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BLOCKADE OF BRAIN ANGIOTENSIN II AT₁ RECEPTORS AMELIORATES STRESS, ANXIETY, BRAIN INFLAMMATION AND ISCHEMIA: THERAPEUTIC IMPLICATIONS

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SUMMARY

Poor adaptation to stress, alterations in cerebrovascular function and excessive brain inflammation play critical roles in the pathophysiology of many psychiatric and neurological disorders such as major depression, schizophrenia, post traumatic stress disorder, Parkinson's and Alzheimer's diseases and traumatic brain injury. Treatment for these highly prevalent and devastating conditions is at present very limited and many times inefficient, and the search for novel therapeutic options is of major importance. Recently, attention has been focused on the role of a brain regulatory peptide, Angiotensin II, and in the translational value of the blockade of its physiological AT₁ receptors. In addition to its well-known cardiovascular effects, Angiotensin II, through AT₁ receptor stimulation, is a pleiotropic brain modulatory factor involved in the control of the reaction to stress, in the regulation of cerebrovascular flow and the response to inflammation. Excessive brain AT₁ receptor activity is associated with exaggerated sympathetic and hormonal response to stress, vulnerability to cerebrovascular ischemia and brain inflammation, processes leading to neuronal injury. In animal models, inhibition of brain AT₁ receptor activity with systemically administered Angiotensin II receptor blockers is neuroprotective; it reduces exaggerated stress responses and anxiety, prevents stress-induced gastric ulcerations, decreases vulnerability to ischemia and stroke, reverses chronic cerebrovascular inflammation, and reduces acute inflammatory responses produced by bacterial endotoxin. These effects protect neurons from injury and contribute to increase the lifespan. Angiotensin II receptor blockers are compounds with a good margin of safety widely used in the treatment of hypertension and their anti-inflammatory and vascular protective effects contribute to reduce renal and cardiovascular failure. Inhibition of brain AT₁ receptors in humans is also neuroprotective, reducing the incidence of stroke, improving cognition and decreasing the progression of Alzheimer's disease. Blockade of AT₁ receptors offers a novel and safe therapeutic approach for the treatment of illnesses of increasing prevalence and socioeconomic impact, such as mood disorders and neurodegenerative diseases of the brain.

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Keywords

Brain Angiotensin; Angiotensin II receptor blockers; Innate immune response; brain ischemia; neuroprotection; aging; anxiety

Focus of the present review

The present review is focused on the translational aspects of the administration of Angiotensin II AT₁ receptor blockers as they relate to the prevention and treatment of neuropsychiatric disorders. For this reason many important aspects of Angiotensin II research, such as alternative pathways and receptors and associated systems, will not be considered here, and the readers may wish to consult recent specialized reviews (Saavedra and Pavel, 2005; Chapell, 2007; Skrbic and Igit, 2009; Barnes et al., 2010; Cuadra et al., 2010; Bader 2010).

The role of Angiotensin II in brain pathology is poorly understood and not widely studied. However, the recent finding that blockers of Angiotensin II AT₁ receptors may significantly decrease the progression of Alzheimer's disease highlights the need for further consideration of this important system. This review has been written with the hope to generate further enthusiasm in the research on the possible role of Angiotensin II in the pathogenesis of neuropsychiatric illnesses, and in the use of antagonists of Angiotensin II AT₁ receptors (ARBs) as therapeutic agents in these disorders.

1. The relevance of stress and brain inflammation, and the role of the cerebral circulation in neuropsychiatric disorders

In response to stress the organism develops complex adaptive responses with participation of emotional, neural, endocrine and immune mechanisms and with a paramount role of the central nervous system. This “general adaptation syndrome” or “allostasis” (McEwen, 2008) is aimed at achieving stability through change, maintaining homeostasis and survival, and requires a well-regulated, timely and adequate response. A disproportionate sensitivity to stress or excessive intensity of stressors may overwhelm the allostatic capacity leading to poor adaptation, manifested by chronic responses with failure of adaptation or excessive compensatory hyperactivity. The resulting “allostatic load”, the physiological cost of excessive stress and adaptation failure, may result in organ damage and disease (McEwen, 2008) (Figure 1).

Systemic inflammation is a particular stressor involving peripheral organs and the brain. Inflammation produces an acute adaptive response, the innate immune response, to initially defend the organism from pathogen toxicity (Dantzer et al., 2008). The central component of the innate immune response includes not only the production of inflammatory factors but a contribution of multiple hormones and the activation of the central and peripheral nervous system (Rivest, 2010). This highlights the natural close connection of all regulatory structures, and in particular that of the neural, hormonal and immune systems (Quan and Banks, 2007). While immune responses are necessary for survival, uncontrolled formation of inflammatory mediators and oxidative radicals may lead to cellular injury and death. In turn, excess of toxic substances originated as the result of cellular injury promote further inflammatory cascades and additional cellular toxicity (Licinio and Wong, 1997). Brain inflammation may not only originate as a consequence of bacterial or viral infection. Inflammatory processes in the brain also develop in response to production of endogenous neurotoxic agents or alterations in the balance of protein oxidation and reduction, for example those occurring during the aging process, neurodegenerative disorders, and

autoimmune disorders such as multiple sclerosis (Glass et al., 2010; Bhat and Steinman, 2009).

The integrity of the brain's circulation and the blood brain barrier is essential to maintain proper allostasis, stability and survival during and after stress. Cerebrovascular alterations, such as those produced as a consequence of cardiovascular disease, diabetes and aging, participate in the vulnerability to stress and brain inflammation characteristic of these conditions (Sparkman and Johnson, 2008; Taguchi 2009). The principal factors involved in this allostatic load include loss of cerebrovascular compliance and alterations in the permeability of the blood brain barrier. While decreased cerebrovascular compliance leads to brain ischemia promoting neurotoxicity and apoptosis (Strandgaard and Paulson, 1992), malfunction of the blood brain barrier increases infiltration of circulatory pathogens and toxins into the brain parenchyma, setting the stage for a poor allostatic response to stress (Quan and Banks, 2007; Farrall and Wardlaw, 2009).

From the above it was not surprising that the consensus emerged of a major role of stress, brain inflammation and cerebrovascular alterations as associated factors which, in different degrees, participate in the origin and progression of many brain disorders. The list includes, but is not limited to: affective and anxiety disorders, schizophrenia, autism, post-traumatic stress disorder, traumatic brain disorder, and many degenerative diseases such as Parkinson's and Alzheimer's disease, amyotrophic lateral sclerosis, multiple sclerosis and HIV-associated dementia (Saetre et al., 2007; Dantzer et al., 2008; Dantzer, 2009; Miller et al., 2009; Glass et al., 2010; Tansey and Goldberg, 2010; Bauer et al., 2010) (Figure 1).

Despite major efforts, the search for therapeutic drugs for these conditions has not been entirely successful. For example, drugs used in peripheral inflammatory conditions are not fully effective in the brain (Nimmo and Vink, 2009) and many novel compounds proposed for the treatment of mental disorders were later found to have a very poor margin of safety (Saavedra and Pavel, 2005).

