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REVIEW ARTICLE

NEW INSIGHTS OF BRAIN RENIN-ANGIOTENSIN SYSTEM FAR BEYOND BLOOD PRESSURE: CENTRAL ANGIOTENSIN II AS A KEY MODULATOR IN THE STRESS RESPONSE AND AMPHETAMINE INDUCED-NEUROADAPTATIONS

(Nuevas perspectivas en la función del sistema renina angiotensina cerebral fuera del control de la presión arterial: Angiotensina II central como modulador clave en la respuesta de estrés y las neuroadaptaciones inducidas por anfetamina)

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ABSTRACT

Angiotensin II is known as a peripheral hormone involved in the control of blood pressure and fluids homeostasis. The study and characterization of angiotensin II and its receptors at the brain has opened a new vision of its physiological role and also offers a variety of research fields. Brain angiotensin II is a well-documented neuromodulator of multiple brain circuits. In this sense, angiotensin II is involved in the stress response and both, the brain and the peripheral (hormonal), angiotensin II systems are stimulated during stress. Activation of brain angiotensin II AT_1 receptors is required for the stress-induced hormone secretion, including corticotropin-releasing hormone, adrenocorticotropic hormone, corticoids and vasopressin and for stimulation of the central sympathetic activity. The blockade of peripheral but also brain AT_1 receptors prevents the hormonal and sympathoadrenal response to stress. Moreover, AT_1 receptors activation is involved in natural reward responses and in the regulation of some responses induced by drugs of abuse such as cocaine, amphetamine, alcohol, among others. Exposure to amphetamine induces neuroadaptations that modify behavioral responses to future pharmacological or environmental challenges.
It is important to consider that studies on the physiological role of brain Ang II offer new pharmacological tools for the treatment of stress and psychostimulants' related disorders.

Keywords: *Angiotensin II, AT_1 receptors, Stress, Amphetamine, sensitization.*

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1) INTRODUCTION

Angiotensin II (Ang II) was first discovered in 1940 and described as a hormone of peripheral origin (Braun-Menéndez et al. 1940). The complete system, known as renin-angiotensin system (RAS), was then characterized; synthesis and metabolism enzymes were identified at peripheral level. The precursor molecule is angiotensinogen which originates in the liver and is cleaved by renin, a renal aspartyl protease, resulting in an (precursor) inactive decapeptide angiotensin I. The latter is converted into the octapeptide Ang II by the action of angiotensin converting enzyme (ACE), a dipeptidyl carboxypeptidase circulating or integral membrane protein that also cleaves and inactivates bradykinin.

The main actions of Ang II include vasoconstriction; stimulation of aldosterone release, sodium and water reabsorption and it also has a key role in regulating blood pressure and fluid homeostasis.
All components of RAS were found in the brain tissue, including Ang II receptors, indicating that they have different roles as a hormone or neuromodulator in the central nervous system.

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Also local RAS has been found in other tissues or organs such as vessel walls, adrenal gland, heart, gonads, adipose tissue, pituitary gland, lung, stomach, pancreas and skeletal muscle (Lavoie & Sigmund 2003, Danser 2003). The role of Ang II at the periphery and in the central nervous system is vast and complex; for this reason, this review will be focused in the role of brain RAS in stress responses and psychostimulant abuse as a related disorder from many other important aspects of Ang II research.

2) ANGIOTENSIN II RECEPTORS

Pharmacological studies have described two major subtypes of Ang II receptors in mammal's cells named AT_1 and AT_2 receptors, both with seven-transmembrane domains. They were first characterized by their affinity to specific ligands and then by molecular cloning (Iwai & Inagami 1992). Most species expressed single AT_1 receptors, but later two subtypes designated AT_{1A} and AT_{1B} receptors were discovered, which have been cloned in rats (Iwai & Inagami 1992, Kakar *et al.* 1992), mice (Sadamura *et al.* 1992) and humans (Konoshi *et al.* 1994). AT_{1A} isoform is responsible for the functions associated with the brain Ang II system (Saavedra 1999, Thomas & Mendelsohn 2003), so we refer to it as AT_1 receptor.

