The renin angiotensin system in the central nervous system.

Marcelo R. Choi, Susana Cavallero and Belisario E. Fernández
Department of Pathophysiology, Faculty of Pharmacy and Biochemistry, Pathophysiology and Clinical Biochemistry Institute (INFIBIOC), University of Buenos Aires, Scientific and Technical National Research Council (CONICET), Junin 956 5th floor, 1113 Buenos Aires, Argentina

INTRODUCTION

The first evidences indicating that angiotensin II (ANG II) was a peptide with action on the brain were shown in 1961 when it was found that the intraventricular injection of ANG II induces a centrally mediated pressor response (1). As a neuropeptide, ANG II belongs to the class of neuromodulators. The brain renin angiotensin system (RAS) exerts paracrine, autocrine and intracrine functions independently of circulating blood-borne ANG II which has a limited access to the brain by the blood-brain barrier (BBB) in the circumventricular organs (CVOs) (2). Brain-generated ANG II controls several physiological processes like stimulation of thirst, water intake and sodium appetite, acting as a neurotransmitter in neurons of brain areas such as the Subfornical organ (SFO) and Organum vasculosum of the lamina terminalis (OVLT). Generated angiotensins (ANGs) at the central nervous system (CNS) also stimulate endocrine secretions like arginine-vasopressin (AVP), oxytocin (OT), corticotrophin-releasing hormone (CRH) and adenocorticotrophin (ACTH secretion). Brain ANG II modulates the sympathetic autonomic functions and regulates blood pressure by increasing AVP and ACTH secretion and modulating the baroceptor reflex and the sympathetic output (3). During the last decade it has been established that, apart from its classical actions, ANG II exhibits other effects induced by direct action on its receptors or via local effects of its metabolites (4). Thereby, central actions of ANGs are not exclusively associated with their traditional roles. Indeed, several studies have shown that central ANGs are also involved in sexual behavior, stress, learning, and memory (5).

The endogenous brain RAS modulates the hypothalamic-pituitary-adrenal axis through the synthesis and secretion control of hypothalamic releasing factors. It also regulates cardiovascular function and hydromineral balance through modulation of water and sodium intake and controlling thirst, salt appetite and water excretion, overlapping many of ANG II peripheral effects. Brain RAS stimulates central autonomic nervous sympathetic activity, controlling central and peripheral sympathoadrenal systems and regulating neuronal norepinephrine (NE) neurotransmission and, as a as a derived action of this, brain and body temperature. Brain ANG II also controls the diurnal rhythms, modulating serotonin transmission by stimulation of neuronal serotonin synthesis and release. The central RAS may be involved in the regulation of multiple additional functions in the brain, which are not completely established, including brain development, neuronal migration, processes of sensory information, cognition, learning, retention and memory, regulation of emotional responses, sexual behaviour, apoptosis as well as the cerebral blood flow (6).

On the other hand, new peptides have been identified as metabolic products of ANG II, like the heptapeptide ANG III (fragment 2-8), the hexapeptide ANG IV (fragment 3-8) and the heptapeptide ANG 1-7 (fragment 1-7). These members of the ANG family are biologically active peptides formed in the CNS and play different roles in the brain as neurotransmitters, exciting neurons with high specificity and also as neuroendocrine, paracrine, autocrine and intracrine factors. Finally, other members like ANG fragments 3-7, 1-9 and 2-10 are relatively poorly known and further research will be needed in order to elucidate their physiological roles (7). Figure 1 summarizes the current overview of the brain RAS.

