7 Brain Renin-Angiotensin System: A Novel Therapeutic Target for Psychostimulant and Alcohol Related Disorders?

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Introduction

Ang II is a neuropeptide with multiple actions on the brain. The distribution of its AT1 receptor in the central nervous system (CNS) coincides with several cerebral regions known to regulate cardiovascular and body fluid homeostasis [1, 2]. It is now known that a brain RAS exists [3], with actions largely complementary to those of the systemic peptide [4, 5].

Ang II does not cross the blood–brain barrier, but, through generation at the periphery, can stimulate the brain RAS at specific brain sites such as the circumventricular organs (specific sites in the CNS that lack the blood–brain barrier). Circumventricular organs are critically involved in the regulation of many homeostatic processes, including the control of cardiovascular functions, hydromineral balance, body temperature, and hormone secretion [6]. The action of peripherally generated Ang II at these sites is believed to influence classical behavioral (drinking), endocrine (vasopressin, oxytocin, and adrenocorticotrophic hormone secretion), and autonomic functions [7, 8]. Ang II belongs to the group of peptides known to stimulate dopamine (DA) release [9]. Furthermore, Ang II receptors are located in DA-rich brain areas [10]. Central actions of Ang II are not exclusively associated with their traditional roles. Indeed, several studies have shown that central Ang II is also involved in sexual behavior, stress, learning and memory [11], and included in drug abuse induced effects such as psychostimulants and alcohol.

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Brain Renin-Angiotensin System: Distribution and Functions

In the brain, the angiotensinogen (AOGEN), synthesized by astrocytes [12] and also present in neurons, is cleaved by renin, which is present in the brain in very low concentrations [13], to generate the inactive decapeptide angiotensin I. By the activity of the angiotensin-converting enzyme (ACE), widely distributed in the brain [14], angiotensin I is hydrolyzed at its carboxy-terminus,

P.Á. Gargiulo, H.L. Mesones Arroyo (eds.), *Psychiatry and Neuroscience Update*,
DOI 10.1007/978-3-319-17103-6_7

which leads to generation of the active octapeptide Ang II. Ang II seems to represent the first neuroactive form of the angiotensins [15] and it is not only generated in the brain via this classical pathway, involving renin and ACE, but can also be produced directly from AOGEN by cathepsin G or tonin [16]. Subsequently, Ang II is metabolized to Ang III, which is itself converted to Ang IV by aminopeptidases. There are further hypotheses that the brain processes alternative enzymatic mechanisms for the formation of neuroactive forms of angiotensin that are distinct from those involved in the classical pathway [17].

The biological actions of Ang II are mediated by seven specific transmembrane-spanning G protein-coupled angiotensin receptors. Studies of non-peptide antagonists have led to the identification of two pharmacologically distinct Ang II receptor subtypes: AT1 and AT2 [18].

The distribution of angiotensin-like immunoreactivity in nerve terminals is well defined [19] and has a good correlation with angiotensin AT1 and AT2 receptors, defined by in vitro autoradiography with 125I-Ang II, or by in situ hybridization histochemistry [2, 20]. In addition, angiotensin receptors and angiotensin-like immunoreactive nerve terminals are present in sites where microinjections of Ang II produce changes in physiological parameters such as blood pressure, drinking behavior, salt appetite, and neuroendocrine function [19]. These observations provide strong support for the hypothesis that angiotensin acts as a neurotransmitter or neuromodulator in the brain. Furthermore, the discovery of non-peptide and selective Ang II receptor antagonists (losartan, PD 123177, candesartan, between others), in addition to the known ACE inhibitors, have helped in understanding some of the central RAS functions.

