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Angiotensin II AT₁ receptor blockers as treatments for inflammatory brain disorders

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Abstract

The effects of brain AngII (angiotensin II) depend on AT₁ receptor (AngII type 1 receptor) stimulation and include regulation of cerebrovascular flow, autonomic and hormonal systems, stress, innate immune response and behaviour. Excessive brain AT₁ receptor activity associates with hypertension and heart failure, brain ischaemia, abnormal stress responses, blood–brain barrier breakdown and inflammation. These are risk factors leading to neuronal injury, the incidence and progression of neurodegenerative, mood and traumatic brain disorders, and cognitive decline. In rodents, ARBs (AT₁ receptor blockers) ameliorate stress-induced disorders, anxiety and depression, protect cerebral blood flow during stroke, decrease brain inflammation and amyloid- β neurotoxicity and reduce traumatic brain injury. Direct anti-inflammatory protective effects, demonstrated in cultured microglia, cerebrovascular endothelial cells, neurons and human circulating monocytes, may result not only in AT₁ receptor blockade, but also from PPAR γ (peroxisome-proliferator-activated receptor γ) stimulation. Controlled clinical studies indicate that ARBs protect cognition after stroke and during aging, and cohort analyses reveal that these compounds significantly reduce the incidence and progression of Alzheimer's disease. ARBs are commonly used for the therapy of hypertension, diabetes and stroke, but have not been studied in the context of neurodegenerative, mood or traumatic brain disorders, conditions lacking effective therapy. These compounds are well-tolerated pleiotropic neuroprotective agents with additional beneficial cardiovascular and metabolic profiles, and their use in central nervous system disorders offers a novel therapeutic approach of immediate translational value. ARBs should be tested for the prevention and therapy of neurodegenerative disorders, in particular Alzheimer's disease, affective disorders, such as co-morbid cardiovascular disease and depression, and traumatic brain injury.

Keywords

angiotensin II type 1 receptor blocker (ARB); brain; inflammation; neuronal injury; renin–angiotensin system

INTRODUCTION

ARBs {AT₁ [AngII (angiotensin II) type 1] receptor blockers} have significant potential for treating conditions of high prevalence and without adequate treatment, such as mood, neurodegenerative and traumatic disorders of the brain [1–3]. Despite the huge burden of disease, we currently have no effective and safe way to protect neuronal tissue [4]. Therapeutic failures are the result of highly complex and poorly understood aetiology. For

this reason, there is a need to find safe and effective central neuroprotective drugs with pleiotropic beneficial effects.

ARBs are known to control excessive activation of AT₁ receptors, which has been associated, in peripheral tissues, with increased blood pressure, vascular inflammation and reduced sensitivity to insulin. For these reasons, these well-tolerated compounds are widely prescribed for the treatment of hypertension, stroke, diabetes and the metabolic syndrome [5–9].

Compounds with benefits in cardiovascular conditions may be also considered for the treatment of brain conditions, because cardiovascular disease affects not only the peripheral organs, but also the brain, which goes far to explain the high co-morbidity of cardiovascular, mood and neurodegenerative disorders [10–12]. Furthermore, brain and peripheral tissues share evolutionarily conserved regulatory and pathogenic mechanisms that may be of direct importance for the incidence and development of brain disease [13,14].

The aim of the present review is to summarize the current evidence of the ability of ARBs to control unwanted brain inflammatory and stress processes, and to protect cerebral blood flow. It focuses on the roles of brain AT₁ receptors, the consequences of increased brain AT₁ receptor activation and brain AT₁ receptor blockade, and the translational value resulting from these findings as they relate to the prevention and treatment of brain disease. Evidence from pre-clinical studies, plus the highly suggestive evidence from clinical observations, is sufficient to justify testing ARBs in the treatment of brain disorders: a promising, safe and novel approach of great potential value.

RISK FACTORS AND THE MECHANISMS OF BRAIN DISEASE

Risk factors for brain disease are many, interact at multiple levels in the context of varying degrees of genetic vulnerability, and their impact increases with age (Figure 1). Major risk factors include hypertension, diabetes and the metabolic syndrome, obesity, and peripheral and brain inflammation [1,4,10,15–18]. These factors, alone or in combination, increase allostatic load and may lead to a loss of homeostasis and, depending on their severity and chronicity, cell dysfunction and injury [6,19] (Figure 1).

Common mechanisms resulting in loss of homeostasis and leading to brain disorders include the inability to regulate physiological inflammatory responses that result in excessive unregulated inflammation [15,20], alterations in blood flow that lead to brain ischaemia [21,22] and failure to adapt to chronic or severe stress [23] (Figure 1). Depending on the context and genetic factors of vulnerability, these interacting processes contribute to the development of different constellations of symptoms that include alterations in behaviour, a progressive loss of cognition and reduced neurological performance. Specific combinations of pathological processes characterize not only mood and neurodegenerative conditions (including major depression, and Alzheimer's and Parkinson's disease), TBI (traumatic brain injury) and autoimmune disorders, such as multiple sclerosis, but also the normal aging process [17,19] (Figure 1).

Excessive brain inflammation is increasingly recognized as a common and major factor participating in brain disease (Figure 1). Uncontrolled, excessive and chronic inflammation injures neurons and contributes to the incidence and progression of brain ischaemia, mood and neurodegenerative disorders, and stress-induced disease. [4,12,15,17,19,24–28]. Consequently, the present review will highlight the pathogenic role of brain inflammation and the novel therapeutic proposal to ameliorate inflammatory processes of the brain.

ROLE OF BRAIN INFLAMMATION

Inflammation is a general name for the host defence against foreign or altered endogenous substances. In particular, brain inflammation may be defined as the contribution of the brain to the general inflammatory defence mechanism [29]. Two major processes may result in brain inflammation: peripheral infection and direct cell injury as a consequence of metabolic alterations within the brain parenchyma.

Effects of peripheral inflammation on the brain

When challenged by peripheral or central bacterial or viral infection, the brain responds with adaptive inflammation, either pathogen-specific or as part of a generalized innate immune response, intended to neutralize neurotoxins and to remove the damaging organisms [15,19].

A commonly used experimental model to study the effects of peripheral inflammation in the brain is the systemic administration of the Gram-negative bacterial endotoxin LPS (lipopolysaccharide). LPS is a classical example of the PAMPs (pathogen-associated molecular patterns), recognized by the organism as produced by invading pathogens. Systemic administration of LPS mimics the effects of peripheral infection and is associated with brain inflammation [15,30].

Peripheral inflammation may affect the brain through several distinct processes, including increased circulating pro-inflammatory factors and pathogen toxins, blood–brain barrier breakdown and macrophage infiltration of the brain parenchyma (Figure 2).

One well-characterized mechanism is the excessive production of pro-inflammatory factors reaching the general circulation and affecting the brain (Figure 2). Systemic administration of LPS produces a generalized peripheral inflammatory response directly proportional to the amount and toxic potential of the endotoxin. LPS directly stimulates macrophages in multiple organs and endothelial target cells throughout the vasculature. These are target cells expressing the LPS recognition molecule CD14 and the LPS receptor TLR4 (Toll-like receptor 4) [15,29,31]. Stimulation of TLR4 by LPS activates multiple well-characterized intracellular pro-inflammatory signal transduction mechanisms. This leads to the activation of pro-inflammatory transcription factors, including, but not limited to, NF- κ B (nuclear factor κ B) and AP-1 (activator protein-1). iNOS (inducible NO synthase) and COX-2 (cyclo-oxygenase-2) activities are up-regulated, with an increased production of pro-inflammatory NO and PGE₂ (prostaglandin E₂). There is increased NADPH oxidase activity and the production of damaging ROS (reactive oxygen species) and excessive formation of pro-inflammatory cytokines [32]. Pro-inflammatory factors, including but not limited to IL (interleukin)-1 β , TNF (tumour necrosis factor)- α and IL-6 are released in large numbers into the systemic circulation, reach the brain and activate cerebrovascular endothelial cells expressing cytokine receptors. [15,29]. In turn, pro-inflammatory cytokines induce COX-2 and PGE₂ production in endothelial and perivascular cells. PGE₂ crosses the blood–brain barrier to further enhance parenchymal inflammation and HPA (hypothalamic–pituitary–adrenal) stimulation [29].

The role of circulating pro-inflammatory cytokines is not limited to their increased production following peripheral bacterial infection. There are many inflammatory scenarios, including, but not limited to, depression, heart failure and TBI, when circulating pro-inflammatory factors themselves, and in particular TNF- α and IL-1 β , exert significant effects in the brain. These effects are mediated through the stimulation of specific receptors in cerebrovascular endothelial cells, circumventricular organs and perivascular macrophages, and include fever and activation of the HPA axis and the central sympathetic system [1,6,10,15,29].

The role of circulating aldosterone is of particular importance. Systemic LPS administration stimulates, in the adrenal cortex, aldosterone production and release into the general circulation [33] (Figure 2). Aldosterone is not only a stress hormone, but also a major pro-inflammatory factor in peripheral tissues and in the brain [34]. Excessive circulating aldosterone activates canonical intracellular and membrane MRs (mineralocorticoid receptors) located in the peripheral vasculature, further enhancing the production and release of pro-inflammatory cytokines [35–37]. In addition, the pro-inflammatory effects of circulating aldosterone may be in part the result of direct activation of brain parenchymal cells [35–37]. As a consequence, aldosterone is a major contributor to peripheral and brain inflammatory processes [35–37].

A second process leading to brain inflammation is the direct effect of circulating LPS in the brain, the result of TLR4 stimulation in target cells, including cerebrovascular endothelial cells in brain capillaries (Figure 2) and in the circumventricular organs. Since LPS is unable to cross the blood–brain barrier [38], direct LPS effects in the brain are limited to its effects on the circumventricular organs, devoid of the blood–brain barrier [39], or to the activation of cerebrovascular endothelial cells.

