Brain angiotensin II involvement in chronic mental disorders

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Abstract: The functioning of the central nervous system is complex and it implies tight and coordinated interactions among multiple components. Neurotransmitters systems imbalance is a hallmark in central nervous system (CNS) disorders. These pathologies profoundly impact on social, cultural, and economic perspective worldwide. The etiopathology of CNS illnesses is still poorly understood making their treatment difficult.

Brain angiotensin II (Ang II), through its AT_1 receptors, modulates dopaminergic, glutamatergic and GABAergic neurotransmission, which are responsible for movement control, cognition, emotions and stress responses. Alterations of these functions, concomitant with modified brain renin-angiotensin system (RAS) components, have been described in CNS pathologies like depression, Parkinson, Alzheimer, and schizophrenia. In this sense, altered functionality of angiotensin I converting enzyme and AT_1 receptors, is associated with augmented susceptibility to the occurrence of these pathologies. Moreover, some epidemiological data showed lower incidence of Alzheimer disease in hypertensive patients under treatment targeting RAS; meanwhile preclinical studies relate RAS with Parkinson and depression. Little is known about schizophrenia and RAS; however Ang II is close related to dopamine and glutamate pathways, which are mainly altered in this pathology. The available evidences, together with the results obtained by our group, open the possibility to postulate brain Ang II as a possible therapeutic target to treat the above mentioned CNS disorders.

Keywords: Angiotensin II, depression, Parkinson disease, Alzheimer disease, schizophrenia, AT_1 receptors, amphetamine sensitization.

MENTAL DISEASE: A GROWING UNIVERSAL HEALTH PROBLEM

The scourge of neuropsychiatric diseases spreads in all dimensions of a patient's life. It impacts directly in life quality due to a large number of distressing symptoms and, on the other hand, it exerts indirect impacts due to exclusion of society, stigma, unemployment and shame. Approximately 25% of adult population develops some mental illness at a point of their life and considering the twenty principal pathologies that induce *years lived with disability*, six are neuropsychiatric. Given their high prevalence and long duration, these pathologies generate high economic costs in public health. Furthermore, the contribution of neuropsychiatric diseases to the *years lived with disability* has a marked increased since 1990 and the World Health Organization has estimated that this will continue rising [1].

Literature shows that mental illnesses are the result of complex processes involving the interaction of many pathological changes with genetic and environmental factors.

Consequently, the etiopathology is still poorly understood and the pharmacological tools currently available address only some of the pathological alterations with high resistance to treatment or loss of response along the progression of the disease [2,3]. Additionally, the adverse reactions during the treatment are frequent, generating a decrease in patients´ life quality leading to discontinuation of the treatment [4,5].

The above-mentioned facts highlight the need of a better understanding about the physiopathological mechanisms involved in mental diseases with the purpose to find more effective and safe pharmacological targets.

THE CENTRAL RENIN-ANGIOTENSIN SYSTEM

In the research field of new pharmacological targets, recent studies are focused in neuromodulatory systems and a good candidate is the renin-angiotensin system (RAS). It was initially described as a peripheral humoral system involved in blood pressure regulation and hydro-electrolyte balance [6]. The main active peptide of the system, angiotensin II (Ang II), is the result of consecutive cleavage of angiotensinogen and angiotensin I by renin and angiotensin-converting enzyme (ACE), respectively. In turn, Ang II, can be generated through alternative ways of synthesis that involve other peptidase activity [7]. Ang II can subsequently lead to a number of bioactive peptides with different physiological functions, including angiotensin III, angiotensin IV and angiotensin-(1-7) [7]. At present, it is well known that there is a complete local RAS in the central nervous system (CNS) where all of its components are synthesized [7]. However, it is important to highlight that peripheral Ang II crosses blood brain barrier under pathological conditions (hypertension) involving inflammatory process or oxidative stress [8].