Brain Ang II is involved in fluid and salt ingestion, neuroendocrine system modulation including vasopressin and corticotrophin-releasing factor release, and interaction with the autonomic control of the cardiovascular system to influence blood pressure [21, 22]. In many instances, these effects are complementary to those of the systemic peptide on peripheral target organs. Thus, systemic Ang II affects the brain through AT1 receptors located in the circumventricular organs: subfornical organ, vascular organ of the lamina terminalis, median eminence, anterior pituitary, and the postrema area of the hindbrain [2, 23]. In addition, endogenous neurally-derived Ang II appears to act at many CNS sites behind the blood–brain barrier [24, 25] such as the median preoptic nucleus, hypothalamic paraventricular nucleus, anteroventral preoptic, suprachiasmatic and periventricular nuclei, and discrete regions of the lateral and dorsomedial hypothalamus. Most of the classical actions of Ang II are mediated via the AT1 receptors present in large amounts in these areas, whereas AT2 receptor stimulation may cause opposite effects.

Ang II generated within the brain can act on AT1 receptors as a neurotransmitter or neuromodulator in neural pathways, influencing the cardiovascular system and fluid and electrolyte balance. Angiotensinergic neural pathways within the brain may have important homeostatic functions, particularly related to the control of arterial pressure, fluid and electrolyte homeostasis, and thermoregulation.

The brain RAS is also involved in the modulation of multiple additional functions, including processes of sensory information [17, 26], learning and memory [27, 28], and the regulation of emotional [26] and behavioral responses [29, 30]. Researchers have reported that Ang II influenced rat behavior in an open field [29], locomotion, and stereotypy [31, 32].

Brain Ang II was found to regulate some responses induced by drugs of choice for abuse such as cocaine, amphetamine, alcohol, as well as others. It was also found that Ang II enhanced the stereotypy induced by apomorphine (APO, D1 and D2 dopaminergic agonist), and this response was blocked by Ang II AT1 receptor antagonists [33]. The presence of Ang II AT1 receptors has been described in pre- and postsynaptic dopaminergic neurons [9] which are involved in behavioral and rewarding responses induced by psychostimulants and alcohol, as well as their modulator action on noradrenergic [34], serotoninergic [35], gabaergic, and glutamatergic neurotransmission [36, 37].

Our goal in this chapter is to present and discuss the evidence supporting an important role of

brain RAS in neuroadaptive responses induced by two of the most abused drugs: amphetamine and alcohol, proposing this system as a potential therapeutic target in the treatment of disorders related to these drugs of choice for abuse.

Renin-Angiotensin System and Dopamine

Increasing ontogenetic, anatomic, and functional evidence has indicated the existence of a brain RAS and its interaction with other putative neurotransmitters and their receptors. During the embryologic period, it was shown that Ang II increased the differentiation of mesencephalic precursors toward the dopaminergic phenotype [38]. Moreover, all RAS components have been observed in the caudate putamen (CPu), as well as in the other basal ganglia structures. AT1 receptors were observed in the cell body in the substantia nigra (SNi) pars compacta, and at the presynaptic terminal in the CPu [39, 40] and in motivated circuitry key areas, such as nucleus accumbens (NAc) and tegmental ventral area (VTA), [41, 42]. Studies in adult human brain revealed the same localization in these structures [43, 44]. Despite the fact that AT1 receptor density is low in the rat CPu and NAc, other authors found that Ang II acts presynaptically in the rat CPu and NAc to potentiate DA release [9, 45]. In human basal ganglia, ACE was located in the SNi pars reticulata and enriched in striosomes of the striatum, which regulates the DA turn-over in CPu [46].

There is evidence that indicates a role of Ang II, through AT1 receptors, in functions mediated by dopaminergic system, such as locomotor and stereotypic behaviors [31]. In this sense, it showed an increase in rat exploratory activity induced by Ang II intracerebroventricular (ICV) administration, which was higher by administration of APO and decreased by dopaminergic antagonists [47, 48]. Other experimental studies have shown that Ang II increased the stereotypy induced by APO, and it was blocked by ACE inhibitor administration [33] or by Losartan, an AT1 receptor blocker [31, 32]. Furthermore, the Ang II induced rotation behavior in 6-hidroxydopamine lesion rat striatum and was reversed by Losartan or dopaminergic antagonists [49].