The combined effects of excessive amounts of circulating pro-inflammatory factors, aldosterone and LPS injure cerebrovascular endothelial cells and induce intracellular pro-inflammatory cascades (Figure 2). As a consequence, large amounts of pro-inflammatory factors are released into the brain parenchyma, where they activate and may alter the function of astrocytes and resident microglia, the central resident immune cells [40] (Figure 2).

When overactivated, microglia initiate further inflammatory cascades, releasing excessive levels of IL-1 β and other cytotoxic factors to the brain parenchyma and contributing, depending on the severity of the inflammation, to alterations in neuronal function or even to neuronal injury and death [15,29] (Figure 2). Astrocyte-dependent mechanisms contribute to sustain inflammation and participate in neuronal dysfunction and damage [41–43] (Figure 2).

There is an additional process leading to brain injury, namely the decrease in the functionality of the blood–brain barrier. The blood–brain barrier, formed by capillary endothelial cells, is organized to protect the brain from circulating toxins and pathogens. Inflammatory activation and injury of the cerebrovascular endothelial cells leads to blood–brain barrier breakdown and the up-regulation of adhesion molecules in endothelial cells, in turn favouring macrophage and T-cell infiltration into the brain (Figure 2), further enhancing parenchymal inflammation and affecting neurons [15,29]. There is an extensive capillary network within the brain. In the human brain, the capillary surface area is approximately 20 m²/1.3 kg of brain, and neuronal cell bodies are typically not more than 10 μ m from the nearest capillary [44]. This clarifies how inflammation-induced endothelial cell dysfunction leads to an inflammatory process extending throughout the brain parenchyma [45]. Vascularization is very high in the hypothalamic PVN (paraventricular nucleus) [46], explaining how the PVN is a prime target for circulating pro-inflammatory factors and LPS [29]. Thus alterations in neuronal function may result from a combination of direct effects of inflammatory factors produced in and released from cerebrovascular endothelial cells, infiltrating macrophages, activated resident microglia and astrocytes.

Additionally, peripheral inflammation activates a neural pathway reaching the brain during inflammation of peripheral origin. A bidirectional communication allows the autonomic nervous system to contribute to regulate immune function and to receive inflammatory signals originated in the periphery and transmitted to the brain through sensory and

autonomic neuronal inputs [47]. In the case of visceral inflammation, the vagal nerve plays a most important role [30,47]. Vagal denervation prevents central responses to visceral inflammation [48], while not affecting the inflammation-induced increase in circulating pro-inflammatory factors [49]. Conversely, vagal efferent stimulation reduces peripheral cytokine production [50].

Effects of central inflammation

Inflammatory processes in the brain are not limited to the response to peripheral inflammation. In the brain parenchyma, TLR4 and related TLRs located in neurons, microglia and astrocytes not only may recognize LPS, as in the case of open brain wounds, but they may also be activated by DAMPs (damaged-associated molecular patterns) released as a consequence of primary cell injury within the brain parenchyma [51–53] (Figure 2). The origin and mechanisms of brain inflammation initiated by parenchymal cell injury are multiple, occasionally occur as a result of genetic defects, but most of the time they are the consequence of unknown factors, as is the case in neurodegenerative disorders or autoimmune disease. In these disorders, parenchymal cell injury activates microglia and astrocytes, with production of inflammatory cascades, blood–brain barrier breakdown and macrophage and T-cell infiltration [31,44,51–53] (Figure 2).

The significance of brain inflammation

Brain inflammation is necessary and beneficial when directed to ameliorate the effects of toxic materials produced in the brain parenchyma. To ensure protective effects, inflammatory reactions must be well-regulated and self-contained. However, when regulatory mechanisms fail and inflammation is unchecked, there is an unrestrained formation of inflammatory mediators and oxidative radicals, which in turn affect mitochondrial function and overall cell metabolism, leading to neuronal damage. In turn, cellular injury exacerbates the situation by promoting additional inflammatory cascades further increasing cellular toxicity [15,20,29].

Relationship between brain inflammation and alterations in cerebrovascular flow

The maintenance of adequate cerebrovascular compliance and contractility, the adequate control of the autoregulatory properties of the cerebral circulation and normal capillary function are essential for the brain to receive the blood supply required for optimal activity and metabolism [54]. Brain inflammation may disrupt blood flow in the brain as a consequence of cerebrovascular inflammation, alterations in the cerebrovascular autoregulation following excessive sympathetic stimulation or brain oedema, in part the result of blood–brain barrier breakdown [28]. There are reciprocal influences between excessive inflammation and disturbances of the cerebrovascular flow. Unregulated inflammation increases the incidence and progression of alterations in the cerebral circulation and in turn brain ischaemia exacerbates inflammatory processes and neuronal injury [26,55].

Influence of inflammation in stress

In a healthy organism, stress activates a ‘general adaptation syndrome’ of well-regulated and integrated emotional, neural, endocrinal and immune responses to change that together maintain homeostasis [23]. Although the neurochemical, hormonal, behavioural and immune ‘signatures’ vary with the type, intensity and duration of the stress [56], there are shared mechanisms of response common to all stress reactions. Exposure to acute stress, including that associated with infection, is characterized by activation of the HPA axis with an excess production and release of CRF (corticotrophin-releasing factor), enhanced pituitary ACTH (adrenocorticotrophic hormone) release to the circulation, and increased

production and release of glucocorticoids and aldosterone from the adrenal gland [33,56,57]. There is a concomitant central and peripheral sympathetic activation, involvement of multiple and widespread sensory receptive and motor components, and major behavioural changes [23,56,57]. A period of adaptation follows this acute response, and again the specific characteristics of adaptation are dependent on the nature and intensity of the challenge [56,57]. When stress challenges are very strong or long-lasting, or when organisms have enhanced sensitivity to stress, the mechanisms of adaptation may be overwhelmed. Failure to adapt to a stress challenge can ultimately result in tissue damage and disease [23].

During stress there is a major influence of the immune system, with activation of pro-inflammatory cytokine production, contributing to regulate the HPA axis and the central sympathetic response [10,58]. Although the role of glucocorticoids in the regulation of the stress response is widely recognized, the participation of aldosterone has not been sufficiently considered [34]. Enhanced stress-induced aldosterone production and secretion, in conjunction with pro-inflammatory cytokines, contribute to the regulation of the HPA axis response, to the increased sympathetic drive and to endothelial dysfunction, enhancing inflammatory responses in the brain [10,34,35,37,58] (Figure 2).

Conclusion

From the above, it must be concluded that brain inflammation, alterations in cerebrovascular function and failure to adequately respond to stress do not work in isolation, but are interacting processes leading to neuronal injury and disease. The observations described above set the stage for the consideration of the brain AngII system, which is a major factor in the regulation of brain inflammation, the cerebral circulation and stress. The pleiotropic effects of brain AngII and the increasingly recognized participation in brain disorders continue to generate enthusiasm in the research community, which, as of March 2012, had produced more than 7700 PubMed citations on the subject of 'brain angiotensin'.

THE BRAIN RAS (RENIN-ANGIOTENSIN SYSTEM)

AngII and AT₁ receptors

[The classical RAS, with its active principle AngII, is a fundamental regulatory mechanism conserved throughout evolution [13]. Although the RAS participates in the control of the physiological activity of the cardiovascular system, renal functions and fluid metabolism, peripheral RAS hyperactivity is associated with essential hypertension, metabolic dysfunction and renal disease [59].

When initially described, the peripheral RAS was thought to be simple, consisting of a precursor polypeptide (angiotensinogen), a rate-limiting forming enzyme (renin) and the inactive precursor [AngI (angiotensin I)], which is a substrate for ACE (angiotensin-converting enzyme). ACE was considered as the single enzyme leading to the formation of the only active principle peptide, circulating AngII [59] (Figure 3).

We now know the actual picture is far more complex (Figure 3). Several novel pathways regulating the function of AT₁ receptors have been proposed. One of them is the result of AngII binding to a second receptor type, the AT₂ receptor (AngII type 2 receptor). It has been hypothesized that AT₂ receptor stimulation by AngII may counterbalance AT₁ receptor activation and play a protective role during brain injury [60] (Figure 3). In the brain, however, AT₂ receptors are predominantly expressed during development, with very limited levels in the adult [61]. There is no clear mechanistic model for its signal transduction, as the receptor can be activated without AngII participation and published results are

controversial [62–66]. The conclusion is that more work needs to be done to clarify the role of AT₂ receptors in the brain.

A second system regulating the effect of AT₁ receptor stimulation involves a novel RAS component, namely ACE2. ACE2 forms Ang-(1–9) [angiotensin-(1–9)] from AngI and Ang-(1–7) [angiotensin-(1–7)] from AngII. In turn, ACE cleaves Ang-(1–9) into Ang-(1–7) [67] (Figure 3). Ang-(1–7) stimulates the Mas receptor, and the ACE2/Ang-(1–7)/Mas receptor axis has been proposed as a vasodilator, antigrowth and antifibrotic pathway balancing enhanced AT₁ receptor activation and protecting from injury [67].

From the above, it may be concluded that AngII may not be the only active RAS principle and that AT₁ receptor stimulation may be intrinsically regulated by the RAS. The complexity of the RAS continues to evolve. AngII and related peptides may be produced and degraded by alternative pathways, novel RAS components have been described, both upstream and downstream of AngII, and circulating inactive pro-renin may be activated by a pro-renin receptor. These discoveries are increasingly the subject of dynamic research. At the moment the precise composition, localization and functions of the additional RAS components remains unclear. For a complete discussion of existing evidence, readers may wish to consult the following reviews [62,67–77] and other reviews in this series (<http://www.clinsci.org/cs/RAAScollection.htm>).