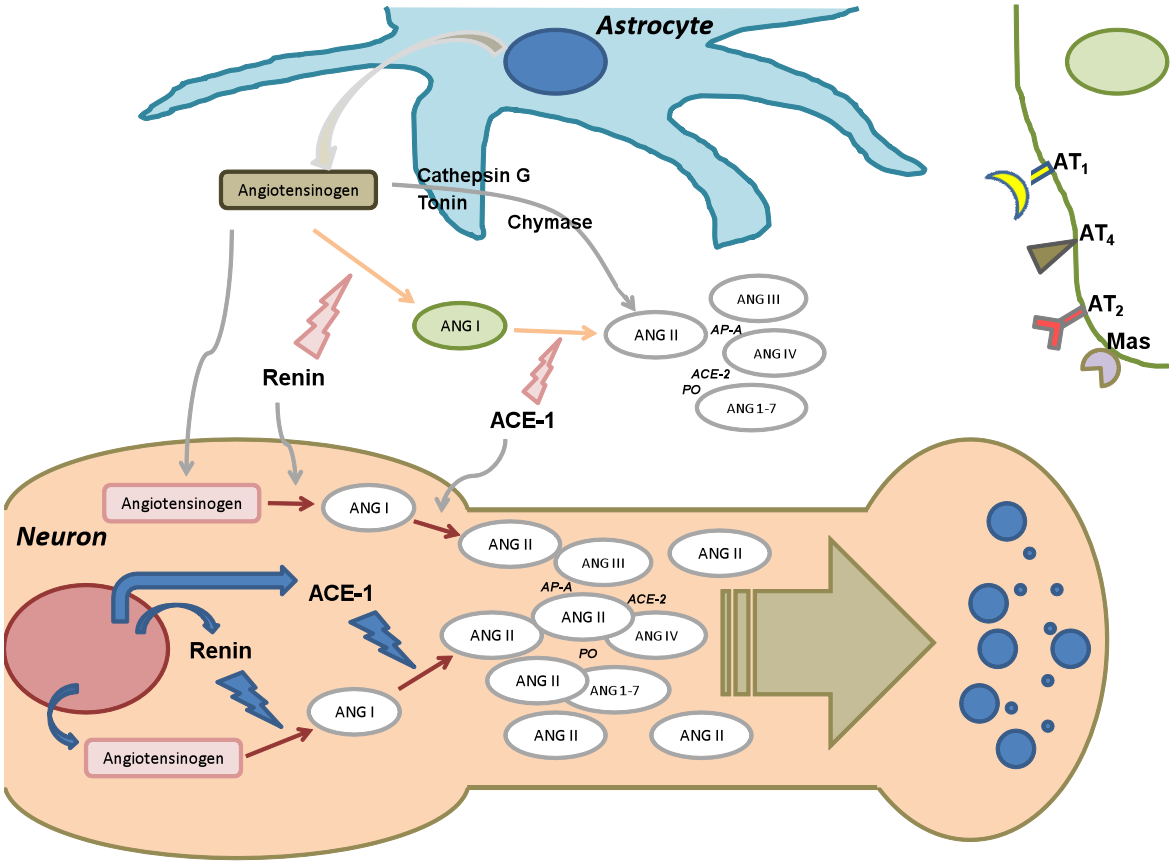

Figure 1. Intraneuronal and extraneuronal synthesis of angiotensin fragments in the brain. ACE: angiotensin converting enzyme; AP-A: aminopeptidase A; PO: propyloligopeptidase. AT_1, AT_2, AT_4, Mas: angiotensin postsynaptic receptors. Adapted from Paul M. et al., *Physiol Rev* 86:747, 2006.

PHYSIOLOGICAL ACTIONS OF ANGIOTENSIN II IN THE CNS

Two mechanisms have been proposed to explain central actions of ANG II. Brain ANG II receptors located in neurons inside the BBB can be stimulated either by ANG II generated in the brain or circulating ANG of peripheral origin as well, and transported into

the brain. On the other hand, some ANG II receptors are located outside de BBB in vascular endothelial cells or CVOs like the SFO, OVLT, median eminence, area postrema (AP) and the anterior pituitary lobe. The CVOs are sensitive and respond to brain ANG II being also a target site for circulating ANG II (6).

One of the main characteristics of ANG system is that it may regulate several physiological actions through either direct or indirect pathways. ANG may exert direct actions on the CNS through stimulation of target organs or tissues, while it induces indirect actions by stimulating synthesis and/or secretions of regulatory hormones or neurotransmitters which in turn, are responsible for modulation of central/peripheral effects on target organs or tissues activities.

Two types of receptors mediate the physiological action of ANG II in the CNS, the AT_1 and AT_2 receptors. Table 1 shows the distribution of these receptors in the CNS.

Forebrain	*Telencephalon*	cerebral cortex		AT_1	
		cingulate cortex		AT_1	AT_2
		piriform cortex		AT_1	
		olfactory bulb		AT_1	
		lateral olfatory tract		AT_1	
		hyppocampus	amygdale	AT_1	
			basolateral amygdaloid	AT_1	
			dentate gyrus	AT_1	AT_2
			limbic system	AT_1	AT_2
			lateral septum	AT_1	AT_2
		globus pallidus	caudate	AT_1	
			putamen	AT_1	
	Diencephalon	hypothalamus	PeriVN	AT_1	
			PON	AT_1	
			MePON	AT_1	
			SON	AT_1	
			suprachiasmatic	AT_1	
			arcuate	AT_1	
			ventromedial	AT_1	
			dorsomedial	AT_1	
		CVOs	SFO	AT_1	
			median emincence	AT_1	
			OVLT	AT_1	
			choroid plexus	AT_1	
		thalamus		AT_1	
		subthalamic nucleus			AT_2
		optic tract nucleus			AT_2
Midbrain	*Mesencephalon*	peduncles	locus coeruleus	AT_1	AT_2
			medial geniculate nuclei		AT_2
			superior colliculus	AT_1	AT_2
	Metencephalon	pons		AT_1	AT_2
		cerebellum cortex		AT_1	AT_2
		cerebellum	interposed nucleus		AT_2
	Mielencephalon	medulla oblongata	inferior olivary nuclei		AT_2
			NTS	AT_1	
			vagal nuclei	AT_1	AT_2
			cranials nerve nuclei	AT_1	AT_2
		CVOs	AP	AT_1	
		spinal cord		AT_1	

Table 1. Distribution of Angiotensin receptors in the Central Nervous System. Adapted from Function of Neuropeptides at Central Nervous System, Chapter 3, Ed. Research Signpost, 2009.

Physiological effects mediated by AT_1 and AT_2 receptors

Brain AT_1 receptors induce stimulation of:

- drinking behaviour
- salt intake

- alcohol intake, via dopaminergic interaction
- stress brain response, including stress–induced gastric injury
- vasoconstriction of cerebral arterioles
- neuronal norepinephrine release and turnover and norepinephrine-mediated neuromodulation
- L and T type calcium channels
- visual and somatosensory areas in thalamus
- anxiety
- inflammation

Brain AT_1 receptors induce inhibition of:
- K^+ channels
- GABA and glutamatergic transmission
- long term potentiation of synaptic plasticity
- neuronal NE uptake
- NMDA (N-methyl-D-aspartate)-induced neuronal stimulation

The function of AT_2 receptors remains controversial. AT_2 receptors counterbalance some of the biological effects of AT_1 receptor signalling on vascular resistance and antinatriuretic effects.