In addition, ICV Ang II administration increases extracellular DA in the NAc which is related to Ang II-induced drinking [50]. This is in accord with the findings of Nicolaidis, who in 1974 found that rats submitted to extracellular dehydration were able to self-inject intracerebral Ang II [51]. These data support the concept that Ang II can contribute to the reinforcement effects of drinking behavior and add to the increasing body of evidence implicating the mesolimbic dopaminergic system in reward-relating behaviors.

On the other hand, new outcomes show that Ang II participates in neuroplastic processes. In that regard it was demonstrated that the sensitization to the hypertensive effect to systemic Ang II was induced by repeated central administration of Ang II [52]. Moreover, there is evidence that RAS is involved in neuroadaptive changes related to behavior and neurochemical sensitization to natural reinforcements and drugs of choice for abuse [53].

The RAS system is involved not only in dopaminergic system regulation, but there is evidence that through AT1 receptors, Ang II mediates the noradrenaline transport increase and the tyrosine hydroxylase and dopamine beta hydroxylase enzymes transcription [34]. It is necessary to clarify that mainly dopaminergic areas of the brain, CPu and NAc, receive projections from other different neurotransmission systems such as the noradrenergic system from locus coeruleus, the serotoninergic system from dorsal raphe nucleus, and the glutamatergic system from the cortex.

RAS and Psychostimulants

There is considerable evidence that DA neurotransmission in the CPu and NAc plays a key role in long-term neuroadaptive changes induced by psychostimulants such as cocaine or amphetamine. Repeated exposure to amphetamine, as with most addictive drugs, results in a progressive

and enduring enhancement of its psychomotor and positive reinforcing effects. The enhanced response to psychostimulants, a phenomenon termed behavioral sensitization, relies on time-dependent neuroplastic changes in the brain circuitry that are involved in motivational behavior [54, 55]. These changes are associated with long-lasting hyperactivity of the mesolimbic dopaminergic pathway [56, 57]. The evidence indicates that exposure to a drug of choice for abuse is not needed to be repeated to induce locomotor sensitization; thus studies in mice and rats showed that a single exposure to psychostimulants (amphetamine or cocaine) induced behavioral sensitization [58, 59]. The sensitization process encompasses two temporally distinct phases: induction and expression [56, 60]. Neuroadaptive changes in mesotelencephalic dopaminergic projections play a key role in the induction and expression of amphetamine sensitization. Sensitization can be induced by microinjection of amphetamine into the VTA; meanwhile its expression is associated with time-dependent adaptations in forebrain DA-innervated areas, such as the NAc and CPu.

Behavioral sensitization is not limited to addictive drugs and can also be induced by strong motivational or affective states (thirst or hunger) associated with natural reward stimuli, such as water, salt, food, etc. [52]. In this sense, repeated sodium depletion was able to induce RAS activation and Ang II synthesis, producing an increase in sodium intake. The increase in sodium intake was parallel to neuronal activation (Fos-ir) in brain nucleus involved in motivation and reward [61]. Moreover, increased Fos expression in the NAc core and shell has been described in animals with sodium depletion submitted to a sham-drinking paradigm, in which the persistent appetitive behavior and prolonged ingestion are similar to the behavior of animals responding to drugs of choice for abuse [62].

In this sense, Roitman and colleagues found that the medium spiny neurons within the shell of the NAc of rats that had experienced sodium depletions had significantly more dendritic branches and spines than controls [63]. Behavioral cross-sensitization between sodium depletion and cocaine has also recently been described [64]. The results from these experiments indicate that treatments generating a sustained salt appetite and producing cocaine-induced psychomotor responses show reciprocal behavioral cross-sensitization, similar to results found using amphetamine [53].