Studies have shown that many tissues, including the brain, contain local RAS systems, and that their activity is perhaps more important than that of the circulating RAS [68–70]. In the brain, as in the periphery, it is accepted that most of the physiological and pathological effects of RAS activation are the consequence of stimulation of AT₁ receptors by AngII [62]. In the brain, AT₁ receptor activation contributes to the physiological regulation of many different functions, including, but not restricted to, the control of the cerebral circulation, the integrity of the blood–brain barrier, central sympathetic activity, hormonal production and release, the response to stress, behaviour and cognition, and the regulation of the brain's innate immune response (Figure 4). In turn, brain AT₁ receptor over-activity is associated with stress-induced disorders, hypertension and brain ischaemia, excessive inflammation, alterations in behaviour and cognitive loss [28,62,68–71,78] (Figure 4).

ARBs (AT₁ receptor blockers)

Attempts to ameliorate hypertension by decreasing RAS activity led to development of the ACEis (ACE inhibitors) that reduce the formation of AngII, and are in common use for the treatment of cardiovascular disorders [59] (Figure 3). The later discovery and cloning of the AT₁ receptors allowed for the development of the potent orally active ARBs, directly antagonizing AngII effects (Figures 3 and 4). Today, ARBs (imidazole derivatives, collectively called 'sartans') are extensively used for the treatment of cardiovascular disorders [79], and their neuroprotective effects are increasingly recognized [80].

In the brain, AngII stimulates highly localized AT₁ receptors. These receptors are highly abundant throughout the cerebrovascular endothelium and the circumventricular organs, where they have access to circulating AngII. Their activity influences cerebral blood flow and, consequently, the overall function of the brain [68,81]. On the other hand, receptors situated within the brain parenchyma, expressed in specific neurons involved in autonomic, hormonal, sensory, cerebrovascular and behavioural regulation, may be stimulated by AngII formed within the brain [62,69–71,78]. Other parenchymal cells may participate in the central effects of AngII. Astrocytes contain significant numbers of AT₁ receptors [42,43] and these cells are the major source of angiotensinogen in the brain [82]. AT₁ receptors have been reported in cultured microglia [83,84], and ARBs are directly neuroprotective in microglia cell cultures [45,83]. However, there are few reports on the presence of AT₁

receptors in brain parenchyma microglia [84]. In spite of major research efforts, our understanding of the role of brain AT₁ receptors is still incomplete and subject of intense scrutiny.

AT₁ RECEPTORS AND BRAIN INFLAMMATION

Brain AT₁ receptors participate in the physiological control of brain inflammation [14,85–87], cerebrovascular function [88–90] and stress [91–95]. Moreover, the results of AT₁ receptor blockade demonstrate that AT₁ receptor overactivity is an important determinant of uncontrolled and excessive inflammation, alterations in cerebrovascular function and pathological responses to stress [28,71,78] (Figure 4 and Table 1).

Inflammation

Enhanced brain AT₁ receptor expression is associated with excessive peripheral and central inflammation leading to neuronal injury [45,96], chronic cerebrovascular inflammation in genetically and experimentally hypertensive rats [97–100], and with the massive acute inflammatory reaction following stroke [101] (Figure 4). AT₁ receptor blockade following systemic ARB treatment demonstrated the pathogenic role of increased AT₁ receptor activation. ARB administration significantly decreased the widespread cerebral inflammation which follows systemic LPS administration [45] (Table 1), hypertension-associated cerebrovascular inflammation [99] and brain inflammation following stroke, cerebral haemorrhage and TBI [98,102–105] (Figure 4 and Table 1).

Analysis of the LPS model of peripheral and brain inflammation clarified some of the mechanisms of the central anti-inflammatory effects of ARBs. Systemic ARB administration antagonizes peripheral AT₁ receptors located in vascular endothelial cells, macrophages and the adrenal gland. The consequence is a reduction in the production and release of pro-inflammatory cytokines and aldosterone into the general circulation. By reducing peripheral inflammation, ARBs substantially decrease the effects of circulating pro-inflammatory factors on their central targets, the cerebrovascular endothelial cells and circumventricular organs [33,45,96,106]. At the same time, ARBs preserve the inflammation-induced augmentation of anti-inflammatory glucocorticoids, shifting the balance, in the general circulation, in favour of anti-inflammatory factors [33,45,96,106]. Consequently, ARBs prevent the production of further inflammatory cascades affecting the brain parenchyma and excessive microglia and astrocyte activation, indirectly reducing neuronal injury [15,33,37,46,96,106]. By reducing circulating aldosterone, ARBs not only indirectly decrease MR stimulation in cerebrovascular endothelial cells, but also the inflammatory effects of aldosterone in the brain parenchyma [36]. In turn, reduced MR stimulation decreases the activity of the brain RAS and the excessive NADPH oxidase-dependent ROS production [36].

ARBs may also exert beneficial anti-inflammatory effects in the brain as the result of the blockade of AT₁ receptors on cerebrovascular endothelial cells (Figure 2), in the circumventricular organs and in the PVN [61,81,98,99,107–109].

There are other indirect mechanisms by which ARBs may indirectly protect neurons. ARBs maintain the functionality of the blood–brain barrier during inflammation, preventing its breakdown and limiting increases in the production of adhesion molecules, in this way reducing macrophage and T-cell infiltration into the brain parenchyma [98] (Table 1). In addition, although circulating AngII does not cross the blood–brain barrier, it up-regulates an AT₁ receptor pathway connecting the circumventricular organs with the PVN [61]. Stimulation of this pathway may then be transmitted to important brain structures regulating

the response to inflammation, and part of the anti-inflammatory effect of circulating ARBs may be the consequence of blockade of such a pathway.

The molecular mechanisms of ARB neuroprotection are beginning to be clarified. Recent findings suggest mutual regulatory mechanisms between AT₁, TLR4 and CD14 receptors. Systemic administration of LPS increases AT₁ receptor expression in the PVN, and incubation in the presence of LPS enhances AT₁ receptor gene expression in primary cerebrovascular endothelial cell cultures [45,96]. In contrast, ARB administration decreases CD14 gene expression in the PVN and TLR4 gene expression in circumventricular organs [45].

Furthermore, stimulation of AT₁ receptors by AngII and of TLR4 by LPS use similar pro-inflammatory mechanisms of signal transduction, including activation of NF- κ B, AP-1, iNOS, COX-2 and NADPH oxidase and excessive ROS generation, leading to activation of microglia and further inflammatory cascades [32,45,110,111] (Figures 2 and 5). If the ARBs do cross the blood–brain barrier (as discussed below), their ability to reduce microglia activation may be considered as a powerful potential mechanism accounting for their anti-inflammatory effects in the brain.

Taken together, this evidence supports the hypothesis that ARBs reduce inflammation induced by LPS by interfering directly at the receptor level and/or by blocking shared pro-inflammatory mechanisms of signal transduction [32,112,113] (Figure 5).

For these reasons, it is logical to hypothesize that most of the beneficial effects of ARBs in the brain may be indirect. The question was raised, however, whether amelioration of brain inflammation was not a simple response to the peripheral effects of ARBs, but included significant direct anti-inflammatory effects in the brain. This hypothesis, which requires adequate penetration of circulating ARBs into the brain parenchyma, is supported by substantial evidence. Systemic ARB administration reduces AT₁ receptor binding not only in areas located outside, but also in all structures situated inside the blood–brain barrier [114,115]. ARBs antagonize effects of centrally administered AngII not only when they are injected into the brain [116], but also when they are administered systemically [117–120]. Neuroprotection also occurs in models of enhanced activity of brain, but not circulating, AngII [97,99,107,121,122]. Direct anti-inflammatory effects of ARBs have been demonstrated in primary neuronal [45], astrocyte [42,123] and microglia cultures [45,83].

Definitive evidence of central effects, however, requires the demonstration of ARBs or their metabolites in the brain parenchyma following systemic administration, but further definite proof is lacking. Nevertheless, the evidence is in favour of the dual peripheral and central neuroprotective effects of ARBs. Direct effects in brain parenchymal cells, together with blockade of inflammatory signals in cerebrovascular endothelial cells, contribute to explain how systemic or oral ARB administration reduces LPS-induced inflammation throughout the brain parenchyma, including the pre-frontal cortex, hippocampus and amygdala [45,124].

It has also been observed that the dorsal motor nucleus of the vagus and the nucleus of the solitary tract express large numbers of AT₁ receptors [61]. This placement suggests that another direct neuroprotection mechanism may be the ability of ARBs to prevent the transfer of inflammatory signals reaching the brain through an important mechanism of systemic inflammation, namely the vagus nerve [30,48,50]. However, there is no direct evidence for a participation of AT₁ receptors in the complex circuit controlling vagal afferent and efferent activity. Further studies are necessary to definitely establish whether AT₁ receptor activation and blockade contribute to regulate these complex interactions.

Direct effects within the brain may also explain how ARBs decrease excessive central inflammation, which is the result of increased DAMP production associated with many neurodegenerative diseases [31,51–53] (Table 1). This property may partially explain how ARBs may be effective in neurodegenerative disorders (Table 1), by decreasing excessive inflammation in response to initial intraparenchymal cell injury and death.

Cerebral circulation

Circulating and locally produced AngII stimulates AT₁ receptors in cerebral arteries, microvessels and capillaries, participates in the control of cerebrovascular contractility, and the autoregulatory properties of the cerebral circulation [54,81,90]. In turn, chronic and excessive activation of cerebrovascular AT₁ receptors contributes to hypertrophy, hyperplasia and inflammation, leading to cerebrovascular remodelling, loss of cerebrovascular compliance and poor brain circulation. ARB administration reverses cerebrovascular remodelling, restores arterial compliance and protects blood flow to the brain [97–99,104,107,121,125,126] (Table 1). The protection of cerebral blood flow contributes to reduce brain inflammation and participates in the neuroprotective effect of ARBs in ischaemic conditions of the brain. There may be additional direct neuroprotective mechanisms responsible for the effects of ARBs during brain ischaemia, since these compounds directly protect cultured neurons against injury produced by oxygen and glucose depletion [127] (Table 1).