AT_2 receptors may also decrease the sensitivity to pain, while they exacerbate several other neuronal activities such as:
- ionic currents
- cell differentiation
- axonal regeneration after nerve crush
- modulation of programmed cell death (growth inhibition and promotion of apoptosis)
- transient K^+ current. Reduces the length of action potentials and the refractory period leading to an increase in membrane excitability
- acquisition of conditional avoidance responses
- growth arrest
- cell migration
- cerebral circulation and cerebrovascular development
- blood flow to basal forebrain and pituitary gland
- β endorphin secretion
- body temperature

Figure 2 summarizes the main actions of ANG II at the CNS.

Body fluid homeostasis, sodium and water balance, dipsogenic action and arginine-vasopressin secretion

ANG II regulates body fluids, stimulating thirst and salt appetite (via AVP and CRH-ACTH-glucocorticoids secretion) in the hypothalamus, and inhibiting natriuresis and diuresis (via AVP secretion). The MePON, SFO and OVLT contain AT_1 and volume-receptors and osmoreceptors for control, regulation and homeostasis of body fluids (8).

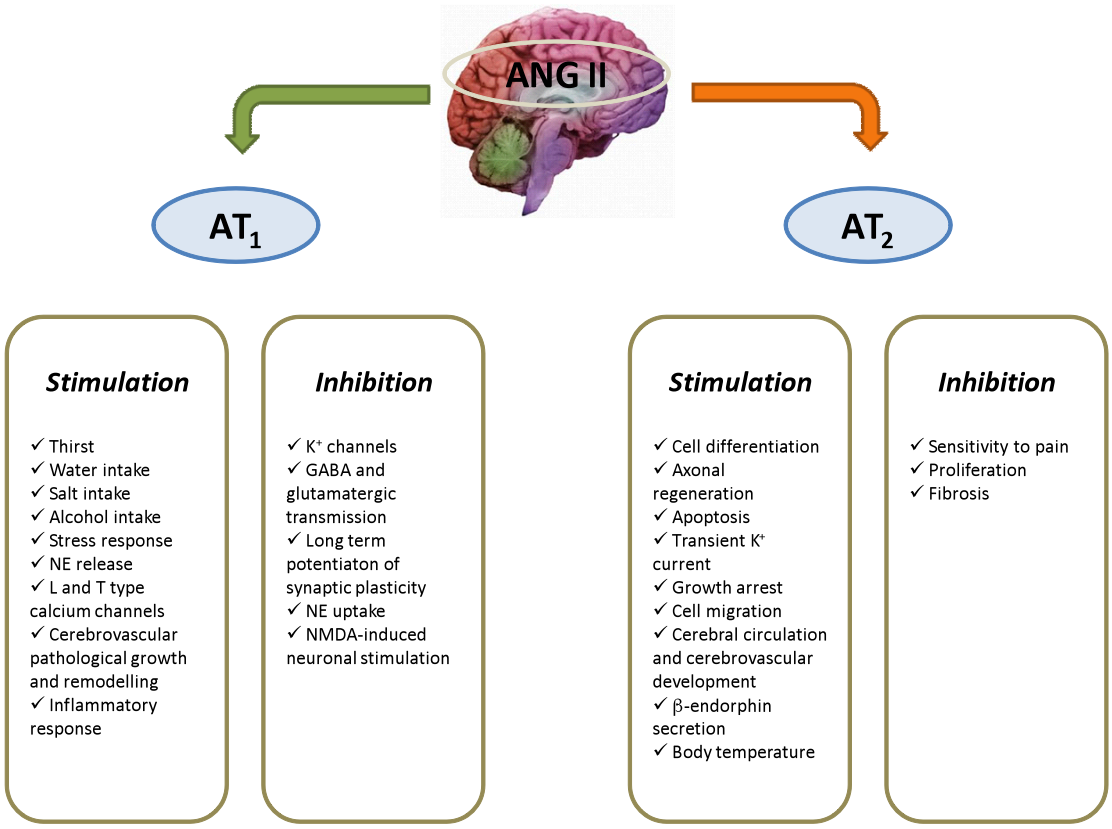

Figure 2. Main actions of Angiotensin II on Central Nervous System. NE: norepinephrine; NMDA: N-methyl-D-aspartate.

Regulation of sympathetic tone and activity and control of cardiovascular function and blood pressure

Brain ANG II modulates the sympathetic tone in the hypothalamus, brainstem and medulla. Indirect effects are exerted on the anterior hypothalamus where ANG II regulates NE transmission and sympathetic activity and stimulates AVP and CRH secretion (9,10). Brain ANG regulates the cardiovascular function and blood pressure. ANG II increases blood pressure through sympathetic activation, AVP, CRH and ACTH secretion and decreases sympathetic baroceptor sensitivity by means of AT_1 receptors activation in the NTS (11). Moreover, enhanced central sympathetic activity results in an increase in vasoconstrictor activity (12). In this way ANG II induces tonic sympathoexcitatory effects through AT_1 receptor stimulation of glutamatergic neurons and sympathoinhibitory effects via GABAergic neurons in the rostral ventrolateral medulla, the brainstem 'pressor area' (13).

Brain generated ANG II acts as neuromodulator or a neurotransmitter in order to process and sense the afferent information received from baroceptors in diverse nuclei associated with cardiovascular control (6,9,12). ANG II modulates neuronal activity through AT_1 or AT_2 receptors, changing the activity of membrane ionic currents and channels in areas implied in blood pressure regulation, like the locus coeruleus, the hypothalamic PVN and the NTS where ANG II receptors receive afferent terminals from

the dorsal motor nucleus of the vagus, the rostral and caudal ventrolateral medulla and the intermediolateral cell column of the spinal cord (14,15).

