Care and Use of Laboratory Animals as approved by the Animal Care and Use Committee of the Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Argentina.

Drugs

D-amphetamine sulfate (Amph, Sigma Chemical Co.) was dissolved in 0.9 % saline (NaCl, Sal) immediately before use.

Two selective AT_1-R antagonists were used: Losartan (LOS, Sigma-Aldrich) dissolved in 0.9 % NaCl (vehicle, Veh), and Candesartan cilexetil (CV, Laboratorios Phoenix, Buenos Aires, Argentina) dissolved in $NaHCO_3$ 0.1 N (vehicle, Veh).

All solutions were protected from light, maintained at 4 °C, and freshly used. Concentrations were calculated on the basis of the weight of the salt of each drug, and each dose was chosen considering previous work (Schmidt et al. 1999; Tilders and Schmidt 1999; Vanderschuren et al. 1999; Paz et al. 2011; Llano Lopez et al. 2012).

Drug administration protocols

Experimental protocol 1

To evaluate the acute effects of Amph, animals were exposed to a single injection of Amph: 0.5 or 2.5 mg/kg intraperitoneal (i.p.) or Sal (Fig. 1c). To evaluate the involvement of AT_1-R in the acute Amph effects, the animals were implanted with a cannula in the lateral ventricle (see below) 1 week before the experiment. Five minutes before the Amph (0.5 mg/kg) or Sal injection, the animals received a cerebral microinjection in the lateral ventricle (intracerebroventricular, i.c.v.) of the AT_1-R antagonist LOS (20 μg/μl, infusion volume 0.5 μl) or Veh (infusion volume 0.5 μl) (Fig. 1e).

Experimental protocol 2

To evaluate the long-term effects of repeated Amph exposure, the animals received Veh by oral administration (by gavage using a feeding needle) once a day along 5 days. From day 6 until day 10, they were injected once daily with Amph 2.5 mg/kg or Sal i.p. and left undisturbed (drug-free period) in their home cages until day 17 when behavioral experiments were performed (Fig. 2a).

To study the involvement of AT_1-R in the development of Amph-induced long-term effects, a different group of animals received CV 3 mg/kg by oral administration once a day along 5 days. From day 6 until the day 10, they were injected once daily with Amph 2.5 mg/kg or Sal i.p. and left undisturbed (drug-free period) in their home cages until day 17 when behavioral experiments were performed (Fig. 2c).

Surgery

Cannulae implantation

Animals were anesthetized i.p. with ketamine (55 mg/kg, Holliday) and xylazine (11 mg/kg, Köing). In aseptic conditions, rats' skulls were exposed and, using a stereotaxic device (Stoelting), they were implanted with stainless steel cannula (22 gauge) and fixed with dental cement (Subiton, Argentina). Also, a stainless steel screw was anchored to the skull. Cannulae were placed 2 mm above the final place of injection. According to Paxinos and Watson Atlas (Paxinos and Watson 2009), coordinates respect to bregma for lateral ventricle were as follows: AP=−0.9 mm; L=−1.6 mm; DV=−2.0 mm. Immediately after surgery and on the next day, the animals received Norciciline (5,000,000 U.I., i.p. Laboratorios NORT, Buenos Aires, Argentina) and were maintained undisturbed in their home cages to allow recovery from surgery during a week.

Intracerebral infusion of Losartan

The day of the behavioral experiment, animals were administered with LOS or Sal by inserting a stainless steel injection cannula (30 gauges) into the guide cannula. This cannula was attached through a polyethylene catheter (P10) to a 10-μl microsyringe (Hamilton). Volumes of 0.5 μl of Sal or LOS solution were gradually injected, over 1 min period, into the lateral ventricle using an infusion pump (HARVARD, model 22). The injection cannula was left in place for additional 30 s to allow complete liquid diffusion.

Histology

After the test session in the passive avoidance test (see below), animals were euthanatized by an overdose of chloral hydrate 16 %; their brains were removed and immersion-fixed in a 4 % formaldehyde solution for a week. Coronal sections of 60 μm were obtained using a cryostat (Leica CM1510S) and analyzed under magnifying glass in order to confirm the guide cannula location. Only animals with correct cannula position were considered for statistical analysis.

Behavior

The passive avoidance test is a widely accepted method to test long-term memory performance. The IA response was determined using a "step-through" apparatus which consisted of an illuminated and a dark compartment (each 60×30×30 cm)