There is evidence that supports a direct relationship between RAS and behavioral sensitization. In our laboratory it was found that Ang II AT1 receptors are involved in the neuroadaptive changes induced by a single exposure to amphetamine and that such changes were related to the development of behavioral and neurochemical sensitization. The study examined the expression of amphetamine (0.5 mg/kg, i.p.)-induced locomotor activity in animals pretreated with an AT1 receptor antagonist, candesartan cilexetil (3 mg/kg, p.o.×5 days) 3 weeks after an injection of amphetamine (5 mg/kg, i.p.) [65]. The AT1 blockade effects became evident 3 weeks after pretreatment with a single exposure to amphetamine, when the adaptive changes in behavioral response had been described to be more pronounced [59]. The dopaminergic hyperactivity associated with sensitization was also tested by measuring ^{3}H-DA release in vitro from CPu and NAc slices, induced by K+ (28 mM) stimulus. The behavioral and neurochemical sensitization to amphetamine was confirmed with this two-injection protocol, and pretreatment with the AT1 blocker, candesartan, blunted these responses [65]. With the same purpose, the involvement of brain Ang II AT1 receptors was studied in the development of neuronal activity changes, and so the immunoreactivity of CPu neurons to FOS antibody (FOS-ir) was measured after 3 weeks of the same treatment described above. There are no previous studies showing a neuronal hyperactivity in CPu and NAc induced by a two injections protocol and the results also showed that the AT1 blocker pretreatment prevented this neuronal hyperactivity [66]. Furthermore, we observed that the same AT1 blocker pretreatment attenuated the phosphorylated extracellular regulated kinase (p-erk) immunostaining increase in NAc induced by amphetamine (unpublished data, Fig. 7.1). These experimental approaches provide evidence that supports the involvement of

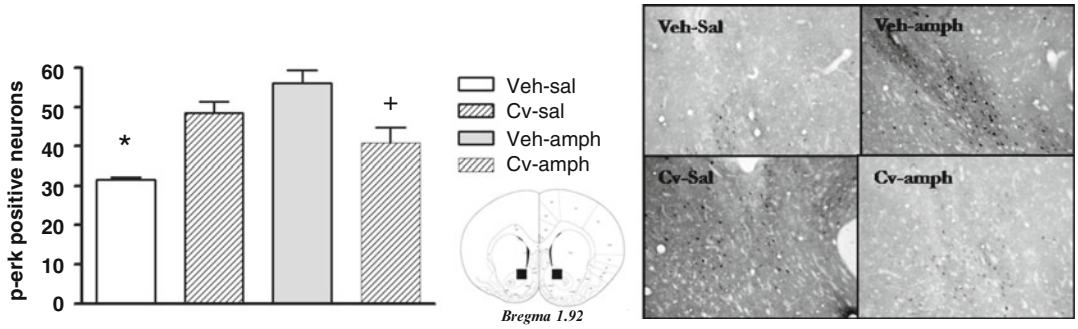

Fig. 7.1 *Left panel*: Average number of p-erk immunoreactive neurons in nucleus accumbens (NAc, *Bregma*: 1.92) in response to a challenge injection of amphetamine (0.5 mg/kg, i.p.), 21 days after a pretreatment with candesartan (Cv, 3 mg/kg, 5 days, p.o.) or vehicle (Veh) and a treatment with amphetamine (amph, 5 mg/kg, 1 day, i.p.) or saline (Veh-sal, Cv-sal, Veh-amph, and Cv-amph). Values are means ± SEM. $*p < 0.05$ significantly different from the other amphetamine-challenged groups, $+p < 0.05$ significantly different from Veh-amph, (1-way ANOVA, post hoc Newman-Keuls). *Right panel*: Photomicrographs ×200 magnifications showing the pattern of p-erk immunoreactive neurons

brain Ang II AT1 receptors in the development of amphetamine-induced behavior sensitization. A new role of brain RAS may be indicated because it has been suggested that the phenomenon of behavioral sensitization is an adaptive process within addiction to psychostimulants and other drugs of choice for abuse [67].