Catecholaminergic, serotonergic, GABAergic and glutamatergic neurotransmission

Brain RAS and catecholamines (NE, epinephrine, dopamine) are co-localized in several areas of the CNS, including several nuclei of the forebrain (mainly hypothalamic nuclei) and the brainstem (i.e., the NTS). Both ANG II and ANG III stimulate central sympathetic activity regulating NE neurotransmission at the presynaptic nerve ending level. There is an inverse relationship between ANG II circulating levels and NE content in the CNS. ANG II increases spontaneous release and potassium or acetylcholine NE-evoked release, and decreases NE neuronal uptake in hypothalamus and medulla oblongata (10). These effects are not tissue-specific as they were shown in different areas of the CNS. ANG II increases NE content in subcellular granular stores and decreases it in cytoplasmatic neuronal compartments, diminishes NE turnover and enhances NE neuronal synthesis, transporter (NET), tyrosine-hydroxylase expression and dopamine β-hydroxylase mRNA transcription. All these actions result in an enhanced NE availability at the synaptic gap, with the consequent increase in sympathetic activity. ANG II also stimulates MAO activity in hypothalamus (10,16). AT_1 receptors mediate ANG II effects on NE neurotransmission, while AT_2 receptors are not involved (17). ANG II effects on NE uptake in the CNS are reversed by low and non-effective doses of ANP (10).

AT_1 receptors located pre-and postsynaptically may influence norepinephrinergic, GABAergic, and/or glutamatergic transmission (18-20). ANG II stimulates spinally projecting neurons in the PVN by attenuation of GABAergic synaptic inputs (21) and inhibits NMDA receptor (N-methyl-D-aspartate)-induced neuronal stimulation in the amygdale (22). ANG II increases GABA (B) receptor expression and augments GABA (B) receptor-mediated responses in the NTS, contributing to central ANG actions that result in dampening of baroreflexes and elevation of arterial blood pressure (23). Figure 3 shows ANG II effects on central neurotransmission.

Atrial natriuretic peptide

ANP, BNP and CNP are synthesized and released in the CNS. There is a strong correlation between ANP and ANG II and their respective receptors localization in the CNS. These natriuretic peptides are the physiological antagonists of brain RAS and exhibit opposite effects to ANG II on neuronal NE uptake, release, endogenous content and turnover in the hypothalamus. ANP also opposes to ANG II-induced increase in MAO activity and inhibits ANG II-induced water intake in the brain as well as ANG II stimulated secretion of CRH, AVP and OT (10).

Development and neuronal growth, differentiation, proliferation, regeneration and apoptosis

ANG II acts through AT_1 receptors as a growth factor and promotes protein synthesis and fibroblast proliferation (24). During the embryonic life, AT_2 receptors are mainly located in areas closely related with the development, and their number, decreases after birth (24). In adults, AT_2 receptors are found in areas related to sensory and motor control and integration, visual pathways, limbic system activity and behavior. AT_2 receptors promote axonal regeneration after nerve crush (25), growth arrest and cell migration. Moreover, AT_2 activation modulates programmed cell death by the inhibition of

growth and apoptosis promotion through activation of MAP kinases (10), promotes nerve generation and neuronal differentiation in cells of neuronal origin, through an increase in NO production and mediates anti-proliferative effects in different cells lines (10).