AT_1 receptors are coupled to G protein producing MAPKinases activation and they mediate the major physiological and pathophysiological actions known of Ang II (Hunyady & Catt 2006). Also, the AT_1 receptor activation can stimulate signaling pathways independent of G protein, such as arrestins and tyrosine kinases (Claing *et al.* 2002, Gaborik & Hunyady 2004, Luttrell & Lefkowitz 2002, Prossnitz 2004, Thomas & Quian 2003). When activated by agonists, the arrestin binds to G protein coupled receptors and causes desensitization of these receptors by uncoupling the binding to the G protein. From there, the AT_1 receptor binds to ß arrestin with clathrin producing receptor endocytosis and internalization.

On the contrary, AT_2 receptors do not exhibit the same characteristics and act mainly through Gi and tyrosine phosphatases (Bottari *et al.* 1991, De Gasparo & Siragy 1999, Kambayashi *et al.* 1993, Mukoyama *et al.* 1993) to exert inhibitory action predominantly upon cellular responses mediated by AT_1 receptors and growth factor receptors (De Gasparo & Siragy 1999, Speth *et al.* 1995).

3) NON-PEPTIDE ANTAGONISTS OF ANGIOTENSIN II RECEPTORS

In 1995, the United States Food and Drug Administration approved losartan for clinical use. Since then, five new AT_1 receptor antagonists have been approved (Jackson 2002). These antagonists are diphenylmethylic or acid diphenylmethyl tienylmetilacrylic derivatives. These drugs bind to the receptor with high affinity and show high selectivity for the AT_1 receptor 10,000 times higher than for the AT_2. The ranges of affinity for the receptor are candesartan (CV)> irbesartan> valsartan = telmisartan = EXP 3147 (active metabolite of losartan)> losartan (Los). Clinical studies using both ACE inhibitors and AT_1 receptor blockers have shown that RAS functions extend far beyond the control of blood pressure (Ferrario *et al.* 2004). These agents have a beneficial effect on the deleterious actions of Ang II on local cardiovascular and renal function in patients with hypertension, left ventricular hypertrophy, heart failure and diabetic nephropathy. In addition, the use of AT_1 blockers produces a decrease in the number of AT_1 receptors and stimulates the Ang II and AT_2 receptor synthesis (Seltzer *et al.* 2004). The increased Ang II exerts its actions primarily on the AT_2 receptor, but it is unclear whether the stimulation of AT_2 receptors contributes to the therapeutic effect of AT_1 antagonists.

4) BRAIN ANGIOTENSIN II

Ang II produced at the peripheral level does not cross the blood-brain barrier (BBB) but stimulates AT_1 receptors in circumventricular organs located outside the BBB (Saavedra 1992). However, a novel Ang II–mediated feed-forward mechanism during hypertension, has been recently revealed by which circulating Ang II evokes increased BBB permeability facilitating, in turn, its access to critical brain regions known to participate in blood pressure regulation (Biancardi *et al.* 2014). The central RAS is capable to produce Ang II and to stimulate receptors in brain areas inside the BBB (Mendelsohn *et al.* 1984). There are detailed neuroanatomical descriptions of the localization of AT_1 and AT_2 receptors. Both Ang II and its receptors have been found located on neurons (Saavedra 1992). The presence of both subtypes of Ang II receptors in astrocytes and oligodendrocytes in the cerebral white matter has also been demonstrated. This last, suggests that glial cells may play a more important role in the brain RAS than it was initially assumed (Fogarty & Matute 2001).

Both receptor subtypes are present in all mammalian species including humans with a similar distribution, although not identical. While AT_1 receptors predominate in adulthood, AT_2 receptors are expressed in the developing brain (Saavedra 1992). AT_1 receptors are found in brain areas related to the control of neuroendocrine function and autonomic regulation of cardiovascular function and the limbic system while AT_2 receptors in the brain seem to have a role in organogenesis and function of sensory and motor systems (Phillips & Sumners 1998). The role of Ang II in the brain is complex, ranging from control of the autonomic system, hormonal system, sensory processes and cognition to the regulation of cerebrovascular flow (Saavedra 1992).