The presence and synthesis of angiotensinogen has been described in neurons and astrocytes. Whereas angiotensinogen production in neurons is restricted to some brain regions, its astrocytes' synthesis is the most important and widespread source [9–12]. Although low renin levels were initially reported in the CNS, nowadays it is known an intra and extracellular location. This last one can be either secreted as pro-renin or renin (inactive and active forms respectively) [13,14]. The ubiquity location of ACE in the CNS has been extensively described, where it exists extracellularly, as soluble and membrane bound

forms, and is related to catalysis of several other peptides as well [13,14]. Alternative central pathways for Ang II synthesis involve elastase, proteinase 3, cathepsin G and tonin activity [14]. Furthermore, direct evidences support intraneuronal generation and activity of Ang II. In that respect, a dose-dependent increase in intracellular calcium was observed after intracellular Ang II microinjections, mediated by receptors present in endolysosomal membranes [15]. Finally, local RAS has been described in brain microvessels where it is implicated in inflammatory responses [16].

Ang II exert a wide range of physiologic actions through two receptors subtypes named AT_1 and AT_2 receptors [17]. The first one is found in many brain areas that include circumventricular organs (vascular organ of lamina terminalis, subfornical organ), hindbrain regions (nucleus of the solitary tract, caudal ventrolateral medulla), hypothalamus, amygdala, hippocampus and cortex areas [7,13]. This anatomical ubiquity gives Ang II, through AT_1 receptors (AT_1-R), a regulatory role in a large number of brain functions that include blood pressure and fluid homeostasis, body temperature, stress response, alcohol consumption, depression and cognition [18–28]. At cellular level and basal conditions, these receptors are actively synthesized in neurons, endothelial cells, microglia and astrocytes. Moreover, under inflammatory conditions, AT_1-R synthesis in glial cells could be stimulated triggering astrogliosis and microgliosis, together with vasoconstrictive and proliferative effects in brain microvessels [16,29–33].

On the other hand, AT_2 receptors (AT_2-R) are highly expressed in fetal tissue and their expression decline after birth. Though AT_2-R knockout mice develop normally, they show several alterations like impaired drinking after water deprivation, increased vasopressor response to Ang II and diminished spontaneous movements [34,35]. The AT_2-R function in adults is poorly understood and it has been reported to play a role in cell growth inhibition, differentiation process, neuropathic pain and axonal regeneration [36–39].

Currently, pharmacological blockade of the RAS system is used to treat hypertension by two groups of compounds including the ACE inhibitors (ACEIs) and AT_1-R blockers (ARBs). The ACEIs diminish Ang II action through a decrease of its productions due to an inhibition of the conversion of Ang I in Ang II. However, these compounds are not able to prevent the formation of Ang II through alternative pathways independent of ACE activity, such as enzymatic degradation produced by cathepsin and tonin. Considering that ACE is

also involved in bradykinin degradation, this action has been reported to contribute in the therapeutic effects of ACEIs but also with several of its adverse effects [40,41]. ARBs are other pharmacological tools that modulate the RAS system. They are competitive antagonists with high affinity for the AT_1-R. Although its binding is competitive, the majority produce a sustained blockade even with high levels of Ang II, due to several mechanism that include internalization, slow dissociation and rebinding distinctions between non-peptide Ang II AT_1-R antagonist [42,43]. All of these actions allow ARBs to produce a potent, long-lasting and selective blockade of biological effects of Ang II and, at the same time, they do not decrease blood pressure in normotensive patients and show low frequency of side effects. In this sense, ARBs therapy has good tolerability, similar to placebo, with high adherence to treatment, better than ACEIs [44–46].

RAS AND MENTAL DISEASES

Given its ubiquity and pleiotropic action in the brain, RAS system has been associated with many pathological processes in the CNS like neurotransmitter systems imbalance, stress, inflammation and ischemia [47–49]. Since these pathological alterations play a key role in several mental illnesses, the modulation of RAS system would provide new pharmacological tools to improve the results of the available treatments.