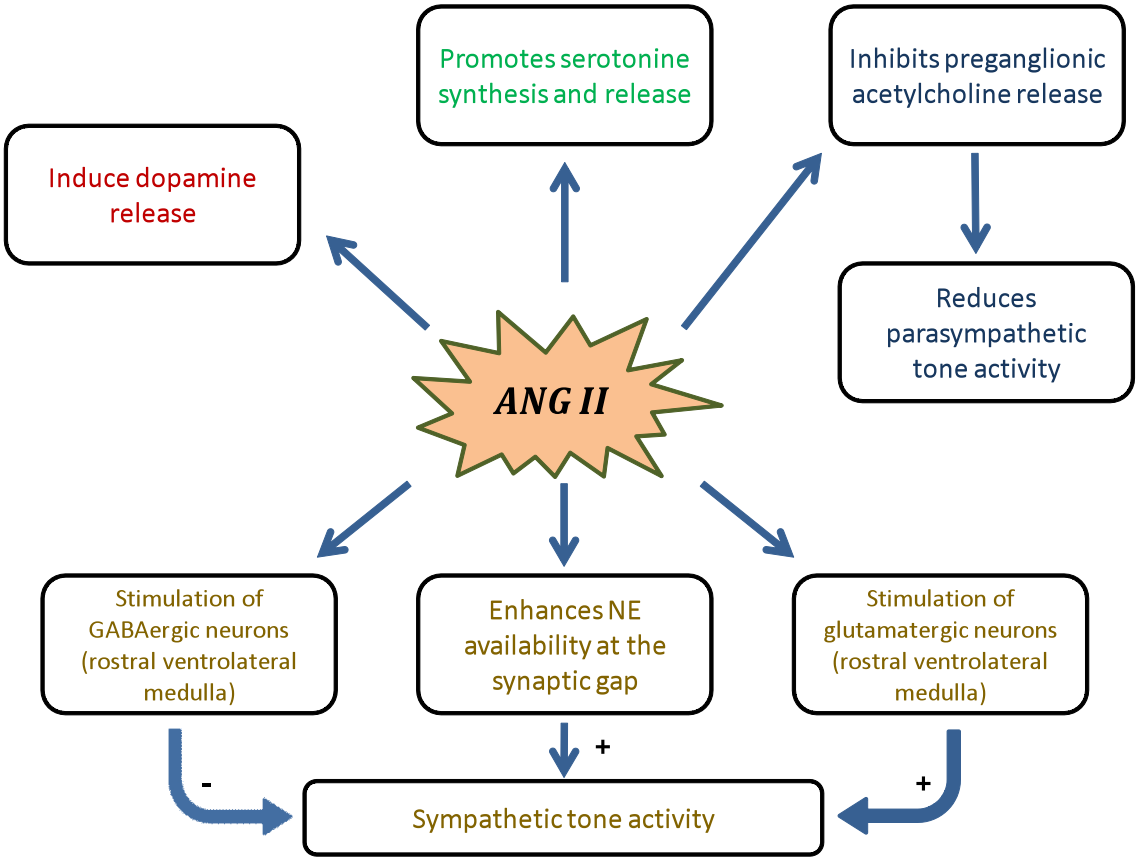

Figure 3. Effects of Angiotensin II on diverse neurotransmission systems (mainly mediated by AT_1 receptors). NE: norepinephrine.

Neuronal ion channels and excitability

ANG II regulates ionic currents in neuronal tissues. AT_1 and AT_2 stimulation cause opposite effects on calcium and potassium channels. AT_1 stimulation enhances calcium release from intracellular stores and its influx from the extracellular space, increasing intracellular calcium in astroglial cells. In hypothalamus and brain stem areas, ANG II increases the neuronal firing rate, which involves the inhibition of the delayed rectifier potassium current. On the other hand, ANG II stimulates both, transient K^+ current and delayed-rectifier K^+ current via AT_2 receptors in brain stem neurons (10). AT_2-induced activation of transient potassium currents is associated with a reduction in the length of action potentials and a shortening of the refractory period, which lead to an increase in membrane excitability (26). AT_2 activation also lowers body temperature. This effect could be related to the increase in membrane excitability of neurons associated to body temperature control, as well as to vasodilation of cerebral vessels in hypothalamic areas.

Moreover, activation of AT_2 increases the firing rate in thalamus and amygdala, suggesting that GABA A receptors are involved in ANG-II-induced effects on neuronal activity (10).

Cognition, memory, behavior and emotion. Motor and somatosensory control

Brain ANG II influences cognitive functions, emotional processes and behavioral changes by acting on specific AT_1 receptors. Treatment with ANG II receptor blockers prevents amyloid beta deposition in the brain and attenuate cognitive impairment in elderly individuals and in Alzheimer disease (27).

In the hippocampus, stimulation of AT_1 and/or AT_2 receptors blocks memory formation, retention and consolidation (28,29). Conversely, ANG II facilitates learning and consolidation of retention and memory, probably through ANG IV formation which interacts with GABA neurotransmission (10). Thus, different responses might be obtained depending on the time intervals between ANG II injection and the behavioral paradigm tested.

Brain administration of ANG II blocks long-term potentiation induction of synaptic plasticity in the amygdala, a specific process of behavioral significance related to learning and memory (10,29). This inhibition is related to presynaptic ANG II action on glutamatergic terminals and with postsynaptic inhibition of NMDA receptors (30,31). The inhibition of AT_2 abolishes the ANG-II-induced acquisition of conditioned avoidance responses (32). The AT_2-mediated increase of neuronal firing rate seems to involve lipoxygenase metabolites of arachidonic acid generation and serine/threonine phosphatase type 2A activation. ANG II up-regulates AT_2 mRNA levels in rat cortical neurons, through regulation of serine/threonine phosphatases activity (10). Taken together, these findings support the hypothesis that, in addition to their role during development, AT_2 receptors may also be involved in cognitive processes in the adult and modulate behavioral effects, mood and pain threshold, and indicate a critical role of ANG II in cognitive impairment associated with vascular disease, Alzheimer disease, metabolic syndrome and other neurodegenerative diseases (27).

In addition, ANG II increases firing rates in the visual and somatosensory thalamus, in the hippocampus and in the superior colliculus and induced neuronal excitation in the inferior olivary nucleus suggesting that it has a role in information processing and in control of locomotor activity. Brain RAS is also involved in sensitivity control. Stimulation of AT_2 decreases the sensitivity to pain and augments β endorphin secretion (10,25).

Anxiety-Alcohol consumption

AT_1 stimulation increases anxiety. This effect is mediated by ANG II interaction with benzodiazepine receptors and by increasing prazosin-binding sites in the amygdala. Conversely, AT_2 receptors stimulation decreases anxiety (33). AT_1 also stimulate alcohol consumption in the CNS, reducing dopamine concentration in the ventral tegmental area, supporting a role for dopaminergic transmission in ANG-II-induced alcohol preference (34).

Cerebrovascular flow. Stroke. Protection against ischemia

ANG II regulates cerebral blood flow, exerting vasoconstriction which favors ischemia and cerebral stroke. AT_1 over-stimulation exacerbates cerebrovascular pathological growth and remodelling with inflammatory reaction in cerebral blood vessels and decreased compliance, impaired cerebral autoregulation, increased cerebrovascular

eNOS/iNOS ratio and NO formation. Centrally AT_1 blockers normalize cerebrovascular flow, decreasing macrophage infiltration and TNF-α, interleukin-1β and NFk-β expression in microvessels in hypertensive rats. AT_1 blockade in SHR rats decreases brain vulnerability to ischemia and neuronal death during experimental stroke and reduces the size of the infarct after occlusion of cerebral arteries. Then, treatment with AT_1 antagonists may be useful for prevention of ischemia and inflammatory diseases of the brain (35,36).