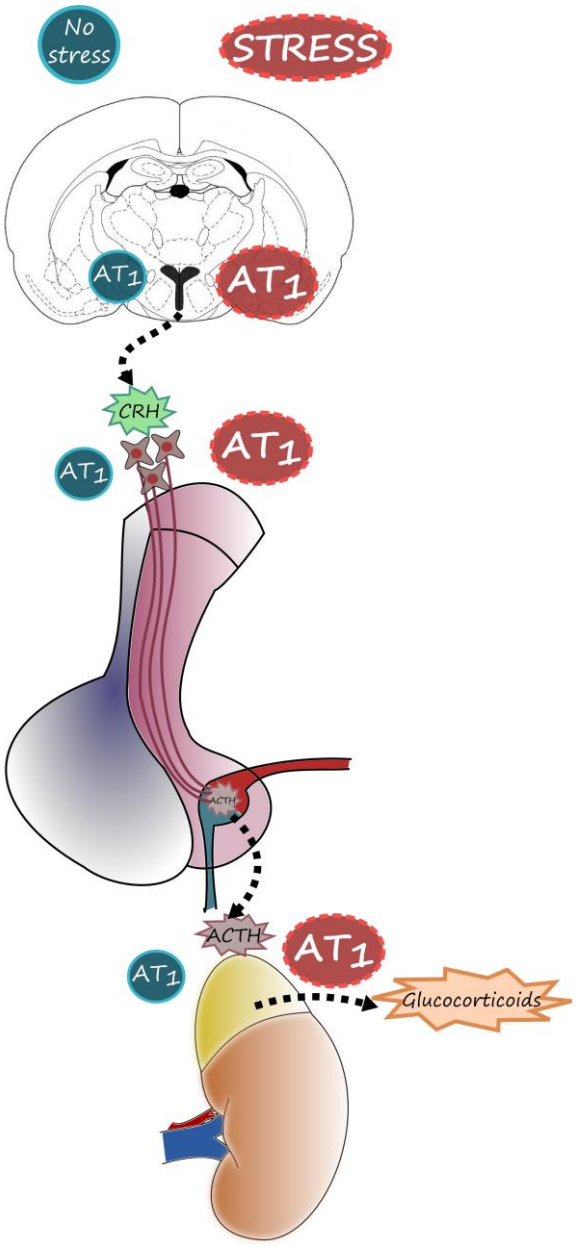
5) ROLE OF ANGIOTENSIN II IN THE STRESS RESPONSE

There is pharmacological, neuroanatomical and physiological evidence showing a key role of Ang II in brain responses to stress, which also includes the regulation of neuroendocrine and sympathetic nervous system (Aguilera *et al.* 1995b, Armando *et al.* 2001, Baiardi *et al.* 2004). The presence of AT_1 receptors has been established at all levels of the hypothalamic-pituitary-adrenal (HPA) axis, being more focused on key areas in the control of the stress response such as the paraventricular nucleus (PVN) (Armando *et al.* 2007), the median eminence, anterior pituitary, zona glomerulosa of the adrenal gland and the adrenal medulla (Tsutsumi & Saavedra 1991a) (Fig. 1).

Exposure to stress causes an increase in circulating and brain levels of Ang II (Xang *et al.* 1993, Yang *et al.* 1996). The Ang II stimulates receptors located outside the BBB whereas the peptide produced in the brain acts on central receptors such as those in PVN and locus coeruleus (LC). Subfornical AT_1 receptors are stimulated by circulating Ang II; this nucleus, in turn, has innervation to the PVN (Shigematsu *et al.* 1986, Tsutsumi & Saavedra 1991a). Chronic exposure to stress increases AT_1 receptor density in PVN (Castrén & Saavedra 1988), where the cell bodies synthesize corticotropin-releasing hormone (CRH) (Shigematsu et al. 1986, Tsutsumi & Saavedra 1991a). It has been shown that stimulation of AT_1 receptors by Ang II increases the production of CRH (Aguilera *et al.* 1995a, Jezova *et al.* 1998). The latter, once released into the circulation, increases the secretion of adrenocorticotropic hormone (ACTH) by the pituitary. In addition, elevated levels of adrenal glucocorticoids- as a result of stress- increase AT_1 receptor expression in PVN (Aguilera et al. 1995a) (Fig. 1). In the same way, acute stress increases the density of AT_1 receptors in the anterior pituitary. There is a local production of Ang II at the level of the anterior pituitary gland which, together with circulating Ang II, increases the secretion of ACTH (Ganong & Murakami 1987).