STRESS AND DEPRESSION

Mood and anxiety disorders are triggered by the interaction of genetic, biological and environmental factors. Among them, chronic stress exposure is considered to be one of the most important environmental risk factor. About one to two thirds of patients with depression display signs of hypothalamic-pituitary-adrenal (HPA) axis hyperactivity, a system deeply linked with stress response [50]. In animals, it has been observed a mutual interaction between HPA axis and RAS, where HPA axis hyperactivity increases glucocorticoids levels and, consequently, stimulate renin secretion, Ang II production and AT_1-R activation [51,52]. Conversely, AT_1-R activation stimulates corticotrophin releasing

hormone (CRH), adrenocorticotropic hormone (ACTH) and adrenal glucocorticoids secretion [22].

A close relationship between stress and serotoninergic and noradrenergic systems has been described. Direct noradrenergic innervation from locus coeruleus (LC) to the paraventricular nucleus (PVN) regulates CRH release. Besides LC projections to forebrain areas coordinates the stress responses. Moreover, chronic stress produce a potential deficit in noradrenaline (NE) activity observed as decreased release of brain NE, increased expression of α_2 receptor and atrophy of NE axonal projection. This effects are observed along with an increase of postsynaptic β adrenergic receptors to counterbalance the noradrenergic deficit [53]. Serotoninergic inputs from the dorsal raphe innervate cortical and limbic areas involved in the stress response (i.e. prefrontal cortex, amygdala, hippocampus, etc.). Chronic stress alters serotoninergic neurotransmission decreasing spontaneous firing and modifying 5-HT_{1A} functioning. Furthermore, the existence of interconnections between LC-NE neurons and raphe-5-HT neurons points out a functional cross-talk between these systems. An imbalance in these neurotransmission systems is a hallmark in mood disorders and supports the role of stress as the main risk factor for depression [54].

Several evidences support the modulatory role of Ang II in the stress response regarding HPA axis activity and NE/5-HT neurotransmission. In this sense, the AT_1 receptors, which are present in the PVN, regulate CRH and ACTH release and show increased levels after stress exposure [55–57]. Moreover, AT_1 receptor blockade prevents CRH synthesis and release in this brain area, as well as, cortical CRH-R_1 decreased expression, induced by stress [22]. Ang II stimulatory effect over noradrenergic activity has been described in PVN and LC by central stimulation of AT_1-R [27,58,59]. Since there is not AT_1-R expression in LC, it has been suggested that their antagonism prevents the stress-induced increase in central sympathetic drive by indirect effects [27,60]. In that respect, the increase in tyrosine hydroxylase (TH) mRNA in LC observed after Ang II i.c.v. administration or cold stress, is prevented by AT_1-R blockade [27,61]. On the other hand, it has been postulated a biphasic effect of Ang II over 5-HT neurotransmission. High concentrations of Ang II stimulate the tryptophan hydroxylase enzyme to increase the 5-HT synthesis, while at low concentration, Ang II inhibits the enzyme to reduce its levels [22]. Transgenic rats with low angiotensinogen levels (TGR (ASrAOGEN) 680) show reduced 5-HT and its metabolite levels in the

hippocampus, frontal and parietal cortices [62]. Moreover, this strain respond in an exacerbated manner to the anxiogenic effect induced by 5-HT2C/1B receptor agonist [62]. Considering the elevated levels of anxiety displayed by these transgenic animals in basal conditions, a link between this phenotype and 5-HT secondary dysfunctions has been suggested [22].

Another important feature observed in depressive patients is the reduction of hippocampal granule cell layer in cell number and volume. Additionally, the depressive-like behavior induced by chronic stress in animals has been associated with negative effects over hippocampal neurogenesis which is reversed by antidepressant treatment. This alteration could be explained by altered serotoninergic and noradrenergic neurotransmission in the hippocampus, given that ablation of this inputs decreased hippocampal neurogenesis [54]. On the other hand, inhibition of hippocampal neurogenesis increases HPA reactivity observed as exacerbated glucocorticoid response. [54]. It has been observed that treatment with valsartan, an AT_1-R blocker, restored hippocampal BDNF levels and neurogenesis in mice [63].