AT_2 receptors also contribute to the autoregulation of cerebrovascular resistance and blood flow. The decreased number of AT_2 in aged rats can be involved in the pathophysiology of cerebrovascular dysfunction. AT_2 stimulation induces cerebrovascular angiogenesis and vasodilation and augments circulation and blood flow to the forebrain and pituitary gland by mean of NO and prostacyclins release during hemorrhagic hypotension in rats. ANG II also alters BBB permeability through prostaglandins release, allowing the transport of substances across the cerebral capillary endothelium (35.37). Therefore, ANG II exerts stroke-protective effects through stimulation AT_2 receptors. ANG II receptor blockers exert a dual influence, since AT_1 blockade decreases local vasoconstriction, allowing free ANG II to stimulate the unoccupied AT_2 receptor and increase local vasodilation, diminishing local brain ischemia and the volume and extent of brain damage (38,39).

Control of hormone secretion. Hypothalamus, hypophysis and adrenal glands

Brain ANG II controls reproductive function and the hypothalamic-pituitary-adrenal axis and increases NE release in the hypothalamus. Considering that NE stimulates hypothalamic releasing factors, brain ANG II may control the anterior pituitary lobe secretion by means of NE-dependent indirect regulation of hypothalamic releasing factors formation and release from de median eminence to the pituitary portal circulation, in order to exert their effects on the hypophysis. Moreover, the complete RAS is present in the anterior pituitary lobe, where ANG II is detected in gonadotrophic (co-localized with LH), lactotrophic, corticotrophic and probably thyrotrophic cells (6).

CRH-ACTH –Glucocorticoids cascade and stress

ANG II is involved in the regulation of adrenocortical hormones, by modulating the synthesis and release of CRH, ACTH and glucocorticoid levels (10). ANG II regulates ACTH secretion, either directly at the pituitary gland or indirectly by increasing CRH or AVP synthesis and release from the hypothalamic PVN (29). ACTH release is also increased by stimulation of ANG II receptors placed outside the BBB in the SFO. ANG II effects on CRH synthesis takes place in the parvocellular PVN and CRH release is produced in the median eminence (10).

Brain ANG II and AT_1 receptors increase during stress and produce anxiety. Brain AT_1 blockade reduces anxiety and prevents ANG II-induced hormonal and sympathoadrenal response to stress, like the increase in CRH release and the consequent augment of ACTH and glucocorticoids secretion and also prevents the ulcerations of the gastric mucosa produced by stress, by preserving gastric blood flow and avoiding inflammation (40).

Mineralocorticoids

A feedback mechanism between brain RAS, sodium levels and mineralocorticoids was described. ANG II controls salt appetite and sodium excretion and conversely, plasma

sodium and mineralocorticoids up-regulate central ANG II receptors. Aldosterone and deoxycorticosterone cross the BBB enhancing ANG II induction on sodium appetite and dipsogenic action, as a result of an increase in brain AT_1 receptor number at the PVN, MePON, SFO, NTS and AP (6).

Prolactin, Gonadotrophins, LH secretion

Brain ANG II controls the reproductive function since it stimulates oxytocin, LH-RH, LH and reduces prolactin release. Central ANG II inhibits pituitary prolactin release indirectly via modulation of dopaminergic activity in the arcuate nucleus. This process depends on estrogen and progesterone levels. Moreover, ANG II can be an intermediate of LHRH on pituitary LH secretion. Since ANG II and LHRH are co-localized in OVLT neurons, ANG II may release NE, enhancing LHRH secretion and thus, indirectly, stimulating LH secretion. AT_{1B} receptors located in pituitary lactotrophic and corticotrophic cells stimulate PLC activity and IP_3 and diacylglycerol (DAG) formation, suggesting a direct paracrine action of ANG II on the anterior hypophyseal lobe. During pregnancy, elevated plasma levels of ANG II may contribute to increase sympathetic nerve activity and attenuate baroreflex gain markedly in this condition (9,10).

Sexual hormones. Estrogens, progesterone and androgens

Pituitary anterior lobe RAS is under the control of sexual hormones. The number of AT_1 receptors changes during the oestrous cycle, being high during metaestrus, decreases during oestrus and diestrus, attaining the lower during proestrus. In addition, AT_1 receptors are very low in male and ovariectomized female rats. 17β-estradiol and progesterone treatment increases AT_{1A}-mRNA expression in tyrosine hydroxylase synthesizing neurons of the dorsal arcuate nucleus, but decreases the expression in the MePON and anterior pituitary. This explains why estrogens diminish some central ANG II effects. On the other hand, androgens increase renin activity and ANG II synthesis in the anterior pituitary lobe (10).

Growth hormone

Pituitary ANG II decreases growth hormone (GH) secretion by a direct action on somatotrophic cells of the hypophysis (36).

Vasopressin and oxytocin

Brain ANG II stimulates AVP and OT synthesis (in the hypothalamus) and secretion (in the posterior pituitary lobe). These effects can be exerted at different levels: a) as a paracrine effect in the hypothalamic nuclei PVN and SON; b) from the median eminence to the portal blood vessels and c) in the posterior pituitary lobe, from the neural terminals of the hypothalamic-hypophyseal tract. AVP synthesis and secretion are exerted mainly in magnocellular neurons of the PVN, where most of AT_1 receptors are located. Moreover, the presence of angiotensinogen, renin, ACE, ANG II and its receptors have been described in the posterior lobe but the functionality of the RAS system in these areas has not been clarified (6).