For these reasons the recent discovery that a group of compounds with a recognized clinical margin of safety, the ARBs, may ameliorate the pathological consequences of allostatic load in the brain is of major interest. ARBs were initially developed to effectively block peripheral Angiotensin II AT₁ receptors, and to be tried, because of their inhibition of Angiotensin II vasoconstrictive and salt retaining effects, as anti-hypertensive compounds (Timmermans et al., 1993). ARBs have been used for years for the treatment of human hypertension, its complications, and associated metabolic disorders such as the metabolic syndrome and diabetes and the prevention of stroke (Papademetriou et al., 2004; McFarlane 2009). Multiple clinical trials demonstrate that ARBs improve end-organ protection in hypertension and associated diseases, and that their therapeutic action extends beyond their reduction of increased blood pressure (Barra et al., 2009). Accumulating preclinical studies and clinical reports call attention on the therapeutic and neuroprotective effects of ARBs in the brain, including reduction of stress, anxiety, brain inflammation and ischemia (Dandona et al., 2003; Saavedra et al., 2006a; Saavedra et al., 2006b; Saavedra and Benicky, 2007; Saxby et al., 2008; Pavlatou et al., 2008; Benicky et al., 2009; Anderson, 2010) (Table 1). This information highlights the major relevance of Angiotensin II in brain function and pathology, and the potential impact of the use of ARBs for the treatment of diseases of the brain. Consequently, this review is focused on the effects of ARBs as they relate to the treatment of neuropsychiatry disorders.

2. Historical perspective on Angiotensin II and the Renin-Angiotensin-System

The octapeptide Angiotensin II was discovered as a circulating pro-hypertensive principle of renal origin (Skrbic and Igic, 2009). A “classical” system was described in mammals, with a precursor molecule, angiotensinogen, predominantly made in the liver and released to the circulation. Angiotensinogen is cleaved by renin, an circulating enzyme of renal origin and the rate-limiting factor for the system, to form an inactive precursor, the decapeptide Angiotensin I. Circulating Angiotensin I is converted to the active principle Angiotensin II by a peptidase, the Angiotensin Converting Enzyme (ACE) predominantly located on the surface of lung endothelial cells. Initially, circulating Angiotensin II was considered as the main effector, stimulating still uncharacterized receptors in the kidney and vasculature, with important roles in blood pressure regulation, and the system was appropriately called Renin-Angiotensin System (RAS) (Skrbic and Igic, 2009) (Figure 2). Further studies continue to reveal the complexity of the RAS, the existence of alternative pathways of Angiotensin II formation, the role of Angiotensin II peptide derivatives and the interactions with associated pathways (Skrbic and Igic, 2009) (Figure 2).

The RAS was established early in evolution, since it is active in invertebrates, being implicated in osmoregulation, reproduction, memory processes, and the regulation of the immune system (Salzet et al., 2001). Additional studies revealed the presence of multiple local RAS systems in mammals, where Angiotensin II could be formed and become physiologically active independent of the circulating RAS. Local RAS systems were described in all tissues studied, including the brain, and it has been increasingly evident that these local RAS systems exert regulatory functions of major importance, in many cases surpassing the influence of the circulating RAS (Paul et al., 2006; Bader 2010) (Figure 2).

3. The brain Angiotensin II system

Initial studies demonstrated that the circumventricular organs, located outside the blood brain barrier, were major target organs for circulating Angiotensin II (Saavedra, 1992). Acting on the circumventricular organs and in particular the subfornical organ (SFO), the organum vasculosum lamina terminalis, and the area postrema, circulating Angiotensin II contributes to regulate drinking behavior and the central autonomic system (Saavedra, 1992). The use of sensitive, selective and quantitative autoradiography allowed the localization and characterization of Angiotensin II receptors in the brain. These and other studies demonstrated: a) localization of Angiotensin II binding sites to selective brain areas; b) the presence of large numbers of Angiotensin II receptors in brain structures inside the blood brain barrier and not accessible to circulating peptide; and c) predominant localization of binding sites to areas involved in hormone and autonomic regulation, sensory perception and emotional behavior (Saavedra, 1992). These findings contributed to establish the presence of an endogenous, local brain Angiotensin II system, as initially postulated (Ganten et al., 1977; Phillips, 1978).

4. Angiotensin II receptor types

Studies on the RAS were hampered for many years by the lack of appropriate selective receptor agonist and antagonist ligands. Development of specific non-peptidic Angiotensin II receptor blockers with good bioavailability (Timmermans et al., 1993), allowed the characterization of two Angiotensin II receptor types, which were named AT₁ and AT₂ receptors. AT₁ receptors were recognized as the main physiologically active Angiotensin II receptor type, and they are expressed in all Angiotensin II target organs (Timmermans et al., 1993; Paul et al., 2006). The role of AT₂ receptors is controversial, and they cross-talk with

AT₁ receptors by mechanisms still not defined (Saavedra, 2005). While human AT₁ receptors consist of only one subtype, rodents express two AT₁ receptor subtypes, AT_{1A} and AT_{1B}, undistinguishable pharmacologically but differentially regulated (Iwai et al., 1992). AT_{1A} receptors were established as the main Angiotensin II AT₁ receptor subtype in the rodent brain. The receptors were expressed in all circumventricular organs, the hypothalamic paraventricular nucleus, the nucleus of the solitary tract, the hippocampus, selective septal and amygdaloid nuclei, cerebral cortex and other restricted areas (Tsutsumi and Saavedra, 1991; Llorens-Cortes et al., 1994; Jöhren and Saavedra, 1996).

5. Angiotensin II receptor blockers (ARBs)

The ARBs are imidazole derivatives, collectively called Sartans (Figure 3). While most of the ARBs include a biphenyl-tetrazole structure, telmisartan is unique, a biphenyl derivative without the tetrazole group (Figure 3). ARBs are selective Angiotensin II AT₁ receptor blockers, and their effects have long been considered exclusively related to AT₁ receptor antagonism (Timmermans et al., 1993). The canonical signal transduction mechanisms associated with AT₁ receptor stimulation have been well characterized in vascular, renal and cardiac cells, including activation of the nuclear transcription factors nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and activator protein-1 (AP-1) (Mehta and Griendling, 2007). The signal transduction mechanisms resulting from AT₁ receptor stimulation in cerebrovascular endothelial cells and in neurons, astrocytes and microglia are similar to those characterized in peripheral cells, also involving NF-κB and AP-1 activation (Zhou et al., 2005; Liu et al., 2006; Miyoshi et al., 2008; Kang et al., 2009; Nagai et al., 2007).