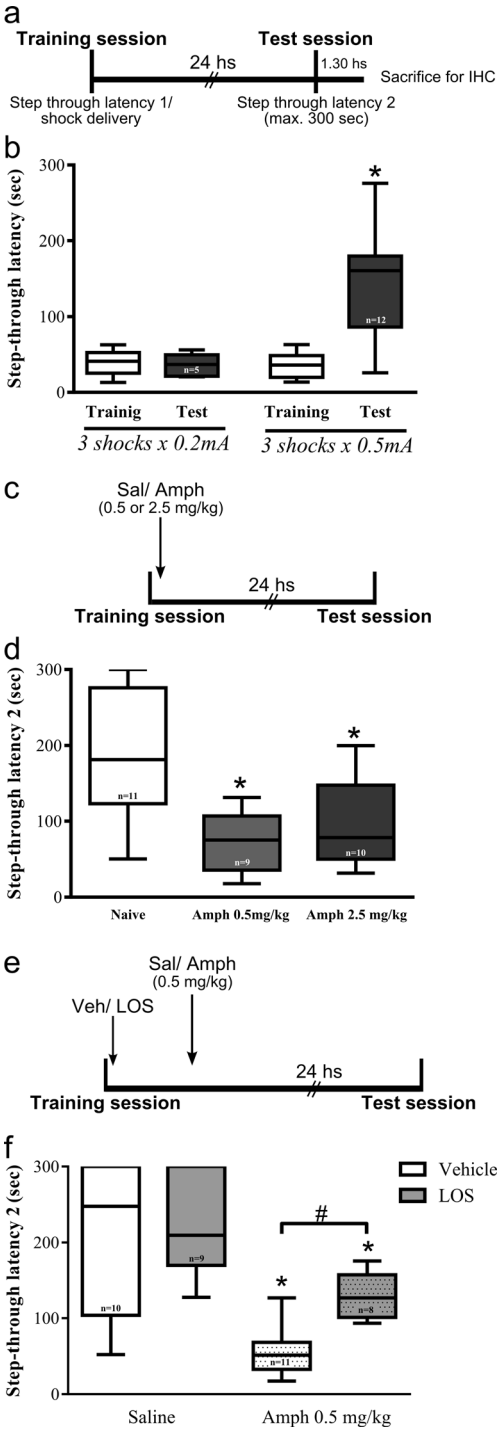

Fig. 1 Acute effects of Amph involve AT_1-R activation. **a** General experimental protocol for the passive avoidance test. **b** Step-through latencies for the training and the test session under two schemes with different shock intensities (0.2 and 0.5 mA), *$p<0.05$ different from training session. **c** Experimental protocol 1 to test the acute effect of post-training Amph administration. **d** Step-through latencies 2 of animals receiving saline or Amph (0.5 or 2.5 mg/kg) immediately after the training session, *$p<0.05$ different from saline group. **e** Experimental protocol 1 to evaluate AT_1-R role in the Amph acute effects. **f** Step-through latencies 2 for the experimental groups, *$p<0.05$ different from control groups (Veh-Sal and Los-Sal), $^{\#}p<0.05$ different from Veh-Amph group. Values are presented as the median, interquartile range, and minimum and maximum values

next to each other and connected by a guillotine door. The floor was constructed of stainless steel rods. The experiment was conducted for 2 consecutive days (training and test session), at the same time each day (between 9.00 a.m. and 1 p.m.).

In order to evaluate the precise shock intensity for all experiments, two schemes with different shock intensities were evaluated in naive animals as follows: on the first day (training session), each rat was placed in the illuminated compartment facing away from the dark compartment. A maximum of 60 s was considered for the animal to enter the dark compartment; otherwise, the animals were dismissed from the experiment. Once the rat entered completely, it received electric footshocks through the stainless steel grid floor (3 shocks×0.2 mA or 0.5 mA, 3 s each, separated by 30 s). On the second day (test session), the same procedure was followed, but no footshock was delivered. The time taken by each rat to enter into the dark compartment in the test session was recorded as a measure of memory retention and described as step-through latency 2. If rats did not enter in the dark compartment within 300 s, the test was concluded and a latency of 300 s was recorded (Fig. 1a). The intensity of 0.5 mA to deliver the footshock was selected for experimental protocols 1 and 2 since it induced the higher latency values in the test (see "Results" section).

Accordingly to the experimental protocol 1, the acute effect of Amph exposure on the IA response was evaluated. For this purpose, animals received an Amph injection (0.5 or 2.5 mg/kg) immediately after the training session. The step-through latency 2 was recorded 24 h later (Fig. 1c). In order to evaluate the involvement of AT_1–R in the acute effect of Amph, animals were first trained and then microinjected in the lateral ventricle with LOS or Veh, 5 min before the Amph injection (0.5 mg/kg) (Fig. 1e).

For the experimental protocol 2, animals from the Veh-Sal and Veh-Amph groups were trained in the passive avoidance test 7 days after the last Amph injection (day 17 in Fig. 2a). Immediately after the shock delivery in the training day, animals were administered with a Sal or an Amph (0.5 mg/kg) challenge injection. The step-through latency 2 was recorded 24 h later (Fig. 2a). To assess the involvement of AT_1-R in the long-term effects of repeated Amph exposure, animals from the CV-Sal and CV-Amph groups were evaluated for the IA response on day 17 as described above (Fig. 2c).

For both protocols, possible drug interferences with memory acquisition were avoided since drugs were administered after training, allowing a drug-free training (McGaugh 1973).