The PVN nucleus is important in the processing and integration of a variety of stress signals (Makara *et al.* 1984). It receives noradrenergic input from the LC and serotonergic from the dorsal raphe nucleus and there are reciprocal connections between the two regions and PVN (Cedarbaum & Aghajanian 1978, Thiboliet & Dreifuss 1981). In addition, there are reciprocal neural connections between PVN CRH neurons and LC noradrenergic neurons. Synaptic contacts were observed between CRH terminals and LC dendrites. It was also found that both adrenergic receptors regulate the secretion of ACTH and, on the other hand, it has been shown that CRH regulates the activity of central noradrenergic system. This and other evidence show that the brain noradrenergic system is the main alarm system that leads to a decrease in autonomic neurovegetatives functions such as food intake and sleep. Much of the evidence available suggests that CRH acts as a neurotransmitter in the LC mediating the noradrenergic activation by various stress conditions (Koob 1999).

Figure 1.



Schematic representation of the HPA axis showing AT1 receptors location and expression under non stress and stress conditions.

With respect to Ang II, the presence of AT_2 receptors has been established in LC (Tsutsumi & Saavedra 1991b). The exposure of animals to stress by social isolation (Saavedra *et al.* 2006) or cold stress (Peng & Phillips 2001) produces a decrease in the AT_2 receptor density in LC (increase in brain AT_1) while social isolation stress (for 24 hours) produces an increase in the enzyme tyrosine hydroxylase (TH) mRNA in the LC. The previous blockade of the AT_1 receptor with a specific antagonist prevents this increase (Saavedra et al. 2006) suggesting that these receptors are involved in the control of central sympathetic activity through transcriptional regulation of TH. Besides, this effect can be influenced by the activation of locus coeruleus AT_2 receptors. This is based on results showing dual control by AT_1 and AT_2 receptors in TH transcription and in the synthesis of catecholamines at the adrenal medulla (Jezova *et al.* 2003).

6) AT_1 ANTAGONISTS ATTENUATE CENTRAL RESPONSES INVOLVED IN BEHAVIORAL STRESS EFFECTS

Although the stress response of the HPA axis mediated by CRH is important in the regulation of physiological responses to stress, a behavioral response to stress mediated by CRH also occurs independently from the HPA axis activation. The existence of a central site of action responsible for the coordination of stress-related behaviors has been postulated (Valdez & Koob 2004). As previously described, there is a reciprocal relationship between noradrenergic and CRH brain systems: CRH stimulates the activation of the LC during stress (Berridge & Waterhouse 2003) while exposure to stress leads to increased concentrations of CRH in LC producing behavioral activation (Chappell *et al.* 1986). Intracerebral administration of a CRH antagonist prevents the increase in extracellular noradrenaline in prefrontal cortex by stress (Shimizu *et al.* 1994). It was found that pretreatment of animals with candesartan, an AT_1 antagonist that cross effectively the BBB, prevents the decrease of cerebral cortex CRH_1 receptor density produced by social isolation stress (Saavedra et al. 2006). Therefore, cortical release of CRH by stress may be positively regulated by cortical AT_1 receptor stimulation, similar to actions at the hypothalamic level.

The presence of AT_1 receptors has been found in piriform and entorhinal cortex but not in the neocortex (Tsutsumi & Saavedra 1991b), although the mRNA expression of AT_1 receptor was detectable by in situ hybridization (Lenkei *et al.* 1998). Thus, AT_1 receptor blockade may reduce the release of CRH directly and may also prevent the decrease in the CRH1 receptor density. It is also possible that AT_1 receptor antagonism could prevent the stress-induced decrease on cortical CRH_1 receptors by decreasing TH transcription in the LC (Saavedra et al. 2006).