Stress

AngII contributes to regulate all aspects of the stress response, including HPA axis stimulation, in particular the regulation of CRF production and release, as well the stress-induced increase in central sympathetic and peripheral sympathoadrenal activity [90,92,93,95]. In many models of acute stress, both peripheral and brain production of AngII and expression of AT₁ receptors increase, leading to augmented HPA axis activation and enhanced sympathoadrenal and hormonal responses [95,96,128–130]. These changes are effectively controlled by ARB administration [85,129,131,132] (Table 1). Since the stress-induced HPA axis and central sympathetic activation are enhanced by a combined effect of pro-inflammatory cytokines and aldosterone [36,58], part of the effect of ARB administration may be indirect through the reduction of stress-induced cytokine and aldosterone production and release.

PLEIOTROPIC NEUROPROTECTIVE EFFECTS OF ARBs

Effects beyond blood pressure control

Normalization of blood pressure in hypertensive subjects is neuroprotective. Therefore it may be concluded that most, if not all, of the beneficial effects of ARB treatment are dependent on their capacity to reduce blood pressure and to antagonize the deleterious effects of excessive AT₁ receptor stimulation, as was initially proposed [79]. This is, however, not the case. Evidence is accumulating for the pleiotropic effects of ARBs beyond blood pressure control and AT₁ receptor blockade. The multiple beneficial effects of ARBs probably contribute to explain their amelioration of a large number of brain conditions, and are currently the subject of intense investigation.

Several lines of evidence support the hypothesis that part of the neuroprotective effects of ARBs are beyond their blood pressure effects. First, low doses of ARBs not affecting blood pressure are neuroprotective in normotensive rodents. Telmisartan (0.3 mg/kg of body weight) protects cognition in normotensive rats injected with A β (amyloid- β) (Table 1) and this is a very low dose not affecting blood pressure [133]. A low dose of candesartan (0.1 mg/kg of body weight) protects normotensive mice from TBI more effectively than higher

doses [105]. As described above, ARBs administered to normotensive rats prevent the central inflammation resulting from LPS administration [33,45,96,106] (Table 1).

The second line of evidence stems from the comparison of ARB-induced neuroprotection in animal models of hypertension (Table 1) with that of other anti-hypertensive drugs reducing blood pressure to a similar degree. In SHR (spontaneously hypertensive rats) submitted to experimental stroke, the ARB candesartan has superior neuroprotective effects when compared with propranolol (a β -blocker) [122] or amlodipine (a calcium channel blocker) [97]. The third line of evidence is the direct neuroprotective and anti-inflammatory actions of ARBs, demonstrated many times *in vitro*, and therefore unrelated to cardiovascular effects.

Effects additional to AT₁ receptor blockade

ARBs are not a homogeneous class of compounds with identical potency and mechanisms of action. Although all ARBs effectively block AT₁ receptors, there is a 5-fold difference in affinity among members of this class [134]. All ARBs are competitive; some of them surmountable, shifting the dose response to the right, and most of them are partial insurmountable antagonists, decreasing the maximal response [135]. Insurmountable antagonistic properties are highest for candesartan and lowest for losartan [135]. Such differences may partially explain how different ARBs lower blood pressure to different degrees [134]. The clinical value of these differences is the subject of intense scrutiny in the cardiovascular field, but has not been explored in the context of the treatment of brain disorders.

Pharmacological and molecular studies have begun to unravel the nature of the additional mechanisms of the beneficial therapeutic effects of ARBs [136–138]. Although most ARBs share a similar molecular structure (biphenyl-tetrazol and imidazole groups) and their AT₁ receptor inhibition is a common (or class) effect, small changes in molecular structure result in substantial differences in pharmacological profile [139]. For example, telmisartan is the only biphenyl derivative containing no tetrazole group [137,139] (Figure 6), a characteristic which may explain why it has different effects than other ARBs.

In addition to AT₁ receptor blockade, some ARBs (telmisartan, to a lesser extent candesartan, but also losartan) may also be agonists for PPAR γ (peroxisome-proliferator-activated receptor γ) [136–138,140] (Figures 5 and 6). PPAR γ is an intracellular nuclear hormone receptor with significant beneficial effects in the regulation of multiple pathways involved in carbohydrate and lipid metabolism [141] and the control of expression of pro-inflammatory genes, including inhibition of the pro-inflammatory transcription factors AP-1 and NF- κ B [142,143]. Because of this, the proposed dual AT₁ receptor blockade and PPAR γ agonist effect of some ARBs is of major interest and is actively investigated in the cardiovascular field. It must be kept in mind, however, that the PPAR γ agonist activity of some ARBs may not be necessarily independent of their AT₁-receptor-blocking properties. There is cross-talk between AT₁ receptor and PPAR γ activation [144]; PPAR γ agonists reduce AT₁-receptor-mediated inflammation and hypertension *in vivo* [145] and down-regulate AT₁ receptor expression [146], whereas AngII, by AT₁ receptor stimulation, down-regulates PPAR γ activity [147] (Figure 5).

Furthermore, not all ARBs display similar PPAR γ agonist effects, and the reasons for the differences reported have not been clarified. Such differences appear to depend on the type and condition of the experiments. For example, telmisartan, candesartan, irbesartan, losartan and the losartan metabolite EXP3179 are good PPAR γ ligands *in vitro*. Conversely, valsartan and olmesartan are inactive *in vitro*. Only telmisartan, and to a lesser extent candesartan, produced significant PPAR γ activation in cells [138] (Figure 6). *In vivo*,

telmisartan has PPAR γ agonist activity, and sustained treatment with candesartan up-regulates PPAR γ gene expression [148]. Overall, of all of the ARBs studied, telmisartan and candesartan appear to be the most effective activators of PPAR γ [136,148,149]. For this reason, it is of interest that, in human monocytes, the reduction of LPS-induced inflammation by telmisartan has been demonstrated to be related to PPAR γ agonist effects [149]. Monocytes are critical in the development of insulin resistance, diabetes and arteriosclerosis, and plasma LPS is elevated in obesity and diabetes [150,151]. In addition, low-grade chronic inflammation with an increased expression of monocyte-derived inflammatory factors is an established component of peripheral vascular inflammatory disease in hypertension [6]. The possibility of using ARBs as effective and safe PPAR γ agonists of therapeutic benefit is of major interest, and there is increasing research on the development of novel ARB derivatives with improved therapeutic spectrum and PPAR γ agonist activity [152,153]. Although most of the studies are focused on the effects of dual AT₁ receptor inhibition/PPAR γ activation for the treatment of cardiovascular disorders, some initial pre-clinical studies have started to address this dual beneficial effect for the treatment of diseases of the brain [101].

It is also becoming apparent that some ARBs may possess additional effects that appear to be not only independent of AT₁ receptor blockade, but also of PPAR γ activation [154]. Such effects include TXA₂ (thromboxane A₂) receptor blockade, decreased platelet aggregation and reduction of serum uric acid levels [154]. However, there is no definitive evidence for these molecule-specific effects giving rise to a therapeutic advantage for the treatment of cardiovascular disease [154]. Consequently, whether selective ARBs have advantage for the treatment of brain disorders is at the present time still an open question.

TRANSLATIONAL POTENTIAL OF ARBs FOR THE TREATMENT OF BRAIN DISORDERS

Because of their demonstrated central anti-inflammatory effects and accumulating pre-clinical and clinical evidence, there is increasing interest in considering the possible benefit of ARB administration for the treatment of neurodegenerative and mood disorders. At present, the strongest evidence for a therapeutic effect of ARB administration in brain conditions is their amelioration of cognitive loss after stroke, in the elderly, and during the progress of Alzheimer's disease (Table 1).

Hypertension, brain ischaemia and stroke

The prevention and treatment of chronic brain ischaemia and stroke, a condition associated not only with chronic cerebrovascular dysfunction, but also with widespread inflammatory reactions, has until recently been based on controlling hypertension. This strategy does not, however, consider the role of persistent peripheral and brain inflammation associated with hypertension, which have also been shown to increase the incidence and severity of stroke [26,55].

Chronic hypertension reduces blood flow to the brain as a consequence of cerebrovascular hypertrophy and hyperplasia (cerebrovascular remodelling), and this leads to chronic cerebrovascular and parenchymal inflammation. In turn, inflammation worsens cerebrovascular function, further increasing the vulnerability to ischaemia [54,155]. Decreased blood flow to the brain is a major factor leading to neuronal injury, to progressive cell damage during chronic brain ischaemia and to catastrophic cell death following stroke [155].

Pre-clinical studies—Neuroprotective effects of ARBs have been demonstrated in numerous pre-clinical studies using rodent models of hypertension and stroke. ARBs reduce brain inflammation and vulnerability to ischaemia, and protect neurological function. The result of ARB administration includes the reversal of cerebrovascular inflammation, remodelling, vasoconstriction, blood–brain barrier breakdown, macrophage infiltration and brain oedema. This reduces the vulnerability to ischaemia, protects blood flow during stroke and decreases the neurological impairment that follows experimental stroke [97–101,104,107,109,121,122,125,126,156] (Figure 4 and Table 1).

Clinical studies—Numerous large controlled clinical studies have concluded that ARBs may be considered the drugs of choice in stroke prevention and post-stroke chronic care, and there are indications that ARBs prevent cognition decline more effectively than other anti-hypertensive medications [5,157–169] (Table 1). Additionally, the protective effect of ARBs in chronic renal disease and heart failure is enhanced with increasing doses beyond full AT₁ receptor blockade [7,170]. On the basis of these observations and on the robust pre-clinical findings described elsewhere, it is reasonable to postulate that the superior benefit of ARBs in hypertension, brain ischaemia and in the prevention of stroke and chronic post-stroke care (Table 1) is in part related to effects beyond a reduction in blood pressure and include the restoration of cerebrovascular compliance, the improvement in blood flow and the reduction in brain inflammation. Whether this therapeutic profile could be helpful for the treatment of brain disorders and if increasing the ARB doses may result in additional neuroprotective effects has not yet been determined.