Recent results from our laboratory have showed an increase in the AT1 receptors protein expression in CPu and NAc, 7 and 21 days after the amphetamine treatment (5 mg/kg, i.p., 1 day), and a decrease in AOGEN RNAm and protein expression in CPu, 21 days after the amphetamine treatment, indicating that amphetamine induced long-lasting changes in brain RAS system [68]. Moreover, in another experiment the functional role of AT1 receptors in the expression of sensitization to amphetamine was studied. The AT1 receptors were blocked (Losartan 8 μg/μL by brain side) in CPu and NAc, 5 min before an amphetamine challenge (0.5 mg/kg, i.p) 21 days after amphetamine (5 mg/kg, i.p) administration. These results showed that the expression of amphetamine-induced sensitization was blunted after the blockade of AT1 receptors in CPu [68].

The experiments provide evidence supporting the brain RAS involvement in behavior sensitization induced by amphetamine, contributing to the knowledge of neurobiological mechanisms involved in the psychostimulant drug effects.

The aforementioned evidence points to a new role of the brain RAS in long-lasting effects induced by psychostimulant drugs.

RAS and Ethanol

Alcohol is another of the major drugs abused today, and alcoholism and alcohol-related disorders are disturbingly prevalent in contemporary society. Despite the ever-increasing contributions to the field of alcohol research, a clinically effective pharmacological treatment for alcohol abuse has yet to be developed [69]. It was extensively studied in animals the relationship between alcohol intake and the RAS [70, 71]. In this sense, it was also found that Ang II induced alcohol consumption throught AT1 receptors activation [71]. In 1988, Spinosa and co-workers assessed the ability of the ACE inhibitors (captopril and enalapril) to change alcohol consumption in laboratory rats. The drugs were found to produce a marked reduction in voluntary alcohol consumption independently of changes in blood pressure and without altering alcohol pharmacokinetics [72]. As was observed with psychostimulant drugs, the mesolimbic DA system had been hypothesized to mediate the reinforcing actions of other drugs such as ethanol. Acute administration of ethanol directly alters the DA neurotrans-

mission. Alcohol-preferring animals exhibited a greater dopaminergic response to acute ethanol administration than alcohol–non-preferring animals [73]. Electro-physiological studies demonstrated that ethanol administration increased the firing rate of VTA DA neurons in vivo [74] and in vitro [75, 76]. Systemic administration of ethanol has been shown to increase extracellular DA levels in the NAc and VTA [77–80]. Additionally, microdialysis studies demonstrated an increase in DA release in the NAc following oral self-administration of ethanol [81–83]. Finally, previous data indicate that microinjections of ethanol matabolite into the posterior VTA increase dopamine release in the NAc shell [84].

Involvement of brain RAS components in drug-induced responses has been investigated by correlating altered RAS function and ethanol consumption. Increased expression of AOGEN was found in microarray studies of brains from different rodent lines selectively bred for high ethanol preference (HAP mice) compared with their respective controls [85]. Supporting this idea, chronic ethanol consumption tended to increase AT1 binding in CPu and NAc in C57BL/6 mice, an ethanol-tolerating strain [10].