7) STRESS & DRUGS OF ABUSE

The hormonal changes, involving increased peripheral glucocorticoid levels and CRH release in different brain sites, initiate a cascade of biological responses to counteract the altered homeostatic balance of the organism in response to stress. The modification in the brain physiology induced by stress triggers the release of neuroactive hormones such as biogenic amines and adrenal steroids which activate the same neuronal circuit as the psychostimulant drugs like cocaine or amphetamine (Amph).

Many years ago, clinical studies on methadone-treated heroin addicts showed atypical stress response in both active and long-term abstinent heroin addicts, similar to the atypical stress response of the HPA axis that has been found in abstinent cocaine addicts (Dole & Nyswander 1966, Kreek 1992). Thus, it has been hypothesized that an atypical response to stressors may contribute to compulsive drug use (Kreek & Koob 1998). Moreover, it has been demonstrated in a series of studies that rats with higher levels of behavioral and neuroendocrine response to stress develop psychostimulant drug self-administration more rapidly than low responders (Piazza *et al.* 1993, Piazza & Le Moal 1998). Together with other evidence, this supports a major role for stress in individual vulnerability to self-administer drugs of abuse. In addition, corticosterone, the major glucocorticoid end-product of HPA axis activation in rodents was shown to be self-administered in rats and pharmacological manipulation of the circulating corticosterone levels altered cocaine self-administration behavior (Goeders 1998, Piazza et al. 1993). These results and many others suggest that the activity of the HPA axis may play a role in different phases of drug addiction.

Amph actions include HPA axis activation and central endogenous CRH actions. After acute administration of Amph, plasma levels of ACTH and corticosterone are increased in a monotonic dose-response function. Under the same conditions, reduced levels of CRH immunoreactivity were found in the median eminence, suggesting CRH release from this region (Swerdlow *et al.* 1993). Adrenalectomy, on the other hand, reduces locomotor activity elicited by acute Amph and the values can be restored and even augmented if the animal receives exogenous corticosterone (Cador *et al.* 1993b). Moreover, cross-sensitization between stress and psychostimulants, and between central CRH and Amph have been described in rodents (Ahmed *et al.* 1995, Cador *et al.* 1993a). Stress exposure induces relapse in drug abuse and promotes acquisition or reinstatement of ethanol self-administration. The evidence available supports a role for stress as a factor involved in the vulnerability to drug abuse.

8) ANGIOTENSIN II AT_1-RECEPTORS AND AMPH SENSITIZATION

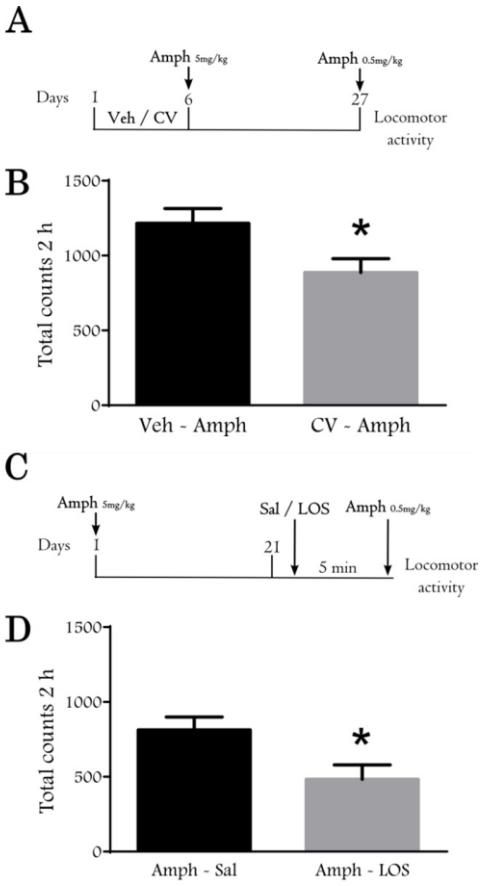
The mesolimbic dopaminergic circuitry is one of the systems strongly involved in drug abuse (Vanderschuren *et al.* 1999a). Ang II belongs to the group of peptides known to stimulate dopamine (DA) release (Brown *et al.* 1996, Tchekalarova & Georgiev 2005). Furthermore Ang II receptors are in brain areas rich in DA, such as the nucleus accumbens (Nacc) and caudate putamen (Cpu) which are heavily involved in the self-administration of drugs of abuse (White & Kalivas 1998). The mesolimbic dopaminergic system is a critical component in the reward circuitry of the central nervous system (White & Kalivas 1998).