While all ARBs effectively block peripheral and brain AT₁ receptors, there is evidence for additional, non-canonical, effects beyond AT₁ receptor blockade. For example, telmisartan, and to a lesser extent candesartan, are effective agonists of the peroxisome proliferator-activated receptor-γ (PPARγ) (Erbe et al., 2006) and candesartan increases PPARγ gene expression *in vivo* (Zorad et al., 2006) (Figure 3). PPARγ agonists, because of their therapeutic effect on the metabolic syndrome and diabetes and because of their anti-inflammatory and neuroprotective properties, have been proposed for the treatment of a number of brain disorders (Sundararajan et al., 2006). The relative contribution of AT₁ receptor blockade and PPARγ activation on the therapeutic effects of ARBs is under study and will not be considered here. In addition, there have been reports of additional, non-Angiotensin II receptor binding sites for ARBs (Ardaillou, 1998) (Figure 3). The nature and the role of such sites have not yet been determined.

Demonstration of central AT₁ receptor inhibition after systemic administration of the ARB candesartan (Nishimura et al., 2000a) allowed pursuing studies to clarify the role of AT₁ receptors in the brain under physiological and pathological conditions. It was also possible to determine the consequences of central AT₁ receptor inhibition resulting from systemic ARB administration. A more complex and widespread functional spectrum for Angiotensin II AT₁ receptors emerged, indicating participation on the central control of endocrine and autonomic functions and behavior. Studies on the role of brain Angiotensin II have been extensively summarized in a number of reviews (Saavedra, 1992; Saavedra et al., 2005; Saavedra et al., 2006a; 2006b; Paul et al., 2006; Phillips and de Oliveira, 2008; Bader, 2010) (Figure 2). We will focus here on the evidence for a role of brain Angiotensin II in stress, anxiety, inflammation and cerebrovascular control, as it relates to the possible use of ARBs for the treatment of neuropsychiatric disorders.

6a. Association of enhanced brain Angiotensin II activity with increased stress, anxiety and depression. Angiotensin II is a stress hormone

1. AT₁ receptors are highly expressed in the Hypothalamic-Pituitary-Adrenal (HPA) axis and in all brain areas regulating the reaction to stress

AT₁ receptors are highly expressed throughout the HPA axis: the hypothalamic paraventricular nucleus, median eminence, anterior pituitary, and in adrenal gland zona glomerulosa and medulla. In the paraventricular nucleus, AT₁ receptors are expressed in parvocellular corticotrophin-releasing factor (CRF) forming neurons controlling CRF release during stress (Aguilera et al., 1995). Significant numbers of AT₁ receptors are located in higher stress-regulatory structures: hippocampus, septum and amygdala. There are many AT₁ receptors in areas participating in the sensory receptive and motor responsive components of the stress response, the nucleus of the solitary tract, sensory ganglia, and ventral and dorsal horns of the spinal cord. In addition, the localization of AT₁ receptors in sympathetic ganglia and nerve terminals contributes to regulate noradrenaline release (Castrén et al., 1987; Tsutsumi and Saavedra, 1991; Strömberg et al., 1991; Pavel et al., 2008).

2. Stress enhances peripheral RAS activity

Through sympathetic activation of β -adrenergic receptors, stress increases the formation of renin, the rate-limiting enzyme in Angiotensin II formation, leading to enhanced Angiotensin II generation and release to the general circulation (Saavedra and Benicky, 2007). Increased circulating Angiotensin II, coupled with increased AT₁ receptor expression in anterior pituitary, adrenal zona glomerulosa and adrenal medulla contribute to the enhanced ACTH, corticosterone, aldosterone and catecholamine formation and release (Armando et al., 2001; Leong et al., 2002; Jezova et al., 2003).

3. Stress increases brain Angiotensin II activity

Many types of stress, including immobilization, restraint, cold-restraint, isolation, and inflammation, increase brain Angiotensin II formation and upregulate brain AT₁ receptor transcription and expression, in particular in the hypothalamic paraventricular nucleus and subfornical organ (Castrén and Saavedra 1988; Armando et al., 2001; 2007; Leong et al., 2002; Saavedra et al., 2006a; Pedreanez et al., 2006; Bregonzio et al., 2008; Sánchez-Lemus et al., 2009b). Moreover, submission to stress early in development enhances Angiotensin II formation in adulthood (Edwards et al., 1999). Circulating Angiotensin II contributes to the stimulation of stress pathways in the brain, by stimulating AT₁ receptors highly concentrated in the circumventricular organs outside the blood brain barrier, such as the subfornical organ (Saavedra, 1992). The subfornical organ is part of a massive Angiotensin II and AT₁ receptor-expressing tract, central to the control of integrated responses to stress, with direct connections to the paraventricular nucleus and the median eminence and projections to the spinal cord (Saavedra, 1992).

4. Stimulation of brain Angiotensin II activity is associated with higher HPA axis activation, enhanced responses to stress, and increased anxiety

In parvocellular CRF neurons from normal rats, AT₁ receptor activation increases CRF formation and release (Armando et al., 2007), leading to stimulation of pituitary ACTH followed by glucocorticoid formation and release. Increased corticosterone secretion during stress upregulates AT₁ receptor expression in the paraventricular nucleus, through stimulation of glucocorticoid response elements in the gene promoter (Castrén and Saavedra 1989; Guo et al. 1995; Jain et al., 2004). During stress, Angiotensin II also stimulates vasopressin formation and release (Saavedra 1992) to participate with CRF in enhancing

ACTH production (Saavedra, 1992; Aguilera et al., 1995). Angiotensin II also plays a fundamental role in the stress-induced stimulation of central and peripheral sympathetic activity. Enhanced brain Angiotensin II activity increases transcription of tyrosine hydroxylase, the rate-limiting enzyme in the synthesis of catecholamines, in the locus coeruleus, the site of origin of most of the sympathetic innervation to the forebrain (Saavedra et al. 2006a; Seltzer et al., 2004; Saavedra et al., 2006b). This effect contributes to the increased adrenomedullary and peripheral sympathetic catecholamine release during stress (Saavedra, 1992).

Analysis of genetic and pharmacological models further substantiates the direct correlation between enhanced activity of brain Angiotensin II, increased anxiety, HPA axis stimulation, and central and peripheral sympathetic activity. These models include the Spontaneously Hypertensive Rats (SHR) with increased brain AT₁ receptor expression, transgenic rats with excess brain Angiotensin II activity, AT₂ gene-deleted mice expressing higher brain AT₁ receptors and models of central administration of Angiotensin II (Saavedra et al., 1986; Horie et al., 1991; Wilson et al., 1996; Armando et al., 2002; Seltzer et al., 2004; Zhou et al., 2006; Krsková et al., 2007; Sagvolden et al., 2009; Macova et al., 2009; Okuyama 1999a) (Figure 4).