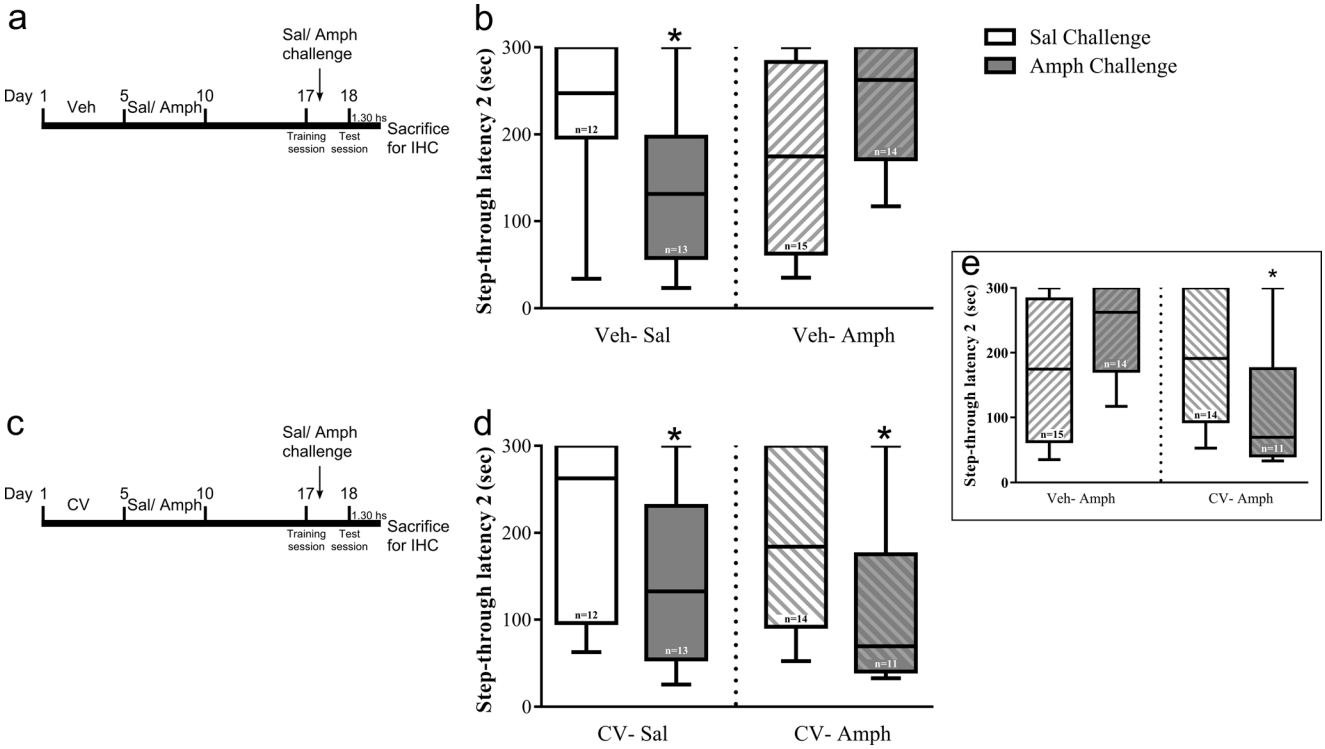

Fig. 2 Amph-induced long-term changes involve AT_1-R activation. **a**, **c** Experimental protocol 2 used to evaluate long term changes after repeated Amph exposure and AT_1 receptors involvement in those changes. **b** Step-through latencies 2 for Veh-Sal and Veh-Amph treated groups when receiving a Sal or Amph challenge immediately after training session, *$p<0.05$ different from Veh-Sal challenged with Sal and from Veh-Amph challenged with Amph. **d** Step-through latencies 2 for CV-Sal and CV-Amph treated groups when receiving a Sal or Amph challenge (0.5 mg/kg) immediately after training session. **e** Step-through latencies 2 for Veh-Amph and CV-Amph treated groups when receiving a Sal or Amph challenge (0.5 mg/kg) immediately after training session, *$p<0.05$ different from Sal challenged groups. Values are presented as the median, interquartile range, and minimum and maximum values

Neurochemistry

c-Fos immunohistochemistry

Fos-immunoreactivity assay was performed taking into account activated brain areas during the test session in IA responses (Fukushima et al. 2014): PFC (Bregma 3.20 mm), HP (Dentate Gyrus-DG-, CA1 and CA3; Bregma −3.30/−3.60 mm) and basolateral amygdala (BLA; Bregma −2.56/−2.80 mm). The motor cortex (M1; Bregma 3.20 mm) was selected as a negative control area. Ninety minutes after the test session, animals were prepared for brain fixation for immunohistochemical detection of Fos as previously described (Paz et al. 2013). Briefly, animals were anesthetized with chloral hydrate 16 % (400 mg/kg i.p.) and perfused transcardially with 250 mL of physiologic solution (0.9 % NaCl) 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 paraformaldehyde solution overnight, and then stored at 4 °C in PB containing 30 % sucrose. Coronal sections of 40 μm were cut 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. Samples were incubated in 10 % normal horse serum (NHS) (Natocor, Villa Carlos Paz, Córdoba, Argentina) in PB 0.1 M for 2 h to block non-specific binding sites. The free-floating sections were incubated overnight at room temperature in a rabbit anti-c-Fos antibody (produced in rabbit against a synthetic 14-amino acid sequence, corresponding to residues 4–17 of human Fos) (Ab-5; Oncogene Science, Manhasset, NY), diluted 1:20,000 in PB 0.1 M containing 2 % NHS and 0.3 % Triton X-100 (Flucka Analytical). The sections were then rinsed with PB 0.01 M and incubated with biotin-labeled universal secondary antibody (diluted 1:2000 in 2 % NHS-PB 0.1 M) and avidin-biotin-peroxidase complex (Vector Laboratories, Burlingame, CA; diluted 1:200 in 2 % NHS-PB 0.1 M), 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.

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 Analytical).

Cytoarchitectural and quantitative analysis

Images containing Fos-immunoreactive (Fos-IR) nuclei were obtained by 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 abovementioned brain areas evidencing Fos-IR nuclei were identify and delimited according to the atlas of Paxinos and Watson (Paxinos and Watson 2009). The brain sections were processed concurrently for subjects across all groups. Counting of Fos-IR nuclei was accomplished using IMAGE J software from the National Institutes of Health (NIH). Images threshold were fixed between intervals of 120–150 in black and white conditions; all lower 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). The measurement for each brain area was done bilaterally in two sections. The value obtained was the average of the four counted sections. The counting was made blinded to the experimental groups. Because the size and section thickness of nuclei did not change between experimental and control groups, any systematic error should be identical for all groups. Hence, the results are meant to provide relative data on expression of Fos-immunoreactivity but are not meant to be accurate estimates of absolute cell counts.

Electrophysiology

Electrophysiological experiments were carried out using the in vitro hippocampal slice preparation (Perez et al. 2010). Rats were treated as described in experimental protocol 2 and sacrificed 7 days after the last Amph administration without receiving any challenge injection (Fig. 4a). To prevent variations caused by circadian rhythms or non-specific stressors, rats were sacrificed between 11:00 a.m. and noon (Teyler and DiScenna 1987). The hippocampal formation was dissected, and transverse slices of approximately 400 μm thick were maintained in a storage chamber containing standard Krebs solution (NaCl, 124.3 mM; KCl, 4.9 mM; $MgSO_4 \cdot 7H_2O$, 1.3 mM; H_2KPO_4, 1.25 mM; $HNaCO_3$, 25.6 mM; glucose, 10.4 mM; $CaCl_2 \cdot 2H_2O$, 2.3 mM; Sigma, Argentina) saturated with 95 % O_2 and 5 % CO_2. At the beginning of the experiments, a single slice was placed in a recording chamber (BSC-BU Harvard Apparatus) perfused with the standard Krebs solution saturated with 95 % O_2 and 5 % CO_2. The perfusion rate was 1.6 ml/min, and the bathing solution temperature was kept at 28 °C with a temperature controller (TC-202A Harvard Apparatus). A stimulating electrode made of two twisted wires, which were insulated except for the cut ends (diameter 50 μm), was placed in the perforant path (PP). Then, a recording microelectrode was inserted in the DG cell body layer. Only slices showing a stable response were included in the study. Amplitude (mV) of field excitatory postsynaptic potentials (EPSP) that responded to 0.2 Hz stimuli were sampled for 40 min until EPSP stabilization (baseline). Once no further changes were observed in the amplitude of EPSP, the stimulation protocol was applied (Perez et al. 2010). The stimulation allowed us to assay different stimulating frequency values in order to determine the minimum value to generate LTP (we call this value "threshold"). The stimulus consisted in a train of square pulses of 2 s length, with 0.5 ms being the duration of each square pulse. We used a stimulus frequency ranging from 5 to 200 Hz, delivered by an A310 accupulser pulse generator (World Precision Instruments Inc.). LTP was considered to have occurred when the EPSP amplitude recorded after the stimulus had risen at least 30 % from baseline and persisted for 60 min. If LTP was not observed at 20 min after of a given stimulation frequency, another hippocampal slice was used to test a stimulus at the next frequency value.