Vision system

In the superior colliculus, ANG II-AT_1 activation markedly reduces the amplitude of visual evoked potentials, and AT_2 binding decreased after bilateral eye enucleation, suggesting that ANG II receptors may be regulated by retinal inputs (10,25).

Hypertension

Higher expression and exacerbated activity of the brain RAS components may play a role in the pathogenesis and development of hypertension in several experimental models of hypertension, as in genetically spontaneously hypertensive rats (SHR), DOCA-salt, Goldblatt 2K-1C, sino-aortic denervated and pregnancy-induced hypertension. Hypertensive states exhibit an enhanced response to ANG II, a decreased catabolism of the peptide and increased ANG II receptors in selected brain and brainstem areas, as it was shown in SHR rats (2,35,36,41). The sino-aortic denervated rat shows enhanced ANG II binding sites in the anterior pituitary. In addition, ANG II receptors are increased in brain nuclei and areas (MePON, SFO, PVN, NTS and AP) of DOCA-salt hypertensive rats. AT_1 stimulation attenuates the hypotensive action of central α_2 receptors and stimulates β adrenoceptors, increasing collagen synthesis and deposition on brain microvessels. Consequently, ANG microinjection in the NTS causes hypertension and inhibition of the baroreflex. The enhanced pressor response to ANG II injection observed in the hypothalamus of fructose-induced hypertensive rats is mediated by stimulation of β_1 adrenoceptors and attributed to increased AT_1 and β_1 receptors tone (10,42).

Inflammation

Stimulation of AT_1 receptors, colocalized with NAD(P)H oxidase in NTS neurons, induces local reactive oxygen species production and the development of inflammation (41). The RAS plays a pivotal role in autoimmune inflammation of the CNS, being its blockade a potential new target for multiple sclerosis therapy. In this way, the renin inhibitor aliskiren, the ECA inhibitor enalapril, or the preventive/therapeutic administration of AT_1 antagonist losartan, strongly ameliorated the course of multiple sclerosis (43).

REFERENCES

1. Bickerton R and Buckley J. Evidence for a central mechanism in angiotensin induced hypertension. *Proc Soc Exp Biol Med* 106: 834-836, 1961.
2. Saavedra JM. Brain and pituitary angiotensin. *Endocr Rev* 13: 329-380, 1992.
3. Ferguson AV, Washburn DL, and Latchford KJ. Hormonal and neurotransmitter roles for angiotensin in the regulation of central autonomic function. *Exp Biol Med* 226: 85-96, 2001.
4. Re RN. On the biological actions of intracellular angiotensin. *Hypertension* 35: 1189-1190, 2000.
5. Von Bohlen und Halbach O and Albrecht D. The CNS renin-angiotensin system. *Cell Tissue Res* 326: 599-616, 2006.
6. Antunes-Rodrigues J, de Castro M, Elias LLK, Valenca MM, and McCann SM. Neuroendocrine control of body fluid metabolism. *Physiol Rev* 84: 169-208, 2004.
7. Haulica I, Bild W, and Serban D. Angiotensin peptides and their pleiotropic actions. *JRAAS* 6: 121-131, 2005.

8. Fitzsimons JT. Angiotensin, thirst, and sodium appetite. *Physiol Rev* 78: 583-686, 1998.
9. Brooks VL, Dampney RA, and Heesch CM. Pregnancy and the endocrine regulation of the baroreceptor reflex. *Am J Physiol Regul Integr Comp Physiol* 299: 439-451, 2010.
10. G.R de Lores Arnaiz. Function of Neuropeptides at Central Nervous System. Chapter 3: 53-99, Research Signpost, 2009.
11. Matsumura K, Averill DB, and Ferrario CM. Angiotensin II acts at AT_1 receptors in the nucleus of the solitary tract to attenuate the baroreceptor reflex. *Am J Physiol Regul Integr Comp Physiol* 275: 1611-1619, 1998.
12. Fernández BE, Domínguez AE, Vidal NA, and Martínez Seeber A. Modifications of arterial pressure and plasma renin: their effects on the norepinephrine content of hypothalamus and medulla oblongata. *Arch Int Physiol Biochim* 85: 287-293, 1977.
13. Dupont AG and Brouwers S. Brain angiotensin peptides regulate sympathetic tone and blood pressure. *J Hypertens* 28: 1599-1610, 2010.
14. Pan HL. Brain angiotensin II and synaptic transmission. *Neuroscientist* 10: 422-431, 2004.
15. Allen AM, Moeller I, Jenkins TA, Zhuo J, Aldred GP, Chai SY, and Mendelsohn FA. Angiotensin receptors in the nervous system. *Brain Res Bull* 47: 17-28, 1998.
16. Fernández BE and Domínguez AE. Angiotensin II increases MAO activity in rat central nervous system. *Rev Esp Fisiol* 47: 37-40, 1991.
17. Rodríguez Campos M, Kadarian C, Rodano V, Bianciotti L, Fernández B, and Vatta M. AT-1 receptor and phospholipase C are involved in angiotensin III modulation of hypothalamic noradrenergic transmission. *Cell Mol Neurobiol* 20: 747-762, 2000.
18. Barnes KL, DeWeese DM, and Andresen MC. Angiotensin potentiates excitatory sensory synaptic transmission to medial solitary tract nucleus neurons. *Am J Physiol Regul Integr Comp Physiol* 284: 1340-1353, 2003.
19. Ozaki Y, Soya A, Nakamura J, Matsumoto T, and Ueta Y. Potentiation by angiotensin II of spontaneous excitatory postsynaptic currents in rat supraoptic magnocellular neurones. *J Neuroendocrinol* 16: 871-879, 2004.
20. Oz M, Yang KH, O´Donovan MJ, and Renaud LP. Presynaptic angiotensin II AT_1 receptors enhance inhibitory and excitatory synaptic neurotransmission to motoneurons and other ventral horn neurons in neonatal rat spinal cord. *J Neurophysiol* 94: 1405-1412, 2005.
21. Li DP, Chen SR, and Pan HL. Angiotensin II stimulates spinally projecting paraventricular neurons through presynaptic disinhibition. *J Neurosci* 23: 5041-5049, 2003.
22. Tchekalarova J and Albrecht D. Angiotensin II suppresses long-term depression in the lateral amygdala of mice via L-type calcium channels. *Neurosci Lett* 415: 68-72, 2007.
23. Zhang Q, Yao F, O'Rourke ST, Qian SY, and Sun C. Angiotensin II enhances GABA(B) receptor-mediated responses and expression in nucleus tractus solitarii of rats. *Am J Physiol Heart Circ Physiol* 297: 1837-1844, 2009.
24. Dinh DT, Frauman AG, Johnston CI, and Fabiani ME. Angiotensin receptors: distribution, signalling and function. *Clin Sci* 100: 481-492, 2001.
25. Paul M, Poyan Mehr A, and Kreutz R. Physiology of local renin-angiotensin systems. *Physiol Rev* 86: 747-803, 2006.
26. Gendron L, Payet MD, and Gallo-Payet N. The angiotensin type 2 receptor of angiotensin II and neuronal differentiation: from observations to mechanisms. *J Mol Endocrinol* 31: 359-372, 2003. 27. Mogi M and Horiuchi M. Effects of angiotensin II receptor blockers on dementia. *Hypertens Res* 32: 738-740, 2009.