The association of enhanced brain Angiotensin II activity, stress and anxiety established in animal models correlates well with clinical studies. It has long been established that HPA axis dysregulation is one of the major neuroendocrine alterations characterizing major depression, and that stress plays a role in the initiation of mood disorders in genetically vulnerable individuals (Holzboer and Barden, 1996). More recent reports demonstrated that Angiotensin II function is elevated in depression, (Johnson and Grippo, 2006; Frasurre-Smith 2009) and is associated with higher responses to stress in depressive patients (Baghai et al., 2002). Genetic studies appear to corroborate an association between AT₁ receptor variants with higher receptor activation and depression (Saab et al., 2007). Moreover, many studies indicate that genetic variants of the Angiotensin II-forming enzyme ACE associated with higher enzyme activity, and presumably higher Angiotensin II formation, are associated with depression, HPA axis hyperactivity and anxiety (Bondy et al., 2005; Heck et al., 2009). In addition, gene polymorphism of the Angiotensin II precursor Angiotensinogen has been reported to be associated with depression (Lopez-Leon et al., 2008).

6b. Blockade of brain Angiotensin II AT₁ receptors or reduction of brain Angiotensin II formation ameliorates the response to stress, anxiety and depression

1. Reducing brain Angiotensin II formation decreases anxiety and depression in animal models

Gene deletion of Angiotensinogen is associated with decreased depression as determined by the forced swim test in rodents (Okuyama et al., 1999b), and blockade of Angiotensin II synthesis with ACE inhibitors reduces the increased anxiety in transgenic rats with excess generation of brain Angiotensin II (Wilson et al., 1996, Krsková et al., 2007).

2. Administration of Angiotensin II receptor blockers reduces stress, anxiety and depression

Subcutaneous or oral administration of candesartan, an ARB blocking not only peripheral but also brain AT₁ receptors (Nishimura et al., 2000a; Seltzer et al., 2004), significantly reduces the hallmarks of the stress reaction, the HPA axis activation and central and peripheral sympathetic response to isolation stress (Armando et al., 2001). The ARB decreases the isolation stress-induced stimulation of CRF formation and the ACTH,

corticosterone, aldosterone, vasopressin, and catecholamine release (Armando et al., 2001; 2007). Moreover, candesartan decreases the stress- and the Angiotensin II-induced increase in the transcription of the catecholamine rate-limiting enzyme, tyrosine hydroxylase, in the locus coeruleus, a finding indicative of a reduction in central sympathetic activation (Seltzer et al., 2004; Saavedra et al., 2006a; Bregonzio et al., 2008) (Figure 4). The anti-stress effects of candesartan are not lost over time, because the ARB reduces the stress-induced hormonal and sympathetic stimulation when administered throughout the life-span (Baiardi et al., 2004).

The anti-stress effects of candesartan correlate well with the reduction of anxiety and depression in rodent models. ARBs have been shown to have a potency similar to that of benzodiazepines in some tests for anxiety (Kaiser, et al., 1992; Saavedra et al., 2006a), and to reduce lactate-induced panic attacks (Shekhar et al., 2006). In SHR, candesartan reduced chronic anxiety, as determined by increasing the number of entries and the time spent on the open arms of an elevated Plus Maze (Saavedra et al., 2006a) (Figure 4).

Hyperactivity of the HPA axis and of CRF neurons regulating higher brain centers are confirmed findings in anxiety and in stress-related affective disorders (Keck and Holsboer 2001). The anxiolytic effect of ARBs correlates with a reversal of stress-induced alterations in cortical CRF₁ and GABA_A receptors, major systems regulating the response of higher regulatory centers to stress (Saavedra et al., 2006a). Prevention of stress-induced cortical CRF hyperactivity and decreased GABA_A function may explain the anti-anxiety effects of the ARB (Saavedra et al., 2006a).

Furthermore, the ARB losartan ameliorates depression in mice, as determined by the forced swim test (Gard et al., 1999). This observation has translational value, since it has been demonstrated that the treatment with ARBs not only improves quality of life in hypertensives (Weber 2005) but also decreases anxiety and depression in diabetic patients (Pavlatou et al., 2008). Blockade of Angiotensin II synthesis with ACE inhibitors appears to produce similar therapeutic effects, since it improves the efficacy of antidepressants (Hertzman et al., 2005) and decreases anxiety and depression in normotensive subjects (Braszko et al., 2003).

3. ARBs prevent a stress-induced disorder in rodents

The effects of candesartan on a stress-induced disorder, acute gastric ulceration as a consequence of cold-restraint stress in rats, further established that AT₁ receptor blockade has meaningful therapeutic benefits. This procedure produces, through local and centrally-induced vasoconstriction, and mucosal inflammation, a significant number of ulcerations of the gastric mucosa. Blockade of AT₁ receptors dramatically decreased the number of gastric ulcerations in this model (Bregonzio et al., 2003) (Figure 4). The protective effect of candesartan was the result of prevention of the stress-induced reduction on gastric blood flow and ischemia, of reduction of central and peripheral sympathoadrenal stimulation, and of direct anti-inflammatory effects in the gastric mucosa (Bregonzio et al. 2003). Conversely, candesartan did not block the cold-restraint-induced HPA axis stimulation and glucocorticoid release (Bregonzio et al., 2003). This is an additional protective effect, because the anti-inflammatory effects of glucocorticoids are essential for protection against gastric ulceration in this model (Bregonzio et al., 2003).

7. Enhanced Angiotensin II activity is associated with loss of cerebrovascular compliance and with cerebrovascular inflammation, leading to brain ischemia and higher vulnerability to stroke

1. General properties of the cerebral circulation

The brain requires a fairly constant blood flow, since it is highly dependent on an adequate delivery of oxygen from the circulation, and brain cells can be irreversibly damaged if the supply of oxygen and glucose is compromised for more than a few minutes (Edvinsson *et al.*, 1993). The cerebral blood flow is maintained constant by autoregulatory mechanisms. The small cerebral resistance vessels and larger cerebral arteries constrict when perfusion pressure increases, and dilate when it decreases, to maintain a constant blood flow (Mraovitch and Sercombe, 1996). The mechanisms controlling cerebrovascular autoregulation can be altered in several disease states such as hypertension, stroke and during the aging process. During hypertension the cerebral blood vessels are remodeled by hypertrophy and hyperplasia, with stiffness and loss of compliance (Figure 5). These processes make vasodilation more difficult when perfusion pressure is reduced. The increased vulnerability to alterations in blood flow is a major factor leading to ischemic or hemorrhagic stroke (Edvinsson *et al.*, 1993). Alterations similar to those of hypertension occur during the aging process, predisposing aging subjects to ischemia and stroke, irrespective of hypertension (Lartaud *et al.*, 1994).

2. Angiotensin II is a major regulator of cerebrovascular function

Both Angiotensin II and the sympathetic system have long been recognized as major regulators of cerebrovascular autoregulation (Saavedra and Nishimura, 1999). Angiotensin II is locally produced and Angiotensin II receptors are expressed in cerebral arteries and microvessels, indicating that both circulating and locally formed Angiotensin II may modulate cerebral blood flow (Zhou *et al.*, 2005). The mechanisms of regulation of cerebrovascular autoregulation by Angiotensin II, however, are complex and depend on the conditions of the experiments (Saavedra and Nishimura, 1999).