In humans, several authors have reported an association between depression and RAS genes variability. The majority of these studies are focused in ACE gene polymorphism constituted by an insertion (I)/deletion (D) of 287 nucleotides in intron 16, responsible for about half of the phenotypic variance in serum ACE levels [64]. Although there is no full consensus, in most of the cases, an increase risk of depression in homozygous subjects for the short allele (D/D) which display higher levels of plasmatic ACE has been reported [65–67]. This RAS hyperactivity would increase cortisol levels and dopamine and serotonin turnover [64]. Furthermore, abnormal ACE gene methylation and some polymorphisms on ACE, angiotensinogen and AT_1-R genes could be associated with depression occurrence and therapeutic outcome [68–71].

PARKINSON´S DISEASE

Parkinson´s disease (PD) is a progressive motor disorder associated with dopamine levels decrease in basal ganglia, as a consequence of dopaminergic neurodegeneration in substantia nigra pars compacta and loss of synaptic endings in the striatum.

Neurodegenerative processes are not limited to basal nuclei and extend to other parts of the encephalon generating other symptoms such as dementia. The physiopathology of neuronal death is not completely understood, but it has been associated with missfolding and proteins aggregation, particularly α-synuclein and parkin, that would promote the cytoplasmic dopamine accumulation [72]. In this sense, inflammation, mitochondrial dysfunction, oxidative stress and impairment of the ubiquitin-proteosome system would be involved in dopaminergic neuron degeneration in PD. This is underpinned by microglial reactivity observed in the nigra and striatum of brains from both PD patients and PD animal models [73].

It has been reported that brain RAS hyperactivity enhances dopaminergic cell vulnerability in animal models of parkinsonism [74]. Striatal neurons, astrocytes and microglial cells express angiotensinogen and AT_1-R [29]. At neuronal level, AT_1-R are present in dopaminergic endings, controlling dopamine release and over striatal projection neurons, where they constitute dopamine-angiotensin receptor heteromers regulating direct and indirect dopaminergic pathways [29,75,76]. Dopamine and RAS interactions are further supported by a counter regulatory expression of D_2-R and AT_1-R observed after dopamine depletion induced by 6-OHDA and aging [77,78]. Striatal RAS components in glial cells play a key role in the inflammatory response and oxidative damage in this brain area, which are the main processes reported in the progression of PD [29]. In this sense, microglial TNF-a release mediated by AT_1-R activation could explain angiotensin-induced dopaminergic cell death [79]. Regarding oxidative stress, transgenic animals for angiotensinogen or AT_1-R, show reduced striatal NADPH-oxidase components in basal conditions. Furthermore, reduced dopamine levels in this area increase the expression of AT_1-R and the NADPH-oxidase complex activity, which decrease as the dopamine function is restored [78]. In the same direction, loss of dopaminergic neurons and oxidative stress indicators decrease with ACEI and ARBs in a 6-hydroxydopamine rat model of Parkinsonism [80,81]. Thus, AT_1-R excessive activation would exacerbate neurotoxins damage through an increase in protein oxidation, lipid peroxidation and NADPH-oxidase activity [82,83]. Since there is a counter regulatory interaction between dopaminergic and angiotensin systems, a decrease in dopamine levels would produce RAS hyperactivity which could accelerate the progression of the pathology [77].