Statistical analysis

For Fos-immunoreactivity and electrophysiological recordings, the results are expressed as means±SEM. The study design used *t* test for Fos-IR comparison regarding shock intensity and two-way ANOVA with Veh/CV or Sal/Amph as treatment factor and Sal/Amph as the second factor analyzed (drug). If an interaction and/or main effect were observed, pairwise comparisons following ANOVA were made using the Bonferroni post-test.

For passive avoidance analysis, maximum latencies were set for training and test session (60 and 300 s, respectively); thus, a non-parametric distribution of the data was considered, and because its variance does not fulfill the assumption of homoscedasticity, non-parametric analyses were performed and the results are expressed as median with interquartile range. Step-through latencies were analyzed by Kruskal-Wallis (acute Amph exposure) or Scheirer-Ray-Hare test (Sal/LOS as microinjection factor and Sal/Amph as the second factor; and Sal/Amph as treatment factor and Sal/Amph as challenge factor). All analyses were followed by the Mann-Whitney test with Bonferroni correction as *posthoc* analysis. In all comparison, $p<0.05$ was considered significant. Statistics were performed by using Prism 6.0 software (GraphPad Software for Science, San Diego, CA, USA) and IBM SPSS Statistic 20 software (SPSS Software for Business Analytics, IBM Software).

Results

AT_1 receptors are involved in the long-term memory impairment induced by acute amphetamine

Figure 1a shows the scheme to test 2 shock intensities in the passive avoidance protocol. The results indicate that 3 shock deliveries of 0.2 mA intensity does not increase step-through latency on the test day (step-through latency 2) compared to the training day (step-through latency 1): Mann–Whitney $U_{(5, 5, 0.05)}=11$ $p=0.80$(Fig. 1b). When the animals received 3 shocks of 0.5 mA intensity on the training day, a significant difference was observed on the step-through latency 2 compared to the step-through latency 1: $U_{(12, 12, 0.05)}=11$ $p<0.001$ (Fig. 1b).

In these animals, the neuronal activation pattern was assessed by Fos-immunoreactivity 90 min after the test session. The results indicate significantly higher Fos-IR neurons in the 0.5-mA shock intensity group compared to the 0.2-mA shock intensity group in brain areas involved in memory and learning: DG $t_{(12, 0.05)}=10.58$ $p<0.0001$, CA1 $t_{(12, 0.05)}=6.76$ $p<0.0001$, CA3 $t_{(12, 0.05)}=8.39$ $p<0.0001$ and BLA $t_{(14, 0.05)}=5.37$ $p<0.0001$, PFC $t_{(14, 0.05)}=4.16$ $p<0.01$. No significant difference on Fos-immunoreactivity was observed in M1 $t_{(10, 0.05)}=0.80$ $p=0.44$ (Table 1).

In another set of experiments, the effects of a single Amph administration immediately after the training session were evaluated (Fig. 1c). The result of the Kruskal-Wallis test showed a significant effect of the acute injection (Sal vs. Amph 0.5 mg/kg or Amph 2.5 mg/kg) $H_{(2)}=8.58$ $p<0.05$. Mann-Whitney with Bonferroni's correction posthoc comparison indicate significant lower values for the step-through latency 2 in animals receiving an Amph injection of 0.5 or 2.5 mg/kg ($p<0.05$) compared to those receiving a Sal injection (Fig. 1d). No significant differences were found in step-through latency 1 between the groups (data not shown, Supplementary Table 1).

Table 1 Pattern of Fos-IR cells

	3×0.2 mA shock	3×0.5 mA shock
Dentate Gyrus	15.52±0.78	25.57±0.54*
CA1	10.07±1.69	34.64±3.58*
CA3	7.98±0.74	22.31±1.72*
Basolateral amygdala	11.02±0.92	19.71±1.33*
PFCx	44.18±2.43	58.65±2.48*
Motor cortex	12.16±2.09	14.14±1.48

Average number of Fos-IR neurons in brain nuclei 90 min after the test session in animals trained under two different schemes of shock intensity (0.2 and 0.5 mA).Values are means±SEM

*$p<0.05$ different from 0.2 mA shock trained group

The experiments performed to evaluate AT_1-R role in the long-term memory impairment observed after an acute injection of Amph are shown in Fig. 1e. The Scheirer-Ray-Hare test results were as follows: MICROINJECTION (Veh or LOS) $H_{(1)}=6.33$ $p<0.01$, DRUG (Sal or Amph) $H_{(1)}=12.21$ $p<0.01$ and interaction MICROINJECTION*DRUG $H_{(1)}=0.37$ $p>0.05$. Mann-Whitney with Bonferroni's correction posthoc comparison indicates significant lower step-through latency 2 for Veh-Amph and LOS-Amph compared to their respective controls (Veh-Sal and LOS-Sal, corrected $p<0.0125$). Moreover, the step-through latency 2 of the LOS-Amph group was significantly higher than the Veh-Amph group (corrected $p<0.0125$, Fig. 1f). These results show a functional role for AT_1-R in the impairment in long-term memory induced by acute post-training Amph administration. No significant differences were found in step-through latency 1 between groups (Supplementary Table 1).