3. Enhanced cerebrovascular Angiotensin II function is associated with cerebrovascular remodeling and inflammation, loss of compliance and vulnerability to brain ischemia and stroke

SHR and other rodent models of hypertension express higher levels of Angiotensin II AT₁ receptors in brain and cerebral arteries (Saavedra *et al.*, 1986; Gutkind *et al.*, 1988; Zhou *et al.*, 2006) in association with hypertension, cerebrovascular remodeling, and with a marked autoregulatory shift towards higher blood pressures. The result is that the brain circulation in hypertension is more sensitive to decreases in perfusion pressure, and this leads to enhanced vulnerability to brain ischemia (Edvinsson *et al.*, 1993). These alterations are similar to those found in human essential hypertension (Nishimura *et al.*, 2000b). A potentially dangerous role of Angiotensin II has been postulated, because Angiotensin II may aggravate stroke by vasoconstriction (Werner *et al.*, 1991). In addition, adult SHR present a conspicuous cerebrovascular inflammation, a trademark of genetic hypertension, and enhanced cerebrovascular endothelial AT₁ receptor expression, indicative of excess local Angiotensin II function (Yamakawa *et al.*, 2003; Ando *et al.*, 2004; Zhou *et al.*, 2005). Cerebrovascular inflammation contributes, together with cerebrovascular remodeling, to the loss of compliance and vulnerability to brain ischemia characteristic of animal and human hypertension.

4. Decreased Angiotensin II formation or AT₁ receptor blockade normalizes cerebrovascular remodeling and autoregulation in hypertension, prevents and reverses

cerebrovascular inflammation, reduces vulnerability to brain ischemia, and protects from stroke

Demonstration of causality was obtained after decreasing Angiotensin II formation or following Angiotensin II AT₁ receptor blockade in hypertensive rodent models. ACE inhibition, by decreasing Angiotensin II formation, reduces remodeling and vasoconstriction and shifts autoregulation towards lower blood pressures, ameliorating vulnerability to brain ischemia, decreasing the magnitude of the blood-brain barrier breakdown, reducing the extent of brain edema, improving neurological outcome after ischemia and decreasing mortality (Hajdu et al., 1991; Nag and Kilty, 1997). These effects occur in models of hypertension not dependent on the circulating Angiotensin II system, highlighting the major role of the local cerebrovascular Angiotensin II system (Zhou et al., 2005; Gutkind et al., 1988). A similar protective effect has been demonstrated when ACE inhibitors were given chronically to normotensive rats, decreasing the age-related vulnerability to stroke (Lartaud et al., 1994). The effects of ACE inhibitors in humans are similar to those in hypertensive animals, reducing hypertension while protecting cerebral blood flow and reducing ischemia (Dyker *et al.*, 1997).

Administration of ARBs restores cerebrovascular autoregulatory mechanisms in hypertensive rats, facilitating vasodilation when perfusion pressure is reduced, and this protective effect is similar to that obtained after treatment with ACE inhibitors (Vraamark *et al.*, 1995; Saavedra and Nishimura, 1999). Chronic treatment with ARBs antagonists protects against stroke in stroke-prone SHR rats even at low doses not significantly affecting blood pressure (Sironi et al., 2004) (Figure 5). The protective effect is the result of a reversal of cerebrovascular remodeling and restoration of compliance and autoregulation, decreasing the loss of cerebral blood flow, and reducing the area of neuronal necrosis (Nishimura et al., 2000b; Ito et al., 2002) (Figure 5).

Pretreatment with candesartan reverses the cerebrovascular inflammatory reaction, as revealed by decreased macrophage infiltration to the brain parenchyma and reduction of the cerebrovascular production of pro-inflammatory factors (Yamakawa et al., 2003; Ando et al., 2004; Zhou et al., 2005) (Figure 5). This cerebrovascular anti-inflammatory effect contributes to the restoration of cerebrovascular compliance and the reduction in brain ischemia in SHR treated with ARBs (Yamakawa et al., 2003; Ando et al., 2004; Zhou et al., 2005) (Figure 5). The anti-inflammatory effects of ARBs during brain ischemia, stroke and cerebrovascular hemorrhage has been confirmed (Sironi et al., 2004; Hallevi et al., 2007; Jung et al., 2007; Ozacmak et al., 2007).

5. AT₁ receptor blockade prevents blood brain barrier breakdown

Angiotensin II is an important factor contributing to the regulation of blood-brain barrier function, through activation of AT₁ receptors highly expressed in cerebrovascular endothelial cells (Zhou et al., 2006; Fleegal-DeMotta et al., 2009). AT₁ receptor blockade prevents Angiotensin II-induced pathological increase in blood-brain barrier permeability (Fleegal-DeMotta et al., 2009). Prevention of blood-brain barrier breakdown by treatment with ARBs may be important for the treatment of hypertensive encephalopathy (Fleegal-DeMotta et al., 2009). In addition, the integrity of the blood-brain barrier is compromised in a large number of brain disorders, including autoimmune diseases such as multiple sclerosis (Wosik et al., 2007; Alvarez et al., 2010; Axtell and Steinman, 2009). The property of ARBs to prevent blood-brain barrier breakdown may be an important factor in their reduction of cerebrovascular inflammation and infiltration of macrophages into the cerebral parenchyma, characteristic of genetic hypertension (Yamakawa et al., 2003; Ando et al., 2004; Zhou et al., 2005) (Figure 5). Reduction of blood-brain barrier breakdown may also be an important

protective mechanism contributing to an explanation of the therapeutic effect of ARBs in experimental autoimmune encephalomyelitis (Platten et al., 2009; Lanz et al., 2010).

8. Blockade of Angiotensin II AT₁ receptors ameliorates brain inflammation

Angiotensin II is a well-known pro-inflammatory factor in peripheral tissues, sharing signal transduction pathways with other inflammatory stimuli (Savoia and Schiffrin, 2007) and the anti-inflammatory effects of ARBs in hypertension and diabetes are well established (Savoia and Schiffrin, 2007). However, the reversal of chronic cerebrovascular brain inflammation in SHR, of stroke-induced brain inflammation, and the prevention of stress-induced gastric inflammation described earlier are independent of the blood pressure reducing actions of ARBs (Bregonzio et al., 2003; Yamakawa et al., 2003; Ando et al., 2004; Zhou et al., 2005; Hallevi et al., 2007).

Inflammatory conditions of the brain not related to hypertension may also be, in part, the result of excessive brain AT₁ receptor activation. This being the case, perhaps the anti-inflammatory effects of ARBs may be of a more general nature. While brain inflammatory reaction is essential to restore homeostasis in response to infection, exaggerated responses may lead to chronic inflammation and neuronal damage (Dantzer et al., 2008).

1. The endotoxin model

A well-characterized experimental model of inflammation is the systemic administration of the bacterial endotoxin lipopolysaccharide (LPS) to normotensive rats (Quan and Banks, 2007) representing pathogen invasion of the organism. Systemic LPS administration initiates a peripheral inflammatory reaction, the innate immune response (Quan and Banks, 2007), and the brain is rapidly involved with additional inflammatory reactions. This is a model of major relevance for the study of psychiatric disorders, because the inflammatory response of the brain is associated with sickness behavior including anorexia, and it is followed by characteristic depressive-like responses in rodents (Dantzer et al., 2008; Dantzer, 2009).