Aging

Multiple insults converge to compromise cells in the aging brain [171] (Figure 1). Aging is associated with increased neuroinflammation as a consequence of progressive age-dependent disruptions in neuronal metabolism. During the aging process, inflammatory responses are initially adaptive but increasingly poorly controlled, and ultimately lead to cell injury and death [24,25,31,52,155,172]. Aging is also associated with progressive cerebrovascular alterations, similar to those occurring during chronic hypertension, making elderly people vulnerable to ischaemia and stroke with or without hypertensive disease [173].

Pre-clinical studies—Pre-clinical experiments support the beneficial effect of ARB administration throughout life. Life-long ARB administration to genetically hypertensive rats, or genetic deletion of AT₁ receptors in mice, extends the life span [174,175] (Table 1). This effect has been associated with renal and cardiovascular protection [176,177], but also includes a life-long reduction in stress responses, strongly suggesting a central component for the beneficial effects of ARBs [174].

Clinical studies—ARBs not only protect from stroke-related cognition decline and in hypertensive patients [178], but also reduce inflammation and cognitive loss during the normal aging process in normotensive individuals [5,157,179–182] (Table 1). As described above, ARBs can be neuroprotective in rodents at doses not significantly affecting blood pressure and by mechanisms additional to AT₁ receptor blockade. These properties may be of particular importance for the use of ARBs in the elderly, since it is necessary to avoid an excessive decrease in blood pressure thresholds that may impair cognitive function.

Alzheimer's disease

Alzheimer's disease increases with age, is subject to genetic determinants of vulnerability, and its incidence and progression are increased by the modifiable risk factors outlined [2,55] (Figure 1). Poorly understood metabolic alterations lead to cellular injury, neuronal death,

cognitive loss and a general decline in brain function. A disturbance in the production and metabolism of $A\beta$ induces neurotoxicity and initially triggers beneficial ‘sterile’ inflammatory responses to DAMPs released from damaged brain cells [31,183,184]. Over time, excessive inflammation facilitates $A\beta$ production and deposition, increases neuronal vulnerability to $A\beta$ and oxidative stress and leads to further neuronal injury [24]. Increased brain inflammation, early alterations in the cerebrovascular endothelium, blood–brain barrier breakdown and the progressive reduction in blood flow to the brain are recognized as major mechanisms contributing to the pathogenesis of Alzheimer’s disease [2,15,27,31,155,185,186].

Pre-clinical studies—Excessive brain AngII activity negatively affects cognition. For example, AngII, through AT_1 receptor stimulation, blocks long-term potentiation in the hippocampus [187–190]. This effect is associated with an inhibition of the cholinergic system, which is a major mechanism necessary for the maintenance of cognitive functions [191,192].

Conversely, ARBs ameliorate, in pre-clinical models, most of the modifiable risk factors associated with Alzheimer’s disease [28,45,105,133,148,149] (Figure 1). In addition, ARBs are protective in transgenic mice models of established Alzheimer’s disease. The central injection of AngII has been reported to stimulate $A\beta$ production [193]. ARBs reduced the toxicity and protected the cognition in a rat model of exogenous brain $A\beta$ administration [133,194] and when administered to some [41,195], but not all [196], transgenic mouse models of Alzheimer’s disease (Table 1). There is also evidence that ARBs reduce memory decline in a mouse model of diabetes, which is a major risk factor for Alzheimer’s disease [197] (Table 1). This indicates a beneficial effect of ARB treatment, dependent on the model studied and the conditions of the experiments.

Clinical studies—There is conclusive clinical evidence that treatment with ARBs reduces several major risk factors for Alzheimer’s disease [5,6,8] (Table 1). ARBs protect age- and stroke-associated cognitive loss [5,157,178,180,181] (Table 1), and they may ameliorate the incidence and progression of this disorder. In patients treated for hypertension with ARBs, selected from the Veterans Administration database, cohort studies revealed a major reduction in the incidence and later development of Alzheimer’s disease [198]. The beneficial effects of ARB treatment were clearly superior to those of other anti-hypertensive medications of similar potency [198]. These findings are supported by a recent nested case-control analysis within the U.K. general practice research database with prospectively recorded anti-hypertensive database [167]. This study compared patients treated with ARBs or ACEis with patients treated with other anti-hypertensive medications. The results demonstrate that treatment with either ARBs or ACEis was inversely associated with Alzheimer’s disease, that ARBs offered superior cognitive protection than ACEi, and that this inverse association persisted over time [167] (Table 1).

However, in spite of their direct neuroprotective effects, their capacity to reduce major risk factors and the suggestive clinical evidence, ARBs have not been directly tested for the treatment of Alzheimer’s disease, and there are no controlled studies to date on their possible preventive and therapeutic benefit.

Mood and stress-induced disorders

The co-morbidity between mood disorders, and in particular major depression, dysfunctional responses to stress, neurodegenerative disorders and cardiovascular disease, has been well-established [10,58,199–203]. Uncontrolled inflammation is a common mechanism partially

explaining such co-morbidity [204–207,218–220]. In addition, brain disease, and in particular mood disorders, frequently involves faulty responses to stress [10,23,58].

Pre-clinical studies—Several lines of evidence demonstrate that AngII is a major stress hormone, as there is enhanced peripheral and central RAS activity during stress [207]. AT₁ receptors are discretely localized to all brain areas involved in the HPA axis response to stress; i.e., stimulation of PVN AT₁ receptors contributes to CRF release and, in turn, glucocorticoids are essential for AT₁ receptor transcription. In all models of stress studied, there is a significant increase in AT₁ receptor expression in the PVN [28].

Furthermore, systemic administration of candesartan blocked the hormonal responses to both acute and long-term isolation stress [131,174,208,209], the central sympathetic response to cold restraint [129] and acute gastric ulceration observed in rats submitted to cold-restraint stress [132] (Figure 4 and Table 1).

Additionally, ARBs prevent, in some stress models such as isolation and cold restraint, the central and peripheral sympathetic activation characteristic of the acute stress response. This effect is shown by the prevention of the stress-induced tyrosine hydroxylase mRNA up-regulation in the locus coeruleus, the main source of catecholamines in the forebrain, and by decreased sympathoadrenal stimulation [117,129,131].

There is significant evidence suggesting that excessive brain RAS activity may be an important factor leading to anxiety and depression (Figure 4). Studies using rodent models of anxiety [209–211] and rodents with genetically enhanced vulnerability to stress [45] confirmed further that treatment with ARBs is equally beneficial, in potency and anti-anxiety effect, to treatment with benzodiazepines and CRF₁ receptor antagonists, which are potent anti-stress medications (Table 1). In addition, the ARB candesartan reduces LPS-induced sickness behaviour, characterized by isolation, decreased social interactions and diminished appetite [45] (Table 1). LPS-induced sickness behaviour is a well-characterized response indicative of anxiety and depression in rodents [15]. Anti-depressant effects have also been reported after the administration of the ARB losartan to rodents submitted to the forced swim test and to rats submitted to the learned helplessness model, both of which validated tests to detect anti-depressant effects [212–214] (Table 1).

The mechanisms of the anti-anxiety and anti-depressant effects of ARBs have only been partially addressed and are not entirely clarified. ARB pre-treatment prevents the isolation-induced decrease in cortical CRF₁ and that of benzodiazepine binding, regulating the GABA_A (γ -aminobutyric acid A) complex [209]. These results indicate that ARBs contribute to control two major upstream systems regulating not only the HPA axis, but also the behavioural responses to stress and anxiety [209,215]. These observations parallel the decrease in anxiety in response to ARB administration (Table 1), as demonstrated in the elevated Plus Maze [209].

Part of the beneficial effect of ARBs may be the consequence of a decrease in stress-induced aldosterone production and release [106,131], since administration of aldosterone or MR agonists induces anhedonia, anxiety and depression in rodent models [34,216], and MR blockade reduces anxiety [217]. Pro-inflammatory cytokines and aldosterone are elevated in the rodent model of depression, and chronic mild variable stress [58] and excessive brain inflammation participates in the cellular and behavioural effects of stress, contributing to depression [218].

For these reasons, inflammation is increasingly recognized as a major factor in the response of the organism to stress and mood disorders [10,58]. Decreased inflammation as a result of

ARB treatment may be an additional important mechanism participating in the anti-stress, anti-anxiety and anti-depressant effects of ARBs in rodent models.

Clinical studies—There is a major influence of the immune system and activation of pro-inflammatory cytokines not only during stress, but also associated with mood disorders, in particular major depression [10,58] (Figure 1).

For example, an imbalance in the MR/GR (gluco-corticoid receptor) activation with enhanced aldosterone production has been reported in depression [219,220], and this is likely to overstimulate brain MRs and consequently enhance brain inflammation [34]. Alterations in aldosterone production and release occur in some subforms of depression, and in particular with atypical depression. This condition frequently fails to respond to SSRIs (serotonin reuptake inhibitors) and is associated with high co-morbidity with cardiovascular disease and diabetes, which are considered as major risk factors for depression in the elderly [34].

The association of enhanced RAS activity with depression and anxiety [10,221] (Figure 3) is supported by clinical evidence indicating that treatment with ARBs or ACEis improves quality of life, decreases stress, anxiety and depression, partially restores decreased sexual activity and improves the efficacy of anti-depressants. These effects occur not only in hypertensive subjects, but also in normotensive patients and in those affected with diabetes [5,179,222–229] (Table 1). This indicates that there appears to be a good correlation between the anti-stress, anti-anxiety, anti-depressant, anti-inflammatory and cerebrovascular-protective effects of ARBs, as revealed in rodent models and observational studies in humans. In spite of the strong pre-clinical evidence and the suggestive clinical findings, the treatment of mood disorders has not been a specific focus of clinical trials with ARBs. It is hoped that future studies will address this most important avenue.