AT_1 receptor blockade prevents the long-term repeated amphetamine-induced alterations in long-term memory

Inhibitory avoidance response

In order to evaluate the long-term neuroadaptative changes induced by repeated Amph exposure, the animals were submitted to the experimental protocol 2 and tested in the passive avoidance bearing a Sal or an Amph (0.5 mg/kg) challenge injection immediately after training (Fig. 2a). The involvement of AT_1-R in the repeated Amph long-term adaptations was evaluated according to the experimental protocol 2 shown in Fig. 2c.

Figure 2b shows the step-through latency 2 from Veh-Sal and Veh-Amph groups. Scheirer-Ray-Hare test results were: TREATMENT (Veh-Sal or Veh-Amph) $H_{(1)}=0.50$ $p>0.05$, CHALLENGE (Sal or Amph) $H_{(1)}=0.79$ $p>0.05$ and interaction TREATMENT*CHALLENGE $H_{(1)}=11.30$ $p<0.01$. Mann-Whitney with Bonferroni's correction posthoc comparison indicates significant difference in the step-through latency 2 between Veh-Sal groups when receiving a Sal or Amph challenge and between Veh-Sal and Veh-Amph groups when receiving an Amph (0.5 mg/kg) challenge (corrected $p<0.0125$). No significant difference was observed in Veh-Amph groups bearing a Sal or Amph challenge nor between Veh-Sal and Veh-Amph when receiving a post-training saline challenge. These results show that repeated Amph induced long-term alterations in the IA response when receiving an acute challenge dose of Amph after the withdrawal period. No significant differences were found in step-through latency 1 between groups (Supplementary Table 1).When animals were administered with the AT_1-R blocker previous to repeated Amph administration and received a Sal or Amph challenge injection immediately after the training session (Fig. 2d), the Scheirer-Ray-Hare Test results were:

TREATMENT (Cv-Sal or CV-Amph) $H_{(1)}=1.21$ $p>0.05$, CHALLENGE (Sal or Amph) $H_{(1)}=8.11$ $p<0.05$ and interaction PRETREATMENT*CHALLENGE $H_{(1)}=0.07$ $p>0.05$. These results demonstrate a functional role for AT_1 receptors in the Amph-induced alteration after repeated administration. No significant differences were found in step-through latency 1 between groups (Supplementary Table 1).

Additional analysis was performed to evaluate Amph-treated groups, Scheirer-Ray-Hare test results were as follows: TREATMENT (Veh-Amph or CV-Amph) $H_{(1)}=0.18$ $p>0.05$, CHALLENGE (Sal or Amph) $H_{(1)}=3.7$ $p>0.05$ and interaction TREATMENT*CHALLENGE $H_{(1)}=8.11$ $p<0.01$. Mann-Whitney with Bonferroni's correction posthoc comparison indicates significant difference in the step-through latency 2 between CV-Amph groups when receiving a Sal or Amph challenge and between Veh-Amph and CV-Amph groups when receiving an Amph (0.5 mg/kg) challenge (corrected $p<0.0125$). No significant difference was observed in Veh-Amph groups bearing a Sal or Amph challenge nor between Veh-Amph and CV-Amph when receiving a post-training saline challenge (Fig. 2e).

Brain distribution of Fos-immunoreactivity

The neuronal activation pattern was assessed in animals from experimental protocol 2 and sacrificed 90 min after the test session, by analyzing the Fos-IR neurons in brain areas involved in memory and learning, as detailed in Figs. 3 and 4.

The results of the two-way ANOVA for vehicle-treated groups (Veh-Sal and Veh-Amph) indicate a significant effect for CHALLENGE (Sal or Amph) in DG $F_{(1,13)}=20.94$ $p<0.01$; CA1 $F_{(1,13)}=27.08$ $p<0.01$; and CA3 $F_{(1,13)}=23.45$ $p<0.01$ (Fig. 3b–d). Meanwhile, the Fos-activation pattern in BLA shows a significant effect for CHALLENGE (Sal or Amph) $F_{(1,13)}=32.78$ $p<0.01$ and interaction TREATMENT*CHALLENGE $F_{(1,13)}=5.31$ $p<0.05$. No significant effect was found for TREATMENT (Veh-Sal or Veh-Amph) $F_{(1,13)}=4.05$ $p=0.66$. Bonferroni posthoc comparison indicates a significant decrease in Fos-IR neurons for Veh-Sal group when receiving an Amph challenge compared to the group receiving a Sal challenge ($p<0.01$, Fig. 4b), while no differences were found in Veh-Amph group receiving either Sal or Amph challenge. Moreover, significant differences were found for Fos-immunoreactivity in the Veh-Sal group compared to the Veh-Amph group when receiving an Amph challenge ($p<0.05$, Fig. 4 b): No differences were found in Fos-immunoreactivity pattern in PFC between groups (Supplementary Table 2).

The results of the two way ANOVA for the CV treated groups (CV-Sal and CV-Amph) indicates a significant effect for CHALLENGE (Sal or Amph) in DG $F_{(1,13)}=42.53$ $p<0.01$; CA1 $F_{(1,13)}=8.09$ $p<0.05$; CA3 $F_{(1,13)}=8.90$ $p<0.01$; and BLA $F_{(1,13)}=36.88$ $p<0.01$ (Figs. 3e–g and 4c). No differences were found in Fos-immunoreactivity pattern in PFC between groups (Supplementary Table 2).