The studies performed in animals with genetic modification in several components of the RAS demonstrated that Ang II via AT1 receptor action is a positive modulator of spontaneous ethanol consumption in rodents [86, 87]. Transgenic rats expressing a specific AOGEN antisense RNA in the brain [TGR(ASr-AOGEN)680] present angiotensin generation and drastically reduced and modified levels of AT1 receptors in the CNS. These animals show lower ethanol consumption and altered responses after ethanol intoxication compared with controls. Supporting the idea that angiotensin-mediated DA release plays an essential role in Ang II-triggered regulation of alcohol intake, altered DA concentrations were found in relevant brain areas. Indeed, concentrations of DA as well as its principal metabolite (DOPAC) were found to be strongly reduced in a region covering the VTA of TGR(ASrAOGEN)680 rats [88]. It is interesting to note that mice lacking the D2 receptor gene were less sensitive to alcohol-induced ataxia than their wild type littermates while they ingested lower amounts of alcohol in free choice experiments [89]. It is believed that Ang II stimulates DA release in NAc and CPu [9], and angiotensin receptors are expressed in brain areas such as the NAc, where dopaminergic transmission has been strongly implicated in alcohol self-administration and sensitivity [10, 46]. Evidence has shown an increase in the voluntary consumption of alcohol in the transgenic mice expressing a rat angiotensinogen transgene (TGM123). These animals have elevated levels of Ang II resulting from additional expression of the AOGEN transgene. Consumption was significantly reduced by administration of fluphenazine, a DA receptor antagonist. Thus, increased alcohol intake in mice over-expressing angiotensin may relate to an interaction of Ang II with dopaminergic systems. Furthermore, the knockout mice lacking the AOGEN gene (TLM), drank even less alcohol than the controls. Furthermore, it was found that the ACE inhibitor Spirapril, known to cross the blood–brain barrier and consequently lower the Ang II levels in brain and blood circulation, suppressed alcohol intake in the TGM123 mice [87]. Ang II ICV infusion in the ethanol-tolerating mice, C57BL/6J, stimulated the intake of 4 % ethanol solution and caused a transient increase in the intake of 10 % ethanol solution. The increase in ethanol solution intake that occurred did not increase progressively over the 3 days of Ang II treatment, as is usually observed when water is available [90], probably indicating a response to hedonic stimulus of alcohol more than to homeostatic deregulation by Ang II infusion.

The stimulation of brain RAS by food depletion also modifies alcohol consumption. Animals deprived of ad libitum food access had higher ethanol consumption than controls during treatment, and the behavior was reversed when free access to rat food was restored [91].

Controversial results have been reported on ICV infusion of Ang II in rats. An increased alcohol intake has been described by Fitts [92], but most experiments indicate no functional effects for this type of Ang II administration [90, 91, 93]. It is important to highlight that these experiments

are based on invasive techniques with unpredictable effects on drinking behavior. Functional stimulation of Ang II receptors in the vicinity of the lateral ventricle does not exert an influence on alcohol consumption. Furthermore, as alcohol consumption does not decrease at the expense of a robust increase in water consumption, it is possible to assume dissociation between the effects of Ang II on alcohol and water intake [93].

Experiments have been conducted with pharmacologic modification of RAS activity. The blockade of the receptors with different doses of the Ang II antagonist SarThr-Ang II does not modify alcohol consumption. Interestingly, ACE inhibitors reduce alcohol intake in a dose-dependent manner in genetically selected alcohol-preferring and –non-preferring rats, as well as in Wistar rats [94–96]. This may indicate that ACE inhibitors are not acting through peripherally based Ang II-related processes to reduce alcohol consumption. Because peripheral administration of ACE inhibitors can elevate central RAS activity, the present findings indicate that if the reduction in alcohol intake produced by ACE inhibition is mediated through the RAS, the locus of this effect is likely to be at a central site not accessible to a peripherally administered Ang II antagonist [95].

These results clearly support the hypothesis that the central RAS, through AT1 receptors, are involved in the control of alcohol intake behaviour, modulating the DA system.

Conclusion

It is widely known that the high incidence in health costs and in patient welfare and its environmental deterioration are a result of drug abuse and alcohol-related diseases worldwide. In this context it is very important to study new targets in order to provide new pharmacological tools for the treatment of these pathologies. A group of drugs that interfere with the RAS, widely used in clinical practice for hypertension treatment and cardio protection, have particular advantages because they are nearly free of severe side effects. Therefore, the results presented in this chapter regarding the key role of the brain RAS in the neuroadaptative response to drugs of choice for abuse show a new therapeutic application for AT1 blockers. More research is needed to reveal the effectivity of long-term treatment of available ACE inhibitors or AT1 blockers that could be used in the treatment of drug abuse disorders.

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