In accordance with the above experimental results, a study performed in human concluded that the dopamine neuron chance to survive increases with lower nuclear AT_1-R expression. The increased nuclear AT_1-R expression is accompanied by elevated levels of NADPH oxidase, oxidative damage to DNA, and caspase-3-mediated cell loss [84]. In this sense, several genetic studies in humans have been developed to evaluate the possible relationship among RAS genes polymorphisms and the risk to suffer PD. As in depression, the I/D polymorphism in the ACE gene was extensively studied, but in most of the cases no evidence of association was found [85–87]. Moreover, the use of ACEIs nor ARBs was associated with a decreased risk to suffer PD [88]; although, these drugs would improve the onset in motor response to L-DOPA and reduce the on-phase peak of dyskinesia [89].

ALZHEIMER´S DISEASE

Alzheimer´s disease (AD) is the most common type of senile dementia, hallmarked by a deep impairment in learning and memory due to a large loss of cholinergic neurons in hippocampus and prefrontal cortex. Early stages of the disease are characterized by episodic memory impairment followed by secondary deficits in spatial cognition, executive functions and personality changes. The underlying neurodegeneration is accompanied by specific pathological features that include extracellular β amyloid peptide (Aβ) deposition in form of senile plaques and in vessels walls, together with intracellular aggregation of hyper-phosphorylated microtubule associated tau protein [90–92]. The subsequent inflammatory scenario implies oxidative stress and extends to synapses loss, microglial and astrocyte activation, vascular damage and disruption of regulatory mechanisms in local cerebral circulation (neurovascular coupling) [90,93]. Since new approaches link the development of AD with hypertension and vascular alterations, numerous studies are being performed in order to establish whether the RAS participates in AD pathogenesis and whether pharmacological interventions over this neuromodulatory system may improve the pathophysiological outcome [91].

Evidence supporting RAS involvement in AD comes from multiple animal models and experimental approaches. Central stimulation of RAS by Ang II i.c.v administration upregulated amyloid precursor peptide (APP) ARNm which was accompanied by

decreased protein levels. Furthermore, when processing enzymes for APP, such as α, β and γ -secretase, were analyzed an augmented activity and increased expression of their subunits was observed [94]. Together with an increased Aβ production, these results suggest a stimulatory action of Ang II, through AT_1-R, in APP expression and further processing [94]. Under similar stimulatory conditions, central Ang II increases the levels of the six representative p-tau types which accumulate in AD and the activated form of the main tau kinase. These events depend on AT_1-R activation as they were blocked by losartan administration [95]. When administered systemically, Ang II increases the β-CTF fragment of APP, reflecting enhanced APP cleavage and Aβ deposition [93]. Interestingly, the above mentioned studies demonstrated that these Ang II mediated effects are independent from hypertensive events given that they were observed with non-pressor doses [93–95]. Oral administration of an ARB ameliorated cerebrovascular dysfunction induced by Aβ, decreased ROS production, restored hippocampal electrophysiological activity and improved cognitive performance, in transgenic animal model of AD [96]. Similar results have been reported with losartan administration in aged APP mice, where the ARB restored the altered neurovascular coupling evaluated as cerebral blood flow and glucose uptake in response to whisker stimulation [97]. These results could be explained by improved astrocytic function, combined with inhibition of oxidative stress by decreased AT_1-NADPH oxidase-superoxide deleterious pathway [97]. Transgenic mice with AT_{1a}-R deficiency further support Ang II direct effects through γ-secretase complex stimulation, enhancement of amyloid deposition and Aβ generation [98]. Regarding hypertensive models, the increased expression of Aβ and p-tau positive neurons observed in spontaneous hypertensive rats (SHR) are proposed to be the result of inflammatory processes with a main role for AT_1-R. In that respect, SHR show elevated number of monocyte chemotactic protein 1 and TNF-α positive neurons, and Iba-1-positive microglia. AT_1-R blockade with telmisartan, at low and high doses, diminished the inflammatory response and Aβ accumulation in SHR [99].