AT_1 receptor blockade prevents repeated amphetamine-induced alterations in hippocampal synaptic transmission

In order to evaluate if repeated Amph alters synaptic transmission in the HP, together with AT_1-R involvement in those changes, animals were submitted to the experimental protocol 2 and sacrificed a week after the last Amph administration without performing the passive avoidance test, as shown in Fig. 5a. Two-way ANOVA analysis indicate a significant effect for DRUG (Sal or Amph) $F_{(1,14)}=6.44$ $p<0.05$ and interaction PRETREATMENT*DRUG $F_{(1,14)}=4.71$ $p<0.05$. No significant effect was found for PRETREATMENT (Veh or CV) $F_{(1,14)}=2.50$ $p=0.14$. Bonferroni posthoc comparison indicates a significant difference in the threshold to generate LTP in the Veh-Amph group when compared to Veh-Sal and CV-Amph groups ($p<0.05$). These results indicate a significant decrease in the minimum effective stimulating frequency (threshold) to generate LTP in DG in animals exposed to repeated Amph. Interestingly, this phenomenon was completely prevented with AT_1-R blockade (Fig. 5c). Then, the increased hippocampal synaptic transmission induced by repeated Amph administration involves AT_1-R activation.

Discussion

The results presented here show that acute Amph impairs memory retention in male rats in the one-trial IA response when administered immediately post-training. This effect involves central AT_1-R activation since i.c.v. LOS administration given before the psychostimulant partially prevented the drug-induced memory impairment. Moreover, a previous experience of repeated Amph followed by 7 days of withdrawal modified the animals' performance in the IA response and the neuronal activation pattern in BLA when receiving an Amph challenge. Furthermore, the long-term Amph-induced alterations were evidenced in the HP synaptic transmission, measured as a lower threshold necessary to generate LTP. It is noteworthy that AT_1-R blockade prevented the behavioral, neurochemical, and electrophysiological alterations observed in the repeated Amph group, pointing out a functional role for AT_1-R in the psychostimulant-induced neuroadaptations.

AT_1 receptors role in the acute amphetamine-induced neurocognitive alterations

Acute Amph administration induces memory impairments in several learning trials (Crabbe and Alpern 1975; James 1975; Seliger 1977; Cabib and Castellano 1997; van den Buuse et al.

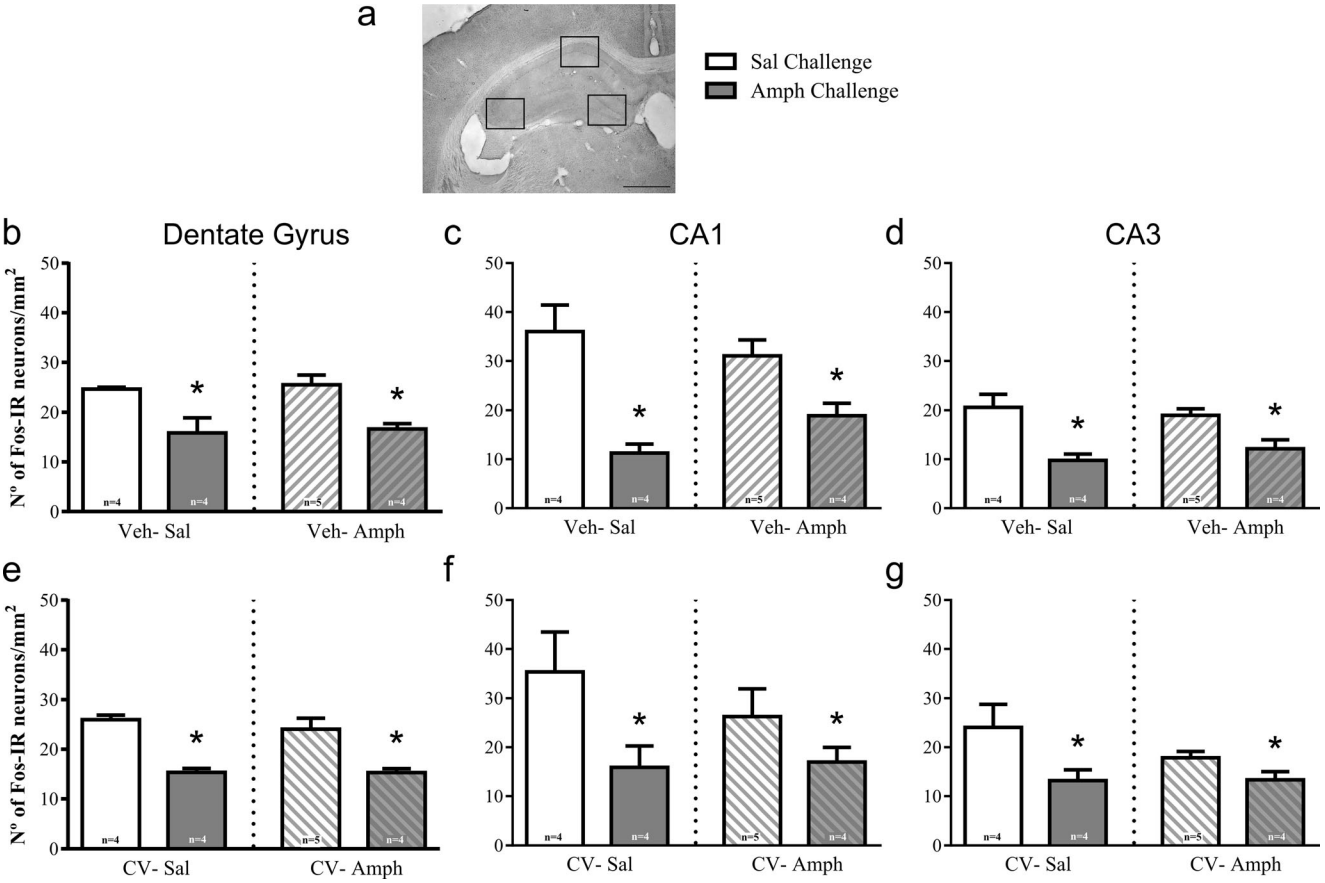

Fig. 3 Involvement of AT_1-R in the expression pattern of Fos-IR cells in HP. **a** Studied hippocampal subareas are indicated in the microphotograph (Scale bar=1 mm). Graphs show the average number of Fos-IR neurons in the brain nuclei from animals receiving a saline (*white bars*) or Amph (*gray bars*) challenge immediately after the training session. For Veh-Sal and Veh-Amph groups: Dentate Gyrus (**b**), CA1 (**c**), and CA3 (**d**). For CV-Sal and CV-Amph groups: Dentate Gyrus (**e**), CA1 (**f**), and CA3 (**g**).*$p<0.05$ different from saline challenged group. Values are means± SEM

2005). Furthermore, the same deleterious effect has been described for acute cocaine, stress, or DA agonists and prevented by DA antagonists in all cases (Castellano et al. 1991; Cestari et al. 1992; Puglisi-Allegra et al. 1994; Cabib and Castellano 1997). Although under different experimental conditions, other authors have reported enhancement or no effect for acute Amph administration (Kaminsky et al. 2001; Nelson and Killcross 2006; Simon and Setlow 2006).