28. Kerr DS, Bevilaqua LR, Bonini JS, Rossato JI, Kohler CA, Medina JH, Izquierdo I, and Cammarota M. Angiotensin II blocks memory consolidation through an AT_2 receptor-dependent mechanism. *Psychopharmacology* 179: 529-535, 2005.
29. Phillips MI and de Oliveira EM. Brain renin angiotensin in disease. *J Mol Med* 86: 715-722, 2008.
30. Albrecht D, Hellner K, Walther T, and von Bohlen und Halbach O. Angiotensin II and the amygdala. *Ann N Y Acad Sci* 985: 498-500, 2003.
31. Drephal C, Schubert M, and Albrecht D. Input-specific long-term potentiation in the rat lateral amygdala of horizontal slices. *Neurobiol Learn Mem* 85: 272-282, 2006.
32. Braszko JJ. AT(2) but not AT(1) receptor antagonism abolishes angiotensin II increase of the acquisition of conditioned avoidance responses in rats. *Behav Brain Res* 131: 79-86, 2002.
33. Braszko JJ, Kulakowska A, and Winnicka MM. Effects of angiotensin II and its receptor antagonists on motor activity and anxiety in rats. *J Physiol Pharmacol* 54: 271-281, 2003.
34. Maul B, Krause W, Pankow K, Becker M, Gembardt F, Alenina N, Walther T, Bader M, and Siems WE. Central angiotensin II controls alcohol consumption via its AT_1 receptor. *FASEB J* 19: 1474-1481, 2005.
35. Saavedra JM, Benicky J, and Zhou J. Mechanisms of the Anti-Ischemic Effect of Angiotensin II AT(1) Receptor Antagonists in the Brain. *Cell Mol Neurobiol* 26: 1099-1111, 2006.
36. Saavedra JM, Benicky J, and Zhou J. Angiotensin II: multitasking in the brain. *J Hypertens* 24: 131-137, 2006.
37. Saavedra JM. Brain angiotensin II: new developments, unanswered questions and therapeutic opportunities. *Cell Mol Neurobiol* 25: 485-512, 2005.
38. Chrysant SG. The pathophysiologic role of the brain renin-angiotensin system in stroke protection: clinical implications. *J Clin Hypertens* 9: 454-459, 2007.
39. Schrader J, Kulschewski A, and Dendorfer A. Inhibition of the renin-angiotensin system and the prevention of stroke. *Am J Cardiovasc Drugs* 7: 25-37, 2007.
40. Saavedra JM and Benicky J. Brain and peripheral angiotensin II play a major role in stress. *Stress* 10: 185-193, 2007.
41. Cheng WH, Lu PJ, Ho WY, Tung CS, Cheng PW, Hsiao M, and Tseng CJ. Angiotensin II inhibits neuronal nitric oxide synthase activation through the ERK1/2-RSK signaling pathway to modulate central control of blood pressure. *Circ Res* 106: 788-795, 2010.
42. Mayer MA, Höcht Ch, Gironacci M, Opezzo JAW, Taira CA, Fernández BE, and Puyó AM. Hypothalamic angiotensinergic-noradrenergic systems interaction in fructose induced hypertension. *Regul Pept* 146: 38-45, 2008.
43. Stegbauer J, Lee DH, Seubert S, Ellrichmann G, Manzel A, Kvakan H, Muller DN, Gaupp S, Rump LC, Gold R, and Linker RA. Role of the renin-angiotensin system in autoimmune inflammation of the central nervous system. *Proc Natl Acad Sci USA* 106: 14942-14947, 2009.