Brain Ang II was found to regulate some responses induced by drugs of abuse such as psychostimulants, among others (Hosseini *et al.* 2007, Watanabe *et al.* 2010, Paz *et al.* 2011, Paz *et al.* 2013, Paz *et al.* 2014). The presence of Ang II AT_1 receptors has been described in pre- and postsynaptic CPu dopaminergic neurons (Brown et al. 1996), which are involved in the motor and behavioral responses induced by psychostimulants as well as their modulatory action on noradrenergic (Gelband *et al.* 1998), serotoninergic (Nahmod *et al.* 1978), glutamatergic and gabaergic neurotransmission (Barnes *et al.* 2003, Oz *et al.* 2005). It has been described that Ang II modulates the neuronal response to glutamate via both AT_1 and AT_2 receptors possibly at postsynaptic level in the superior colliculus, locus coerulus and dorsal lateral nucleus among other areas (Albrecht *et al.* 1997, Mooney *et al.* 1994, Xiong & Marshall 1990).

Sensitization is an extensively described phenomenon for several drugs of abuse, including psychostimulants where repeated exposure to the drug promotes long term changes in the neuronal circuits involved in reward responses. In this way, they become sensitized to a challenging event such as re-exposure to the drug, stress and even directly by DA agonists (Ahmed et al. 1995, Robinson & Kolb 2004, Stewart & Badiani 1993). Two stages have been identified for this process: induction and expression (Robinson & Berridge 2008). The first one is responsible for the long term changes that take place and it can be achieved by single or repeated administration of the drug. It requires DA release in Cpu and Nacc and Ventral Tegmental Area activation (Robinson & Berridge 2008, Vanderschuren et al. 1999a, Kalivas *et al.* 1998). Expression reveals these changes after a re- exposure to the drug and it can be measured as augmented DA release, electrical activity, neuronal activation and locomotor activity (Valjent *et al.* 2010, Vanderschuren *et al.* 1999b, Vanderschuren *et al.* 1999c).

Considering the dopaminergic neurotransmission as a common target for Amph and brain Ang II actions, the results obtained in our laboratory indicate that Ang II AT_1 receptors are involved in long-lasting behavioral sensitization associated with neurochemical adaptations induced by a single exposure to Amph. The AT_1 receptor blockade attenuated the behavioral sensitization and blunted the dopamine hyper-reactivity and neuronal activation in a two injection protocol (Paz et al. 2011, Paz et al. 2013) (Fig. 2A-B). Moreover, it did not interfere with changes in the sensitivity of dopamine postsynaptic receptors involved in the neuroadaptive changes induced by Amph (Paz et al. 2011). The effects of AT_1 receptor blockade became evident 3 weeks after pretreatment with a single exposure to Amph when the adaptive changes in behavioral response have been described to be more pronounced (Vanderschuren et al. 1999b).