The RAS system also participates in memory processes since Ang II injected either before or after training sessions impairs memory retention when evaluated 24, 48, or 72 h latter (Morgan and Routtenberg 1977; Lee et al. 1995;

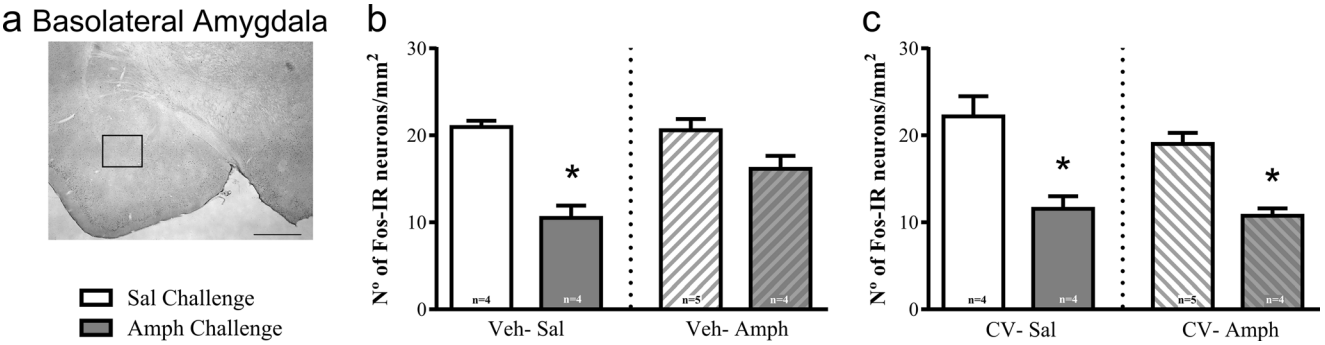

Fig. 4 Involvement of AT_1-R in the expression pattern of Fos-IR cells in the BLA. **a** Studied brain area is indicated in the schematic microphotograph (Scale bar=1 mm). Graphs show average number of Fos-IR neurons from animals receiving a saline (*white bars*) or Amph (*gray bars*) challenge immediately after the training session. Veh-Sal and Veh-Amph groups (**b**) and CV-Sal and CV-Amph groups (**c**). *$p<0.05$ different from saline challenged group. Values are means±SEM

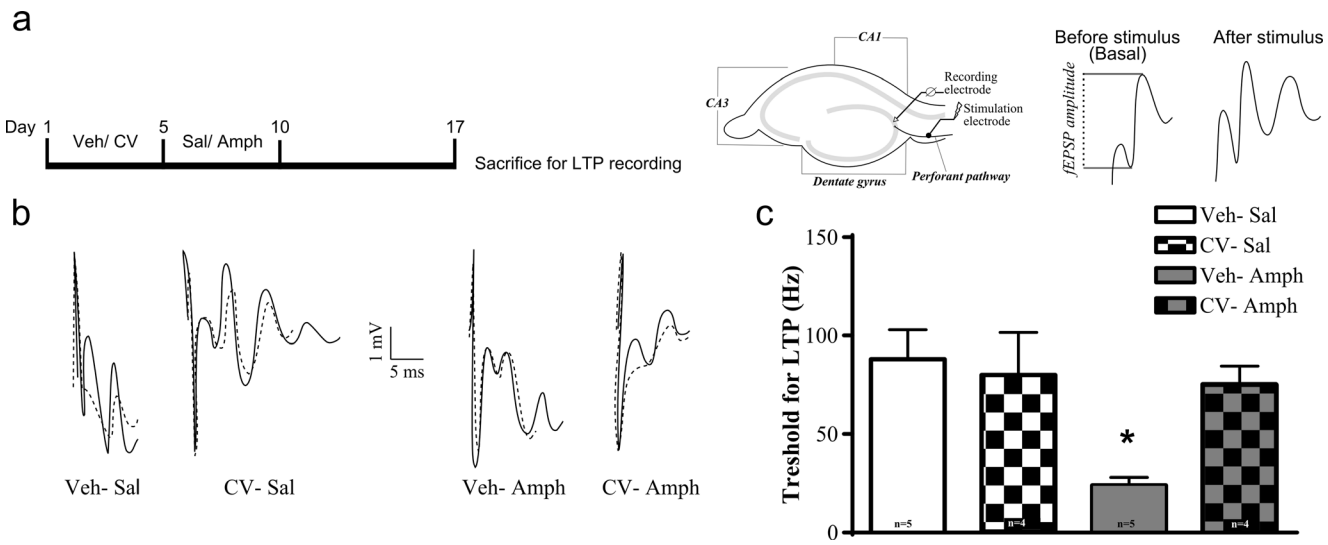

Fig. 5 Amph-induced HP synaptic plasticity involves AT_1-R activation. **a** Experimental protocol used to evaluate synaptic plasticity after Amph exposure and AT_1-R role. **b** Hippocampal slice cartoon indicating position of stimulating and recording electrodes and fEPSP sample traces showing how measurements of fEPSP are taken. **c** fEPSP sample traces forVeh-Sal, CV-Sal, Veh-Amph, and CV-Amph groups before (*dotted line*) and after (*full line*) effective tetanus. **d** Threshold to generate LTP in the four experimental groups. *$p<0.05$ different from Veh-Sal and CV-Amph groups. Values are means±SEM

Raghavendra et al. 1999; de Souza et al. 2004). Similar results were obtained after Ang II synthesis stimulation by renin i.c.v administration (Koller et al. 1979; DeNoble et al. 1991). Moreover, these reports also indicate that the deleterious effect induced by Ang II upon memory is AT_1-R activation dependent (DeNoble et al. 1991; Lee et al. 1995).