Multiple sclerosis

Autoimmune diseases of the central nervous system, such as multiple sclerosis, share some mechanisms with Alzheimer's disease and other neurodegenerative disorders, leading to neuronal injury. Common mechanisms include the breakdown of the blood–brain barrier, chronic parenchyma inflammatory processes with recruitment of T-lymphocytes and alterations in cerebrovascular function [230–232].

Pre-clinical studies—RAS up-regulation has been demonstrated in an animal model of multiple sclerosis, namely EAE (experimental autoimmune encephalomyelitis) [232] (Table 1). Administration of ARBs or ACEis reduces blood–brain barrier breakdown, infiltration of inflammatory T-lymphocytes and ameliorates the neurological deficits characteristic of this model [232,233] (Table 1). From these experimental results, it appears reasonable to predict a beneficial effect of ARBs in multiple sclerosis [234]. However, there are to date no clinical data indicating that this may indeed be the case.

Parkinson's disease

Parkinson's disease is an age-associated degenerative condition where inflammation also plays a significant role [235,236].

Pre-clinical studies—Recent pre-clinical studies have been focused on the effect of ARBs on dopamine cells in the substantia nigra. Brain AngII promotes dopaminergic injury in animal models of Parkinson's disease, and ARBs reduce oxidative stress and dopaminergic neuronal death during brain inflammation [237,238] (Table 1).

Clinical studies—A participation of brain AngII was initially suggested on the basis of changes in AngII receptors in the brains of patients affected with the disease [239]. In spite of the suggestive pre-clinical evidence for the beneficial effects of ARBs, these compounds have not been tested in clinical trials.

Irradiation-induced cognitive loss

Whole-brain irradiation is commonly administered for the treatment of brain tumours, but the resulting cell injury and inflammation frequently results in severe and irreversible cognitive impairment. In rodent models, ARBs [240] and ACEis [241] reduce irradiation-induced inflammation and partially prevent cognitive decline (Table 1). These findings suggest that ARBs may ameliorate irradiation-induced cognitive loss and improve the quality of life for patients with brain tumours. Again, there are no published clinical studies to test the effectiveness of ARBs in this condition.

TBI

TBI is a dynamic, multifaceted and complex process with great variability between individuals. After a direct impact, and to variable degrees, TBI commonly includes cerebral vasospasm and ischaemia, brain oedema, haematomas and subarachnoid haemorrhage, followed by inflammation, blood–brain barrier disruption and diffuse axonal injury [1]. The complexity and variability of TBI explains why, while *in vitro* and animal studies have consistently demonstrated beneficial effects of many drugs, clinical trials have been disappointing [242,243]. The pleiotropic and synergistic neuroprotective effects of ARBs make them excellent candidate therapeutics for this condition.

Pre-clinical studies—A recent report has demonstrated, in a rodent model of TBI, a significant neuroprotection after treatment with low doses of the ARB candesartan not affecting blood pressure, which was associated with a considerable decrease in brain inflammation [105] (Table 1). Whether or not treatment with ARBs offers additional benefit for the treatment of TBI requires carefully designed and controlled clinical trials.

ARBs, ACEis, MR ANTAGONISTS OR THIAZOLIDONES?

The present review provides substantial evidence justifying the testing of ARBs for the treatment of brain disorders. The question remains whether RAS inhibition with the use of ACEis or MR antagonists is equally effective. As some ARBs activate PPAR γ [136,138,149], it is reasonable to question whether established PPAR γ agonists have a place in the treatment of brain disease.

ACEis

Administration of ACEis inhibits the RAS by reducing the formation of AngII [70], and ACE inhibition may offer equal or superior neuroprotection when compared with ARB administration.

Pre-clinical studies—Pre-clinical experiments suggest that ACEi administration is neuroprotective. ACEis reduce brain ischemia and blood–brain barrier breakdown, and partially restore age-related alterations in cerebrovascular regulation [89,97,173,244]. Additionally, ACEis reduce inflammation [245,246], protect dentate gyrus neurogenesis during brain irradiation [210] and reduce depression in animal models [216,247].

Clinical studies—In clinical studies, ACEis protect from stroke [70,248], although their effects are reported to be inferior to those of ARBs [161]. ACEis also preserve cognition [221], improve quality of life [249,250] and augment anti-depressant responses [224].

Clinical and retrospective studies suggest that ACEis reduce the incidence and progression of dementia and, in particular, Alzheimer's disease, although to a lesser extent than ARBs [167,168,178].

However, although ARBs reduce RAS activation by selectively blocking AT₁ receptors, ACE inhibition interferes with the production and metabolism of additional peptides, for example substance P and bradykinin [70,251]. This lack of specificity is associated with side effects such as cough and angio-oedema [252]. In addition, ACEis interfere with the production and metabolism of A β , and the significance of these findings for the treatment of Alzheimer's disease has not been clarified [251]. In conclusion, although both ARBs and ACEis are neuroprotective, it appears that ARB administration may be preferred to that of ACEis.

A clear conclusion is lacking, since there are no large-scale controlled clinical trials focused on the treatment of brain disorders or the protection of cognition by RAS inhibition, either using ARBs or ACEis alone, in comparison with one to another or in combination.

MR blockers

Because of the association of excessive MR stimulation with some models of depression and anxiety, it is important to determine whether MR blockers may ameliorate mood disorders.

There are indications that MR blockade may be beneficial in patients affected with premenstrual syndrome, leading to amelioration of depressive symptomatology, and a combination of oestradiol with an MR blocker is used for the treatment of premenstrual atypical disorder [34]. However, there are very few clinical trials with MR antagonists in mood disorders, and a recent study reported that MR receptor antagonism did not affect treatment outcome in depressed patients treated with an SSRI [253]. For these reasons, it is too early to conclusively establish the role of MR antagonists for the treatment of diseases of the brain.

Thiazolidones

Classical PPAR γ agonists reduce inflammation and metabolic alterations associated with cardiovascular disease [254,255] and have been proposed for the treatment of a number of brain disorders [256]. Indeed, activation of PPAR γ has been reported to reduce inflammation and A β pathology, to improve mitochondrial function, energy utilization and insulin sensitivity, and to promote lipid homeostasis [257]. Two thiazolidones, rosiglitazone and pioglitazone, have been assessed in clinical trials for the treatment of Alzheimer's disease [257]. Both thiazolidones have been reported to improve cognition in these patients [257]; however, rosiglitazone penetrates the brain poorly and is associated with risk of myocardial infarction and death [258,259]. In contrast, pioglitazone is not associated with negative cardiovascular events [257] and its side effects may be limited to frequent development of oedema [260]. However, a common side effect of thiazolidones is weight gain and the use of thiazolidones with brain penetration can promote leptin resistance and obesity via stimulation of hypothalamic PPAR γ [261]. For this reason the suggestion has been made to use thiazolidones without penetration into the brain for the treatment of peripheral metabolic abnormalities [261]. These factors limit the therapeutic value of thiazolidones for the treatment of brain disorders [257,262,263]. Although there is initial evidence of possible cognitive protection, further studies are necessary before the use of thiazolidones may be recommended for the treatment of brain disorders.

LIMITATIONS OF THE USE OF ARBs IN CLINICAL STUDIES

Many different ARBs have been developed, and continue to be developed, by modifying the sartan structure. This very large group of compounds shares class effects, the capacity to block AT₁ receptors and to decrease blood pressure, but it is not homogeneous. However, the clinical efficacy of the ARBs tested, when considered as a group, has been well established, and their safety profile is superior to that of other classes of RAS inhibitors and central anti-inflammatory compounds. Nevertheless, there is a need for further comparative studies to definitively demonstrate whether or not ARBs, and individual ARBs within the group, are superior to other classes of available therapeutic compounds. The limitations are still important for clinical studies on cardiovascular, renal and metabolic disorders.

As the use of ARBs for the therapy of brain disorders has been considered only recently, these limitations will become even more relevant for clinical studies on neurodegenerative and mood disorders. There is a need for more complete pre-clinical studies to determine the relative neuroprotective effect of different available ARBs, and those to be developed in the future, since the comparative neuropharmacological profile, including the capacity of individual ARBs to penetrate the brain parenchyma, has not been adequately clarified.

Although pre-clinical evidence on the beneficial effects of ARBs continues to accumulate, clinical studies have lagged behind. Many early clinical reports of the beneficial effects of ARBs in brain disorders were observational and not controlled. More recent randomized controlled studies are strongly indicative of clinical benefits; however, the evidence is indirect because, in these studies, cognition and alterations in mood were not considered as primary outcomes [159].

Future studies should take into account the inherent difficulties in performing randomized controlled clinical trials, requiring long-term follow-up of large numbers of patients, will require in-depth analysis of cognition and must include a comprehensive evaluation of mental function as a primary outcome [159].

The accumulated evidence for the beneficial effects of ARB treatment, obtained in multiple controlled clinical studies on cardiovascular and renal disease, diabetes and stroke, may be the basis for future studies on the effect of ARBs in brain disorders. At the present time, the most judicious use of resources in clinical settings may be achieved by first testing the most powerful, pleiotropic and better characterized ARBs, such as candesartan or telmisartan. Initial steps may include: (i) cohort studies in patient populations affected with cardiovascular, renal and metabolic diseases and already treated with ARBs and comparing the incidence of depression and cognitive loss with that found in patients treated with medication of similar potency but not affecting the RAS; (ii) controlled clinical trials with selected ARBs, in particular on Alzheimer's disease, since there is suggestive evidence of a major benefit, as reported in cohort studies; (iii) initial controlled studies on patients affected with depression and chronic anxiety, testing ARBs alone and/or in combination with standard therapies; and (iv) initial studies including ARBs in the treatment of TBI.

CONCLUSIONS

In conclusion, ARBs are well tolerated, have beneficial cardiovascular and metabolic profiles, and are commonly used for the treatment of hypertension, diabetes and stroke, which are major risk factors for brain disorders.