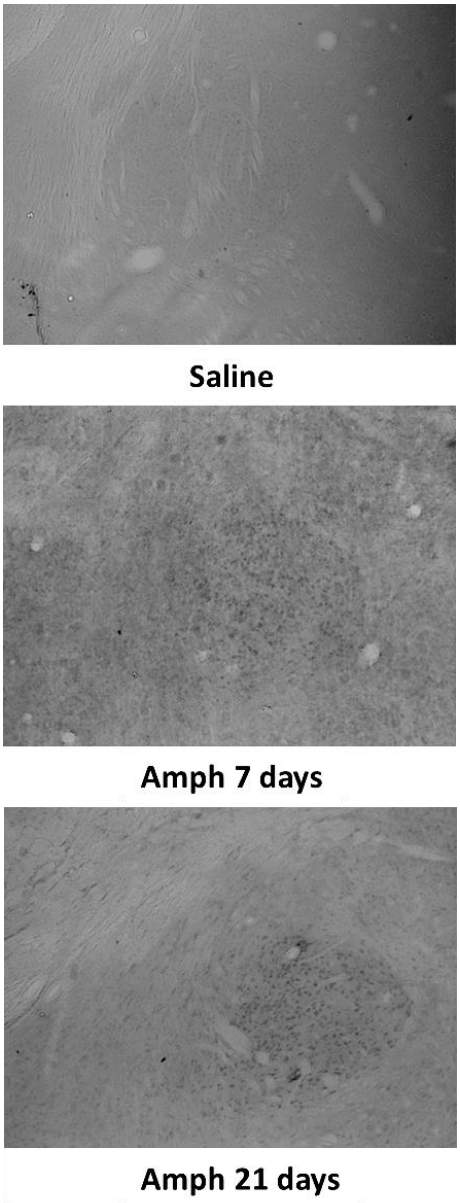
Figure 2.



Total counts of locomotor activity in animals receiving AT1 receptor blocker in the development (A-B) and in the expression (C-D) of locomotor sensitization to a single injection of Amph (5 mg/kg) *p<0.05.

On the other hand, there are long-term changes in brain RAS components after a single exposure to Amph. In this way, while Angiotensinogen RNAm was decreased in CPu only 21 days after Amph injection, AT1 RNAm and receptor density were augmented in CPu and NAcc 7 and 21 days after (Paz et al. 2014), the elevated AT1 receptor immunostaining was also observed in Central Amygdala (Fig. 3).

Figure 3.



Microphotographs (200X magnification) showing AT1 receptor immunostaining in central Amygdala in basal condition and 7 or 21 days after a single Amph administration (5 mg/kg).

Moreover, a key role for the AT1 receptors was found in CPu, in the expression of behavioral sensitization to Amph since the AT1 receptor blockade in CPu blunted the augmented locomotor activity observed after an Amph challenge (Paz et al. 2014) (Fig. 2C-D.)

9) CONCLUDING REMARKS

The role of brain RAS extends beyond the control of blood pressure and fluid homeostasis as evidenced by its involvement in the stress response. The studies to elucidate the physiological role of brain RAS will provide new pharmacological tools for tackling diseases of high incidence in our society such as disorders associated with stress and drug abuse.

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RESUMEN

Angiotensina II es conocida como una hormona periférica involucrada en el control de la presión arterial y la homeostasis de fluidos. El estudio y la caracterización de angiotensina II y sus receptores en el cerebro han abierto nuevos campos de investigación para el abordaje de sus nuevos roles fisiológicos. En este sentido, angiotensina II cerebral ha sido caracterizado como neuromodulador en múltiples circuitos cerebrales de neurotransmisión. Es así, como se ha descripto la participación de angiotensina II cerebral y periférica (hormonal) en la respuesta de estrés. Las evidencias muestran que es necesaria la activación de los receptores AT1 de angiotensina II para la liberación de hormonas inducida por estrés, incluyendo las hormonas liberadora de corticotrofina, adenocorticotrófica, corticosterona y vasopresina, así como también, para la estimulación del sistema adrenérgico central. En este sentido, se ha encontrado que el bloqueo de los receptores AT1 periféricos y centrales previenen la respuesta hormonal y simpato-adrenal al estrés. Además, los receptores AT1 están involucrados en las respuestas de recompensa a reforzadores naturales, así como también en la regulación de algunas respuestas a drogas de abuso como cocaína, anfetamina y alcohol, entre otras. La exposición a anfetamina induce neuroadaptaciones que modifican las respuestas conductuales frente a nuevas desafíos farmacológicos y ambientales.

Es importante considerar que el estudio del rol fisiológico de angiotensina II cerebral aporta información que contribuye al abordaje farmacológico en el tratamiento de desórdenes inducidos por estrés y drogas psicoestimulantes.

Palabras Claves: *Angiotensina II, receptores AT1, Estrés, anfetamina, sensibilización.*

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