The present work shows that central LOS administration partially prevented the memory impairment observed after acute Amph exposure, highlighting the implication of the Ang II AT_1-R in the psychostimulant's deleterious effect. These pioneering findings are supported by the fact that brain RAS interacts with the DA neurotransmission system. Ang II by AT_1-R activation stimulates DA synthesis and release in the striatum and also participates in nicotine and electrical stimulation evoked DA release in this structure (Simonnet and Giorguieff-Chesselet 1979; Dwoskin et al. 1992; Mendelsohn et al. 1993; Brown et al. 1996; Jenkins et al. 1997; Narayanaswami et al. 2013). Furthermore, the disruptive effect in pre-pulse inhibition induced by acute Amph or a DA agonist was not evidenced in angiotensin converting enzyme 1 −/− transgenic mice (van den Buuse et al. 2005).

Our results clearly demonstrate a neuromodulatory role of Ang II through its AT_1-R in DA-related alterations elicited by acute Amph administration in neurocognitive processes.

AT_1 receptors involvement in long-term amphetamine-induced neurocognitive alterations

The activation of the limbic system with single or repeated psychostimulant administration triggers the development of neuroadaptations that can be revealed at behavioral and neurochemical levels, after long withdrawal periods with the administration of a drug challenge (Pierce and Kalivas 1997; Vanderschuren and Kalivas 2000). In accordance with previous reports (Kokkinidis 1983; Tse et al. 2011; Eldred and Palmiter 2013), our results indicate that repeated Amph administration did not affect the animals' performance in the passive avoidance test. Interestingly, the repeated Amph-induced neuroadaptations were evidenced after a week of withdrawal as a resistance to the deleterious effect of the post-training Amph challenge administration; therefore, these results can be interpreted as a tolerance to the acute effect of Amph.

In the present work, we demonstrated that AT_1-R blockade effectively prevented the resistance to the deleterious effect on memory observed after Amph challenge. Meanwhile, the AT_1-R blocker per se had no effect in the IA response. Indeed, these results point out that AT_1-R blockade could prevent the long-term neuroadaptations underlying the resistance to the deleterious effect on memory induced by repeated Amph administration without affecting memory disruption after acute Amph.

The Amph-induced long-term neuroadaptations were also evaluated by Fos-immunoreactivity, a recognized tool that provides a pattern of the ongoing neuronal activation in the central nervous system (Morgan and Curran 1991; Herdegen and Leah 1998). Reduced number of Fos-IR cells was observed in BLA and HP after Amph challenge in animals with previous saline exposure which also displayed reduced performance in the passive avoidance test. These results are in accordance with recent evidences suggesting that Fos-IR cells in these regions are increased synchronously in response to

memory reactivation in the passive avoidance test (Fukushima et al. 2014). Oppositely, previous Amph history affected the Fos-immunoreactivity pattern after Amph challenge, again evidencing a resistant effect to the reduced neuronal activation induced by acute Amph only in BLA, while in HP reduced neuronal activity remains even with previous Amph exposure. Excitatory and inhibitory transmission in the BLA–PFC pathway is modulated by DA activity, and it can be differentially modified by acute or repeated Amph administration. Electrophysiological evidences showed that under a similar repeated Amph administration and withdrawal schedule, animals display resistance to the acute effects of Amph over BLA excitatory and inhibitory evoked responses in PFC (Tse et al. 2011). Moreover, our results show an increased synaptic transmission (lower threshold to generate LTP) within the hippocampal DG in the repeated Amph group without receiving a drug challenge. This phenomenon has been previously reported for repeated cocaine administration during withdrawal, with or without cocaine challenge (Perez et al. 2010; Gabach et al. 2013), and implies an increased neuronal sensitivity to further challenges and a subsequent potentiation of the output response. In the present work, the already described resistant effect of repeated Amph over decreased BLA neuronal activity and the increased HP synaptic transmission observed evidences a neuroadaptative change after repeated Amph that may underlie the lack of impairment in the memory task performance in the passive avoidance after Amph challenge. Once again, AT_1-R were found to play a functional role in the development of this altered responses in BLA and HP because their blockade prevented the long-term changes induced by repeated Amph exposure concerning Fos-immunoreactivity and synaptic transmission efficacy, respectively.

The absence of changes in Fos-IR observed in the PFC between all groups cannot discard the participation of this important center of stimulus integration in the acute or repeated Amph-induced effects (Bush et al. 1998; Bush et al. 2000; MacDonald et al. 2000; Kerns et al. 2004). To this respect, it is important to hallmark the limitation of Fos-immunoreactivity technique because a multitude of stimulations, including sensory, electrical, and epileptogenic, can increase c-Fos expression (Alberini 2009).

Conclusions

Taken all together, our results clearly stand out the brain RAS as a neuromodulatory system of superior brain activities and further validate the Ang II involvement in Amph-induced alterations by activating AT_1-R. This is the first time, for our knowledge, that AT_1-R are shown to play a functional role in Amph-induced alterations over neurocognitive processes. We showed that AT_1-R activity mediates the acute impairing memory effect of Amph as well as the resistance to this effect induced by a previous history of repeated Amph administration. Because AT_1-R blockers are currently and safety used in clinics for different pathologies, our results suggest that they would be prominent candidates for pharmacological treatment in pathologies related to altered DA neurotransmission such as drug addiction, schizophrenia, or even depression. More studies need to be performed in order to further characterize Amph-RAS interactions and also evaluate the effectiveness of AT_1-R blockers not only in prevention of altered responses induced by Amph but also in their reversion.

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Compliance with ethical standards

Conflict of interests The authors declare that they have no competing interests.

Ethical approval All procedures were handled in accordance with the NIH Guide for the Care and Use of Laboratory Animals as approved by the Animal Care and Use Committee of the Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Argentina (RES 46 2015).

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