Cell culture studies have shown that ARBs have direct neuroprotective effects. Studies in animal models reveal that these compounds reduce brain ischaemia, anxiety, depression,

stress-related disorders and brain inflammation. ARBs have also been shown, in rodents, to ameliorate neurodegenerative disorders and TBI and to increase the life-span.

ARBs are not a single class of compounds and there are significant differences in their pharmacological profiles. Some ARBs use pleiotropic mechanisms to achieve neuroprotective effects. These mechanisms may not be related to AT₁ receptor blockade exclusively and may include significant activation of PPAR γ .

The demonstrated anti-stress, anti-ischæmic and anti-inflammatory effects of ARBs indicate that they have great therapeutic potential for a wide range of brain diseases. Since brain inflammation is known to exacerbate the progression of many brain disorders, in particular, ischaemia, stroke, age-associated cognitive decline and depression, ability of ARBs to reduce excessive inflammation could make them particularly well suited for the treatment of neurodegenerative and traumatic disorders of the brain. Recent clinical studies suggest that ARBs protect cognition after stroke and in aging, reduce multiple risks for, and even delay the incidence and progression of, Alzheimer's disease and improve mood. In particular, ARBs need to be tested as potential therapies for Alzheimer's disease, affective disorders (such as co-morbid cardiovascular disease and depression) and TBI.

The use of safe centrally active compounds with PPAR γ agonistic properties offers the promise of major benefit for the treatment of brain disorders.

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Abbreviations

Aβ	amyloid- β
ACE	angiotensin-converting enzyme
ACEi	ACE inhibitor
AngI etc	angiotensin I etc
Ang-(1–7)	angiotensin-(1–7)
Ang-(1–9)	angiotensin-(1–9)
AP-1	activator protein-1
AT₁ receptor	AngII type 1 receptor
AT₂ receptor	AngII type 2 receptor
ARB	AT ₁ receptor blocker
COX-2	cyclo-oxygenase-2
CRF	corticotrophin-releasing factor
DAMP	damaged-associated molecular pattern
HPA	hypothalamic–pituitary–adrenal
IL	interleukin

iNOS	inducible NO synthase
LPS	lipopolysaccharide
MR	mineralocorticoid receptor
NF-κB	nuclear factor κ B
PGE₂	prostaglandin E ₂
PPARγ	peroxisome-proliferator-activated receptor γ
PVN	paraventricular nucleus
RAS	renin–angiotensin system
ROS	reactive oxygen species
SHR	spontaneously hypertensive rats
SSRI	serotonin reuptake inhibitor
TBI	traumatic brain injury
TLR	Toll-like receptor
TNF	tumour necrosis factor

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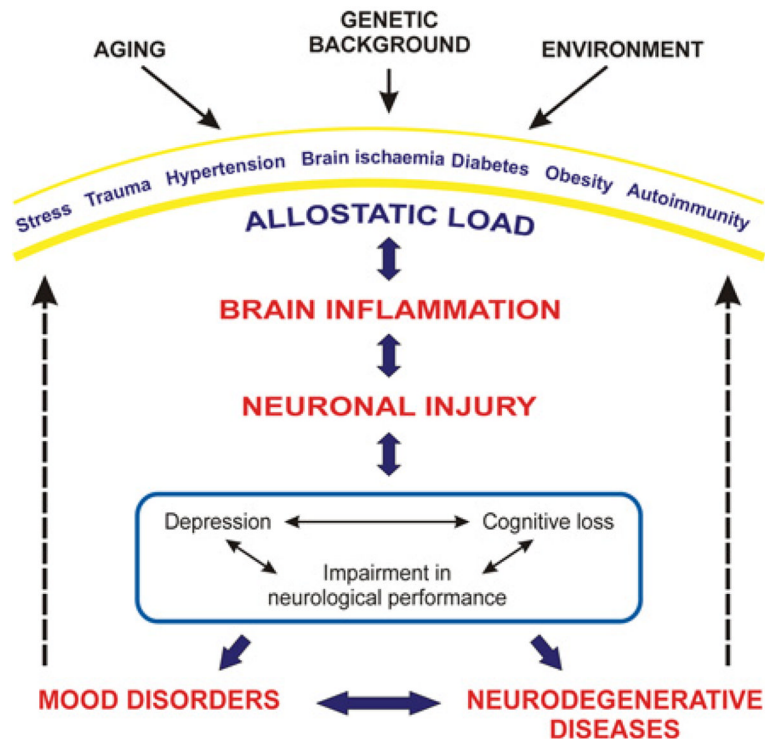


Figure 1. Central role of brain inflammation in brain disorders

When faced with environmental challenges, the brain attempts to maintain homeostasis by adjusting its response to stress, regulating cerebrovascular flow and activating defensive inflammatory mechanisms. On a background of genetic vulnerability and over time, multiple environmental factors may enhance allostatic load. Loss of homeostasis translates into pathological reactivity to stress, alterations in blood flow and uncontrolled inflammation. Excessive stress, brain trauma, cardiovascular disease, including hypertension and brain ischaemia, metabolic disorders, such as diabetes and obesity, and autoimmune processes contribute in variable degrees to the initiation and progression of brain disorders. The universal participation of excessive unregulated inflammatory processes is increasingly recognized. A vicious circle is established, with injured neurons contributing to further aseptic inflammation and progressive loss of function. The consequences are dependent on the systems involved and the different constellations of risk factors and include, to variable degrees, depression, impaired neurological performance and cognitive loss. Depending on the circumstances, the processes and mechanisms involved, the regulatory systems affected and the localization of neuronal injury, the loss of homeostasis takes the form of one of multiple mood and degenerative disorders, which in turn further challenge homeostatic mechanisms. Pathological disease mechanisms interact and this explains the high degree of co-morbidity between metabolic, cardiovascular, mood and neurodegenerative disorders.

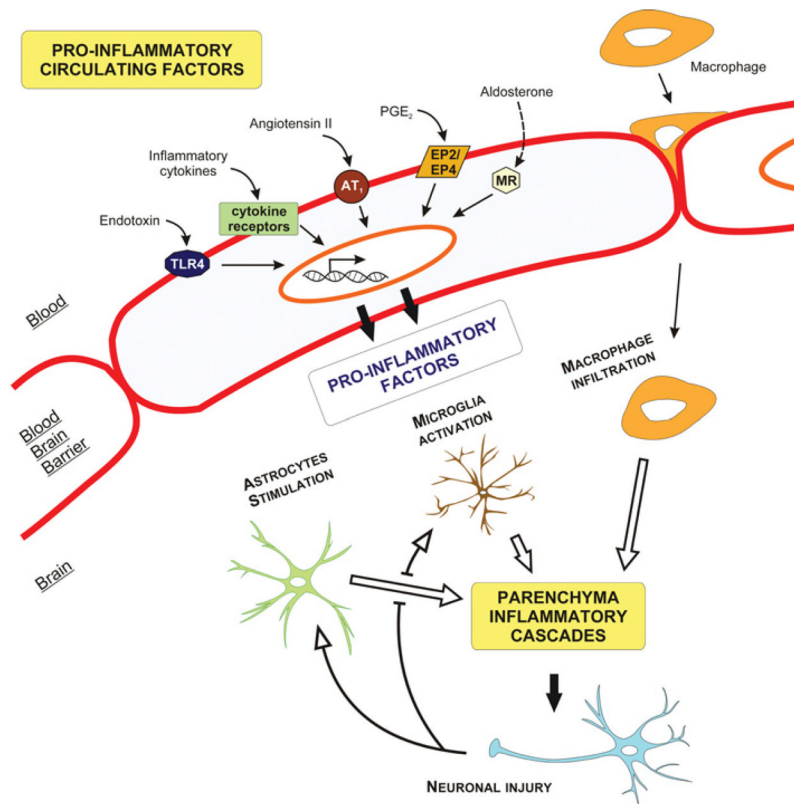


Figure 2. Circulating pro-inflammatory factors and brain inflammatory cascades
 Circulating inflammatory factors (bacterial endotoxins, pro-inflammatory cytokines, AngII, PGE₂ and aldosterone) stimulate brain cerebrovascular endothelial target cells through activation of TLR4, cytokine receptors, AT₁ receptors, PGE₂ receptors (EP₂ and EP₄) and MRs respectively. The consequence is activation of intracellular inflammatory cascades with excessive production of PGE₂, NO, pro-inflammatory cytokines, and adhesion molecules, and increased oxidative stress. Pro-inflammatory factors are released into the brain parenchyma, activating microglia and stimulating astrocytes, with further production of inflammatory cascades within the brain parenchyma. Blood–brain barrier breakdown allows macrophage infiltration into the brain parenchyma, increasing inflammation. Combinations of these factors result in neuronal injury. In turn, injured neurons produce danger signals with further microglia activation and astrocyte injury. When not adequately controlled, the continuous dialogue between peripheral and central inflammation leads to chronic inflammatory responses and permanent cell damage.