Considering the extended clinical use of ARBs for hypertensive therapy and the low incidence of side effects, they are prominent candidates as a new pharmacological approach to this pathology [91]. However, the clinical results are controversial regarding ARBs and AD. Analyses in the US population, using the "Veterans health system decision support system database", indicate that hypertensive treatment with ARBs is associated with a

reduced incidence of Alzheimer's disease and dementia in men over 65 years old [100]. Furthermore, when compared to other anti-hypertensive drugs, ARBs treatment show reduced incidence and disease progression rates among people with AD [100]. In the same direction, studies performed with data from the UK general practice research database, showed inverse dose-response relationship between ARBs and AD (cases of AD aged ≥60 years and prescribed with anti-hypertensive) [101]. Association of ARBs with reduced amyloid accumulation in humans has also been provided by post-mortem analyses. Autopsy data, across the US Alzheimer Disease Centers obtained from hypertensive patients treated with ARBs, show reduced post-mortem neuropathological diagnosis of AD along with fewer amyloid plaques [102]. However, the risk of developing future AD is not significantly associated with the use of ARBs among Asian patients with essential hypertension. It is important to point out that this study covered a 5-year average period in middle-age patients and considering the time-course of cognitive function decline in the disease, this interval might not be sufficient to demonstrate ARBs effects on AD [103].

There is growing evidence of Aβ degradation by ACE activity, which would indicate a role for this enzyme in the characteristic chronic imbalance in Aβ processing in AD [91,92]. Post-mortem studies have shown an important increase in RAS components staining in AD brain tissue, where large pyramidal neuron from the prefrontal-cortex express more ACE immunoreactive neurons, meanwhile there are lesser amount of neurons expressing Ang II and AT_1-R [104]. Once again, genetic studies indicate that ACE gene variability is associated with an increased risk of this pathology [91,92]. Initial studies demonstrated that AD was associated with I/D polymorphism within intron 16 of the ACE gene [105]. Later on, meta-analysis indicated that both the I/D and I/I genotypes were associated with significantly increased AD risk, suggesting the dominant effect of the I-allele [106]. Specifically, it was found that homozygous women for the ACE gene I-allele had a small increased risk to develop AD in association with early AD-related markers [107]. This was also demonstrated for Chinese population, where ACE I-allele confers susceptibility for AD, whereas I homozygous have an increased risk [108].

SCHIZOPHRENIA

Schizophrenia is a severe psychiatric disease characterized by a deep distortion in thought and perception. According to World Health Organization, it affects more than 21 million people worldwide and increases 2-2.5 times the probability of early death than the general population, due to its association with cardiovascular, metabolic and infectious diseases.

This pathology is triggered by the confluence of genetic, epigenetic and environmental factors and is characterized by cognitive deficits, negative and positive symptoms [109]. To this respect, positive symptoms are mainly observed as delusion and hallucinations; negative symptoms include apathy, blunting of emotional responses and social withdrawal; meanwhile cognitive deficits can be observed on attention, working memory and executive functions. Typically, a prodromal period appears during childhood or adolescence with negative symptoms and cognitive deficits, which are persistent along the illness. However, the pathology becomes evident in late adolescence or early adulthood with the expression of positive symptoms in the first psychotic episode [110,111].

Among the many theories that attempt to explain the pathoaetiology of schizophrenia, the most widely accepted are the glutamatergic and dopaminergic hypotheses [112]. The first one is supported by several findings in animals and humans. Alterations in expression, trafficking and downstream signaling pathways of N-methyl-D-aspartate receptors (NMDA-R) have been observed in post-mortem studies [113,114]. In the same way, an association between NMDA-R 2B subunit gene polymorphisms and schizophrenia susceptibility was found [115]. Furthermore, the administration of NMDA-R antagonist, like ketamine, to healthy subjects resembles positive and negative symptoms, and are used for animal models of schizophrenia [116,117]. Regarding RAS, it has been reported a relationship with glutamatergic system where Ang II would modulate glutamatergic activity via AT_1-R [118–120].