ARB administration reduces the LPS-induced peripheral and brain inflammation

The ARB candesartan markedly reduces, in normotensive rats, LPS inflammatory effects in macrophage-rich tissues such as the spleen, in the adrenal gland and in the pituitary gland. The ARB also significantly decreases the excessive production of pro-inflammatory cytokines and aldosterone and their release to the circulation (Sánchez-Lemus et al., 2008; 2009a; 2009b) (Figure 6). Conversely, the ARB does not reduce the LPS-induced release of corticosterone, a glucocorticoid with major anti-inflammatory effects (Sánchez-Lemus et al., 2009b). This indicates that the overall peripheral effect of ARB pretreatment is to shift the balance in favor of anti-inflammatory factors in the circulation during the initial phase of the inflammatory response.

Pretreatment with candesartan also reduces the inflammatory reaction in the brain, as revealed by decreased production of cytokines and other inflammatory factors in the brain cortex (Benicky et al., 2009) (Figure 6). Stimulation of inflammatory cascades in the brain is followed by activation of microglia, the central resident immune cells (Henry et al., 2009), with induction of additional inflammatory cascades and resulting, if not controlled, in glial and neuronal damage (Henry et al., 2009). Treatment with the ARB significantly reduces the LPS-induced microglia activation in the cortex (Benicky et al., 2009) (Figure 6). Our demonstration of the capacity of the ARB to reduce microglia activation *in vivo* is supported by a recent report of inhibition of inflammation-induced activation of cultured microglia by the ARB losartan (Miyoshi et al., 2008).

ARBs diminishes LPS-induced brain inflammation by several mechanisms. First, ARBs reduce the LPS--induced peripheral innate immune response, limiting the enhanced production of multiple inflammatory factors, such as pro-inflammatory cytokines, prostaglandin E₂ (PGE₂) and aldosterone, and their release to the systemic circulation (Sánchez-Lemus et al. 2008) (Figure 7). This reduces the effect of circulating inflammatory factors in their brain targets, endothelial cells in the circumventricular organs, the choroid plexus and the cerebral vasculature. As a consequence, the activation of pro-inflammatory transcription factors such as nuclear factor κ B (NF- κ B) and activator protein-1 (AP-1) is also reduced (Figure 7). In turn, this limits the stimulation of inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2) and NADPH oxidase (Nox), and the overproduction of inflammatory nitric oxide (NO), PGE₂, and reactive oxygen species (ROS) (Figure 7). Second, the ARBs protect the blood brain barrier from inflammatory breakdown and limit the increase in production of adhesion molecules, reducing macrophage infiltration into the brain parenchyma (Ando et al., 2004) (Figure 7). Third, the ARBs block the direct pro-inflammatory effects of AT₁ receptor stimulation in cerebrovascular endothelial cells (Figure 7). Systemically produced LPS reaches the target brain microvascular endothelial cells where it is recognized by CD14, and complexes with its receptor, TLR4, initiating additional inflammatory cascades (Licinio and Wong, 1997; Singh and Jiang, 2004) (Figure 7). Interference with the direct effects of LPS in its target cells may be an additional mechanism responsible for the anti-inflammatory effects of ARBs (Figure 7). The limitation of the LPS-induced inflammation in its target cells and of the inflammation-induced macrophage infiltration as a result of ARB administration leads to major reductions in inflammatory cascades (Figure 7), decreased astrocytes and microglia activation, and neuroprotection (Figure 7).

3. Therapeutic effect of ARBs in autoimmune diseases of the brain

Blood-brain barrier breakdown and sustained, uncontrolled inflammation associated with T lymphocyte recruitment into the brain parenchyma are characteristic of autoimmune diseases of the brain such as multiple sclerosis (Alvarez et al., 2010; Axtell and Steinman, 2009; Schulze-Topphoff et al., 2009; Platten et al., 2009; Bhat and Steinman, 2009; Lanz et al., 2010). Upregulation of the brain RAS has been recently demonstrated in an animal model of multiple sclerosis, the experimental autoimmune encephalomyelitis (Platten et al., 2009). In this model, ARBs reduced infiltration of inflammatory TH1 and TH17 cells and ameliorated paralysis (Platten et al., 2009; Lanz et al., 2010). These findings indicate that ARBs may be therapeutically beneficial in autoimmune diseases of the brain.

4. Are ARBs protective in most, if not all, inflammatory conditions of the brain?

Evidence continues to accumulate to suggest that ARBs may protect the brain from additional types of injury resulting in parenchyma inflammation and neuronal damage. For example, ARBs have been reported to prevent dopaminergic neuronal death during brain inflammation (Mertens et al., 2010) and to reduce irradiation-induced inflammation (Robbins et al., 2009; Jenrow et al., 2010).

9. Blockade of Angiotensin II AT₁ receptors increases lifespan

From the above, it is not surprising that life-long oral administration of ARBs increases the lifespan of genetically hypertensive rats (Linz et al., 2000; Baiardi et al., 2004). This is the result of the protection of cardiac function (Linz et al., 2000), life-long anti-stress effects, including the blockade of isolation-induced sympathetic and HPA axis stimulation (Baiardi et al., 2004) and neuroprotective effects as described above.

10. Cellular targets for the therapeutic effects of ARBs in the brain

ARBs influence the response of the brain to systemic inflammation indirectly by regulating the production of circulating pro-inflammatory and anti-inflammatory cytokines and hormones with effects in the brain (Sánchez-Lemus et al., 2008; 2009a; 2009b).

In addition, ARBs directly act on multiple brain targets. Cerebrovascular endothelial cells of the blood-brain barrier express large numbers of AT₁ receptors and a complete RAS (Zhou et al., 2006), and are confirmed targets for the anti-inflammatory and neuroprotective effects of ARBs (Yamakawa et al., 2003; Ando et al., 2004; Zhou et al., 2005; Liu et al., 2006; Fleegal-DeMota et al., 2009). Inhibition of pro-inflammatory cascades in endothelial cells, and reduction of inflammation-induced macrophage and T-cell infiltration indirectly reduce microglial activation and cellular damage in the brain parenchyma (Figure 7). Large numbers of AT₁ receptors are also expressed in the endothelial cells and neurons of the circumventricular organs located outside the blood-brain barrier (Tsutsumi and Saavedra, 1991). These receptors respond to influences arriving both from the circulation and from the brain parenchyma, and they are the neuroanatomical connection between the circulating and brain RAS (Saavedra, 1992).