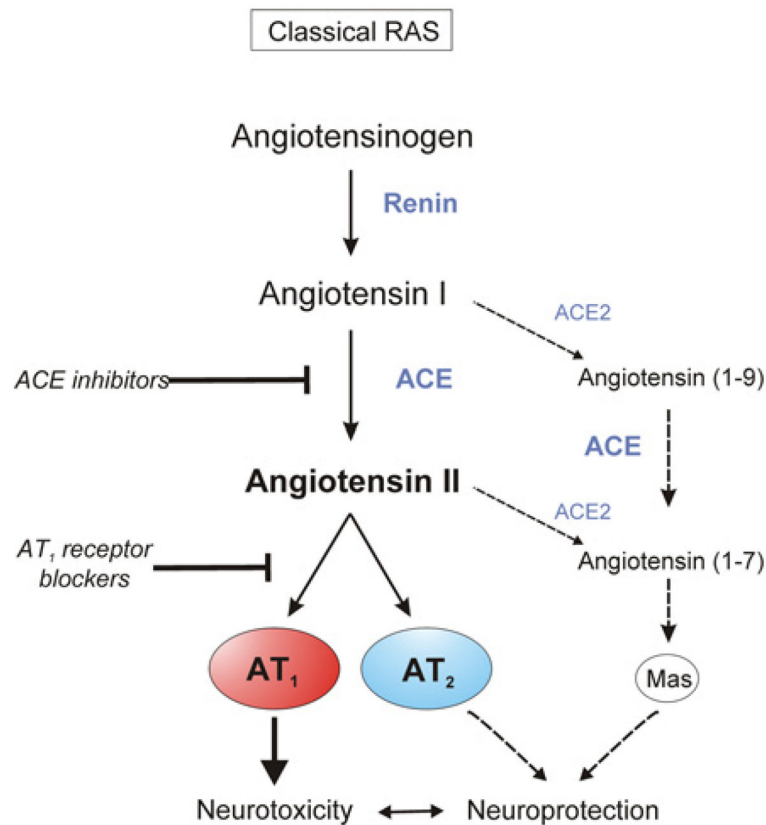


Figure 3. The RAS

The classical RAS includes the precursor angiotensinogen, the rate-limiting enzyme renin, forming the inactive peptide AngI, ACE producing the active peptide AngII, and the AT₁ receptors responsible for the physiological and pathological effects of the RAS. RAS blockade may be achieved by decreasing AngII formation with ACEis or by directly antagonizing the effects of AngII with ARBs. Two balancing systems have been described: AT₂ receptor stimulation by AngII, and Mas receptor activation by Ang-(1-7), produced by direct cleavage of AngII by ACE2, and by cleavage of AngI to yield Ang-(1-9), in turn converted into Ang-(1-7) by ACE. Neurotoxicity or neuroprotection has been proposed to depend on the interplay between AT₁ receptor activation and AT₂ and Mas receptor stimulation.

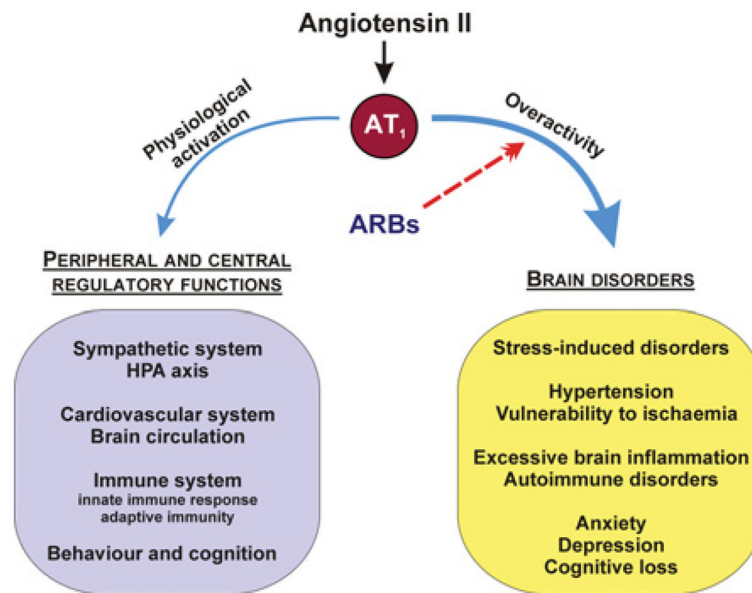


Figure 4. Physiological activation of AT₁ receptors and the consequences of AT₁ receptor overactivity

The physiological activation of AT₁ receptors contributes to regulate the central sympathetic system, the HPA axis response, the peripheral cardiovascular system, the brain circulation, the brain and peripheral immune system, behaviour and cognition. In turn, overactivity of AT₁ receptors is associated with stress-induced disorders, hypertension and vulnerability to ischaemia, excessive brain inflammation and autoimmune disorders, anxiety, depression and cognitive loss. Excessive AT₁ receptor activity may be controlled by direct AT₁ receptor blockade with ARBs.

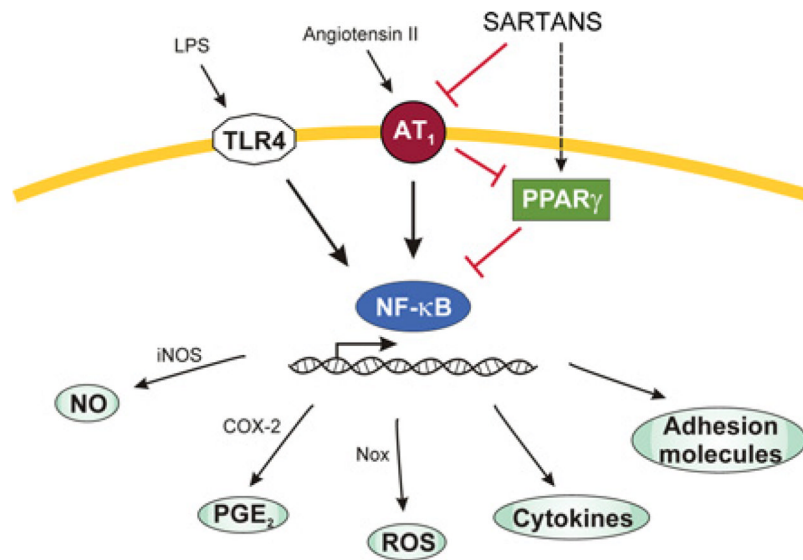


Figure 5. TLR4 and AT₁ receptors share common signal transduction mechanisms leading to inflammation

Stimulation of TLR4 and AT₁ receptors in target cells up-regulates common pro-inflammatory mechanisms activating transcription factors, such as NF- κ B, with the production of intracellular inflammatory cascades and increased oxidative stress. In addition, AT₁ receptor stimulation inhibits the anti-inflammatory PPAR γ system, indirectly activating NF- κ B and other pro-inflammatory pathways. ARBs, also called sartans, act by inhibiting AT₁ receptors to reduce inflammation and NF- κ B activation directly or by removing AT₁-receptor-mediated PPAR γ inhibition, and, in some cases, by directly stimulating PPAR γ .

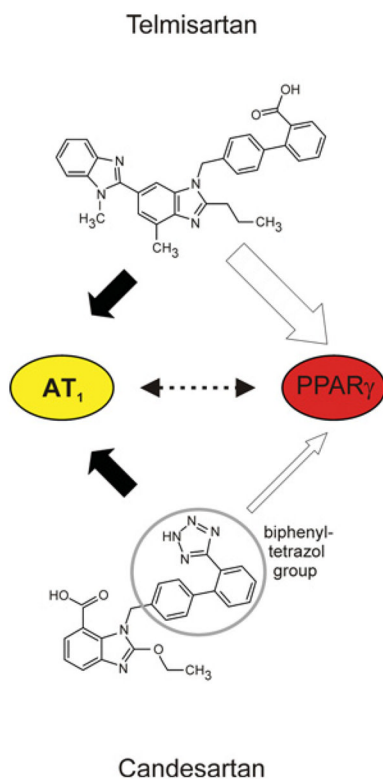


Figure 6. Specific sartans display differential pharmacological profiles

Candesartan and most other sartans are imidazole derivatives containing a biphenyl-tetrazole group. Telmisartan is unique and does not contain the tetrazole group. Although both sartans share common class effects, such as AT₁ receptor blockade, telmisartan activates PPAR γ more effectively than candesartan. The AT₁ receptor and PPAR γ systems interact, with AT₁ receptor stimulation decreasing PPAR γ activity and PPAR γ activation reducing AT₁ receptor stimulation. This inverse balance between AT₁ receptor stimulation and PPAR γ activation indicates that the effects of ARBs on PPAR γ may not be necessarily independent of AT₁ receptor blockade.

Table 1

Neuroprotective effects of ARBs of translational value

Effect	Reference(s)
Cellular cultures	
Reduce LPS-induced inflammation (human circulating monocytes, rodent microglia and cerebrovascular endothelial cells)	[45,83,108,112,116,124,125,140,149]
Direct neuroprotection (LPS, oxygen and glucose depletion)	[41,45,127]
Animal models	
Reduce stress response (cold-restraint, isolation and inflammation)	[45,129,131,174,208,209,215]
Prevent a stress induced disorder (gastric ulcerations)	[132]
Protect cerebrovascular autoregulation	[89,122]
Reduce cerebrovascular remodelling (hypertension)	[98,122]
Reduce ischaemia (stroke)	[97,99,101,102,104,121,122,126,156]
Protect the blood–brain barrier	[109,230,233]
Diminish peripheral inflammation (LPS administration)	[33,45,96,106]
Reduce brain inflammation (genetic hypertension, stroke, LPS administration and experimental autoimmune encephalomyelitis)	[45,98–100,104,107,125,232,233]
Decrease anxiety	[45,209–211]
Ameliorate depression (sickness behaviour, learned helplessness and forced swim test)	[45,212–214]
Protect from irradiation-induced injury	[240]
Protect from traumatic brain injury	[105]
Protect dopamine cells from injury	[237,238]
Diminish neurological deficits (stroke and Parkinson’s disease)	[66,73–75,232,233,238]
Protect cognition (diabetes and Alzheimer’s disease)	[123,133,188,192–195,197]
Reduce A β neurotoxicity (transgenic mouse models of Alzheimer’s disease)	[133,195]
Prolong life	[174–177]
Clinical studies	
Ameliorate hypertension, the metabolic syndrome and diabetes	[7–9,79,139,154,161,168,169,225,226]
Protect from stroke	[5,158,159,161–164,166]
Improve quality of life, and reduce anxiety and depression (hypertensive, normotensive and diabetic subjects)	[157,160,212,223,228,229]
Protect cognition (hypertension, stroke and aging)	[5,80,159,160,162–164,178–182]
Meta-analysis	
Reduce the incidence and progression of Alzheimer’s disease	[167,198]