The dopaminergic theory postulates that positive symptoms could be the result of mesolimbic dopaminergic hyperactivity, while mesocortical dopaminergic hypoactivity would explain negative symptoms and cognitive deficits [121]. This theory is underpinned by a positive correlation between clinically effective concentrations of antipsychotic drugs and the percentage of blocked D_2 receptors in the striatum [122]. Moreover, several changes on dopaminergic system have been described in the brains of schizophrenic post-mortem

patients, including increase in striatal dopamine levels and D_2 receptor density, and in tyrosine hydroxylase expression in substantia nigra and striatum [112,123]. In agreement with these results, Caucasian population shows positive correlation between D_2 receptors polymorphisms and schizophrenia [124,125]. Furthermore, increases in extracellular dopamine elicited by psychostimulants, like amphetamine (amph) and derivatives, can recreate schizophrenia symptomatology and exacerbate psychotic episodes in schizophrenic patients; while dopamine depletion reduce psychotic symptoms [112,126]. Based on these observations, several animal models of schizophrenia have been developed with psychostimulants administration. In rodents, acute and repeated amph administration induces progressive and enduring enhancement of locomotor activity and stereotypic behavior. This phenomenon is known as behavioral sensitization and it has been associated with an increase of dopamine release in mesolimbic areas [127]. Since mesolimbic dopaminergic hyperactivity seems to underlay hallucinations and delusions, amph is a pharmacological tool useful to resemble positive symptoms in animals. Moreover, repeated amph exposure can induce several long-term cognitive impairments, such as working memory and cognitive flexibility deficits [116]. Disturbances in dopaminergic modulation over medial prefrontal cortex (mPFC) may underlay amph-induced cognitive deficits [128]. Furthermore, amph-induced sensitization resembles sensory gating impairment observed in schizophrenic patients, evidenced as prepulse inhibition [116]. However, this model poorly recreates negative symptoms such as associability and anhedonia [116].

A large body of evidence points to a deep relationship between dopaminergic system and RAS. In this sense, dopamine innervated areas express high AT_1-R density where they positively regulate tonic and evoked DA synthesis and release [75,129–132]. Recently, a bidirectional relationship between these two systems and the existence of functional D_2-R/AT_1-R heteromers in rat striatum has been found [76–78].

Results from our laboratory showed that AT_1-R are involved in the development of amph-induced behavioral and neurochemical sensitization [133,134]. Moreover, amph exposure induced an enduring increase in AT_1-R expression concomitant with angiotensinogen decrease in rat striatum and altered AT_1-R functionality [131,135]. Striatal AT_1-R are involved in the expression of behavioral sensitization, since their blockade blunted the

hyperlocomotion induced by an amph challenge [131]. Furthermore, the amph-induced neurocognitive alterations involve AT_1-R activation [27].

In order to establish an association between RAS and schizophrenia susceptibility, most of the genetics studies focused on ACE I/D polymorphism have obtained heterogeneous results. Several authors found a high frequency of D allele in schizophrenic patients, meanwhile others reported no association [136–141]. Given the multiplicity of factors that influence the incidence of schizophrenia, the lack of congruence among the studies is not surprising. In this regard, a possible explanation could be that ACE polymorphisms would influence the development of schizophrenia only when they are present together with other genes' variants. Interestingly, it has been reported that concomitant genotypes for low COMT activity and high ACE activity were over 10 times higher in schizophrenics with poor response to conventional neuroleptics [142].

FINAL CONSIDERATIONS

Since the available therapeutic treatments for the revised pathologies have low efficacy and high incidence of side-effects, new pharmacological approaches become necessary. The above mentioned evidence suggests that AT_1-R blockers as prominent candidates for psychiatric disorders' pharmacological treatment. In addition, they are currently and safely used in clinics for cardiovascular pathologies, although further studies are needed to postulate the AT_1-R antagonists as an alternative pharmacological tool in chronic mental disorders.

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