Direct blockade of AT₁ receptors in target cells within the brain parenchyma also play a major role. Neuronal AT₁ receptors are selectively localized in many brain areas located inside the blood-brain barrier (Jöhren and Saavedra, 1996; Mendelsohn et al., 1984). AT₁ receptors have been clearly identified, within the brain and spinal cord parenchyma, not only in neurons but also in astrocytes and resident microglia (Pavel et al., 2008; Imboden et al., 2009; Tang et al., 2009; Lanz et al., 2010; Wosik et al., 2007). Enhanced AT₁ expression in brain neurons has been described, both *in vivo* and *in vitro*, in rodent models of genetic hypertension (Saavedra et al., 1986; Yang and Raizada, 1998). More recently, enhanced AT₁ receptor expression has been reported in brain lesions of patients suffering from multiple sclerosis (Platten et al., 2009). A complete RAS has been described in cultured microglia, and ARBs reduce LPS-induced inflammation in these cells (Miyoshi et al., 2008). Since ARBs have been shown to cross the blood-brain barrier and to inhibit neuronal AT₁ receptors not accessible to circulating Angiotensin II (Nishimura et al., 2000a), it is likely that inhibition of AT₁ receptors located in neurons, microglia and astrocytes play a significant role in the anti-inflammatory effects of ARBs.

11. Clinical evidence of the therapeutic properties of ARBs in brain disorders

The translational value of the pre-clinical experiments described here is increasingly supported by clinical evidence. Studies in humans indicate that ARBs are very well tolerated, with infrequent and mild side effects (Table 1). A recent study of patients suffering from renal failure demonstrates that the ARB candesartan protects from end-organ damage more effectively when used at doses ten-fold higher than those indicated for the treatment of high blood pressure and producing complete AT₁ receptor blockade (Burguess et al., 2009). This finding may be interpreted both as a demonstration of a good margin of safety and as indirect evidence of additional effects of ARBs beyond their AT₁ receptor blocking capacity.

Most of the earlier studies relate to the effect of ARBs on the incidence and severity of stroke in patients treated for hypertension (Table 1). Controlling excessive systolic blood pressure is the basis to reduce stroke incidence and severity, and this has been established beyond doubt. The question raised in the studies listed here (Table 1) was whether or not the use of ARBs offered additional advantages when compared to other anti-hypertensive

medications of similar potency. Most of the evidence appears to support the initial hypothesis suggesting that treatment with ARBs prevented and ameliorated stroke to a greater degree than other anti-hypertensives (Table 1). In addition, several studies indicated that the protective effect of ARBs in the brain was in part the consequence of actions of these compounds beyond their effects on blood pressure (Fogari and Zoppi, 2004; Devereux and Dahlöf, 2007). This being the case, we may postulate that the central anti-inflammatory effects of the ARBs may play a significant role.

More recently, several clinical trials reported protective effects of ARBs on cognition, both in hypertensives and in the elderly (Table 1). In particular, some studies demonstrated that, in patients treated for hypertension with ARBs, the incidence and later development of Alzheimer's disease was very significantly reduced (Table 1) (Li et al, 2010). The therapeutic effect of ARBs was clearly superior to that of other anti-hypertensive medications, another indication of therapeutic effects beyond AT₁ receptor blockade (Li et al., 2010). If these reports are confirmed, they will represent the first major advance in the treatment of cognitive deficits, a finding of great medical and economic impact.

Other studies are very suggestive of improvement in the quality of life, including medication side effects, depression and sexual function during ARB treatment (Weber 2005) (Table 1), and one study (Pavlatou et al., 2008) reported major anti-depressant effects of candesartan in patients affected by diabetes. On the other hand, the treatment of psychiatric conditions has not been a specific focus of clinical trials with ARBs, and it is hoped that future studies will address this most important avenue. To this date there are no published studies on the effect of ARB treatment in autoimmune diseases or neurodegenerative diseases other than Alzheimer's disease.

12. Conclusions

Brain Angiotensin II, through AT₁ receptor stimulation, is a master regulator of the cerebral circulation and of the central response to stress and inflammation. Excessive AT₁ receptor stimulation contributes to determine the extent of allostatic load. Inhibition of brain AT₁ receptor activity may be achieved with the use of orally administered ARBs, of tested efficacy in the treatment of cardiovascular disease and a good margin of safety. ARB treatment is neuroprotective: reduces brain ischemia, stress-related disorders and brain inflammation, and increases the lifespan. Preclinical data in rodent models has translational value, as indicated by increasing evidence of beneficial effects of ARBs in brain disorders, such as recent reports of significant decrease in stroke, protection of cognition, and amelioration of Alzheimer's disease, depression and stress. The anti-ischemic, anti-stress and anti-inflammatory effects of ARBs indicate that these compounds may be considered as contributors to the therapy of a wide range of conditions, including mood disorders and neurodegenerative diseases of the brain. It is hoped that in the near future ARBs will be tested, in controlled and carefully designed clinical trials, for the therapy of neurological and psychiatric disorders.

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Figure 1. Mechanisms of neuronal injury leading to neuropsychiatric disease

Environmental and genetic factors interact, leading to failure of compensatory mechanisms of different degrees and with diverse localizations within the brain. The increased allostatic load to the brain translates into pathological reactivity to stress, uncontrolled inflammation and alterations in blood flow, resulting in variable degrees of neuronal dysfunction and injury. Particular combinations of alterations and their localization within the brain may affect many or selective regulatory systems. The initiation, development and combinations of particular affective, psychotic, stress-related, cognitive, and neurodegenerative diseases of the brain is dependent on the individual vulnerability, the combination of pathological factors involved, the localization of the neuronal injury, and the regulatory mechanisms affected.

Figure 2. The Renin-Angiotensin System and the regulatory functions of Angiotensin II AT₁ receptors in the brain

Angiotensin II is the main active principle of the RAS, physiologically stimulating the AT₁ receptor type. In the brain, Angiotensin II is a multitasking regulatory factor, involved in the regulation of stress, the autonomic and hormone systems, the circulation, and the response of the brain to endogenous and peripheral inflammation. The RAS is far more complex than originally described, and there are multiple associated and interactive synthetic and metabolic pathways, active molecules and receptors. The RAS does not function in isolation, but it is tightly related to associate regulatory systems in the brain. Decreased RAS activity may be achieved by blockade of Angiotensin II formation with Angiotensin Converting Enzyme (ACE) inhibitors or with Angiotensin II AT₁ receptor blockers (ARBs).

Figure 3. The sartan molecular structures

Candesartan and other sartans (irbesartan, valsartan, olmesartan, losartan) are imidazole derivatives containing a biphenyl-tetrazole group. Telmisartan is unique, since it does not contain the tetrazole group. In addition to AT_1 receptor blockade, telmisartan and to a lesser extent candesartan possess $PPAR_\gamma$ agonist activity, a property likely to represent additional therapeutic benefit. The presence of non-Angiotensin II binding sites for some sartans has been documented but their relevance has not been clarified.

Figure 4. ARBs protect from stress and reduce anxiety?

Candesartan reduces the central sympathetic response to stress. **A:** Bars represent tyrosine hydroxylase mRNA expression. Open bar: isolation stress; closed bar: isolation pretreated with candesartan. * $P < 0.01$. Isolation stress increases tyrosine hydroxylase transcription in the rat locus coeruleus and this is prevented by candesartan pretreatment. *Candesartan prevents a stress-induced disorder.* **B:** Figures represent H&E staining of gastric mucosa. Left: rat submitted to acute cold-restraint stress; right: cold-restraint pretreated with candesartan. Acute cold-restraint stress produces multiple gastric ulcers in the rat and this is prevented by pretreatment with candesartan. *Candesartan reduces anxiety.* **C:** Bars represent time spent on the open arm of a plus maze. Open bar: vehicle-treated rat. Closed bar: rat pretreated with candesartan. Rats placed in an elevated plus maze spend increased time in the open arm, a sign of decreased anxiety, when pre treated with candesartan. Modified from Bregonzio et al., 2008 (A), Bregonzio et al., 2003 (B) and Saavedra et al., 2006 (C).

Figure 5. ARBs reverse cerebrovascular remodeling and inflammation and reduce ischemia and stroke in SHR

Candesartan reverses cerebrovascular remodeling. A: Figures are H&E images of middle cerebral artery in untreated SHR (left) and after candesartan treatment (right). Chronic hypertension in SHR leads to cerebrovascular remodeling with increased medial thickness and decreases compliance. Candesartan reverses remodeling and arterial stiffness, restoring compliance to changes in blood pressure and protecting from ischemia. This reverses the cerebrovascular stiffness and decreased compliance to changes in blood pressure.

Candesartan reverses chronic cerebrovascular inflammation in hypertension. B: Immunostaining with macrophage-microglia specific ED-1 antibody. Figure on the left reveals macrophage infiltration in a microvessel located in the cerebral cortex of an SHR, reversed by treatment with candesartan (figure on the right). Candesartan reduces brain ischemia and stroke volume. C: Candesartan decreases experimental stroke as a consequence of permanent ligation of a branch of the middle cerebral artery in SHR. Figure on the left: untreated SHR, section visualized with the 2, 3, 5-triphenyltetrazolium chloride method to determine volume of tissue damage. Figure on the right: decreased stroke volume in SHR pretreated with candesartan. Modified from Ando et al., 2004 (A and B) and Nishimura et al., 2000 (C).

Figure 6. ARBs decrease peripheral and brain inflammation produced by systemic administration of bacterial endotoxin

Candesartan reduces peripheral inflammation produced by LPS. A: Bars represent the concentration of plasma aldosterone (left figure) and plasma IL-6 (right figure). Open bars: rats injected with LPS; closed bars: pretreatment with candesartan and injected with LPS. * $P < 0.01$. Candesartan reduces the LPS-induced increase in circulating pro-inflammatory aldosterone and IL-6. Candesartan reduces brain parenchymal inflammation. B: Bars represent mRNA expression of iNOS and IL-1 β in the cerebral cortex. Open bars: rats injected with LPS; closed bars: pretreatment with candesartan and injected with LPS. * $P < 0.01$. *Candesartan decreases microglia activation*. C: Figures represent microglia in cerebral cortex of rats injected with LPS (left figure) and pretreated with candesartan and injected with LPS (right figure). Microglia were stained with OX-42 antibody. (Modified from Sánchez-Lemus et al., 2009b) (A) and Benicky et al., 2009 (B and C).

Figure 7. Proposed role of Angiotensin II AT₁ receptors in bacterial endotoxin-induced brain inflammation

Systemic administration of LPS increases circulating inflammatory factors targeting cerebrovascular endothelial cells, followed by activation of pro-inflammatory transcription factors such as NF-κB and AP-1. This leads to activation of inflammatory cascades with production and release of inflammatory factors into the brain parenchyma. Circulating macrophages infiltrate the brain parenchyma as a consequence of blood-brain barrier breakdown and upregulation of adhesion molecules, provoking a further enhancement of inflammatory cascades. Excess pro-inflammatory factors activate resident microglia and astrocytes with additional increase of inflammatory signals. Unregulated inflammation leads to neuronal injury and brain disease.

The neuroprotective effect of ARBs is the consequence of the reduction of circulating inflammatory factors, blockade of pro-inflammatory AT₁ receptors in cerebrovascular endothelial cells, protection of the blood-brain barrier and reduction of macrophage infiltration. Additional neuroprotective effects may result from AT₁ receptor blockade in parenchymal microglia, astrocytes and neurons.

AP-1: activator protein 1. COX-2: cyclooxygenase-2. EP2/4: prostaglandin E receptors 2/4. iNOS: inducible nitric oxide synthase. MR: mineralocorticoid receptor. NF-κB: nuclear factor κB. NO: nitric oxide. Nox: NADPH oxidase. PGE₂: prostaglandin E₂. ROS: reactive oxygen species. TLR4: toll-like receptor 4.

Table 1

Clinical studies on the effect of ARBs on brain disorders.

Authors	Type of study	Diagnosis	ARB	Major findings
Anderson, 2010	editorial	Hypertension, stroke	multiple	Neuroprotection
Matsumoto et al., 2010	open trial	Stroke	Olmesartan	Protects from stroke
Hong et al., 2010	double-blind	Stroke	Losartan	Protects from stroke
Lüders, 2007	review	Stroke	multiple	Protects from stroke
Devereux and Dahlöf, 2007	review	Stroke	Losartan	Protects from stroke
Chrysant, 2006	review	Hypertension, stroke	multiple	Protects from stroke
Schrader et al., 2005	prospective randomized	Stroke	Eprosartan	Protects from stroke
Oku et al., 2005	open trial	Hypertension	Losartan	Preserves cerebrovascular flow
Li et al., 2010	prospective cohort	Hypertension, Alzheimer's	multiple	Protects cognition, reduces incidence of Alzheimer's
Fournier et al., 2009	review	Stroke, dementia	multiple	Protects cognition
Saxby et al., 2008	double-blind, randomized	Hypertension, elderly	Candesartan	Protects cognition
Schrader et al., 2007	review	Stroke	multiple	Protects cognition
Trenkwalder 2006	double-blind	Stroke, elderly	Candesartan	Protects cognition
Zanchetti and Elmfeldt 2006	prospective, randomized, double-blind	Hypertension, elderly	Candesartan	Protects cognition, improves quality of life, reduces anxiety
Fogari and Zoppi, 2004	review	Elderly	multiple	Protects cognition, improves quality of life and sexual activity
Weber, 2005	review	Hypertension	multiple	Improves quality of life; few side effects
Pavlatou et al., 2008	open trial	Diabetes	Candesartan	Anti-depressant, anti-stress
Julius et al., 2006	randomized	Prehypertension	Candesartan	Reduced occurrence of hypertension; well tolerated, no psychiatric disorders, no anxiety
Chaturvedi et al., 2008	randomized	Diabetes	Candesartan	reduced incidence of retinopathy, no adverse effects
Palma-Gámiz et al., 2006	Randomized, double-blind	Hypertension	Candesartan	well-tolerated