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REVIEW

What have we learned about the kallikrein-kinin and renin-angiotensin systems in neurological disorders?

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Abstract

The kallikrein-kinin system (KKS) is an intricate endogenous pathway involved in several physiological and pathological cascades in the brain. Due to the pathological effects of kinins in blood vessels and tissues, their formation and degradation are tightly controlled. Their components have been related to several central nervous system diseases such as stroke, Alzheimer's disease, Parkinson's disease, multiple sclerosis, epilepsy and others. Bradykinin and its receptors (B1R and B2R) may have a role in the pathophysiology of certain central nervous system diseases. It has been suggested that kinin B1R is up-regulated in pathological conditions and has a neurodegenerative pattern, while kinin B2R is constitutive and can act as a neuroprotective factor in many neurological conditions. The renin angiotensin system (RAS) is an important blood pressure regulator and controls both sodium and water intake. Ang Ⅱ is a potent vasoconstrictor molecule and angiotensin converting enzyme is the major enzyme responsible for its release. Ang Ⅱ acts mainly on the AT1 receptor, with involvement in several systemic and neurological disorders. Brain RAS has been associated with physiological pathways, but is also associated with brain disorders. This review describes topics relating to the involvement of both systems in several forms of brain dysfunction and indicates components of the KKS and RAS that have been used as targets in several pharmacological approaches.

Key words: Kallikrein-kinin system; Renin-angiotensin system; Neurological disorders; Alzheimer's disease; Epilepsy; Parkinson's disease

Core tip: This review is a description of the involvement of the kallikrein-kinin and renin-angiotensin systems in neurological disorders. We describe all components of both systems, relating them to several brain diseases such as Alzheimer's disease, Parkinson's disease, epilepsy, multiple sclerosis, blood brain barrier disruption, stroke and inflammation, including the involvement of each molecule, their receptor and specific enzymes in individual pathologies. We also show that brain homeostasis depends on a dynamic balance between the kallikrein-kinin and renin-angiotensin systems.

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KALLIKREIN-KININ SYSTEM IN NEUROLOGICAL DISORDERS

Components of the kallikrein-kinin system

The kallikrein-kinin system (KKS) is an intricate endogenous pathway involved in blood pressure regulation, inflammation, cardiovascular homeostasis, analgesic responses, pain-transmitting mechanisms, cytokines release, prostacyclin, nitric oxide and cell proliferation[1,2].

Initial studies on the importance of the KKS in mammals were performed at the beginning of the last century, when Abelous *et al*[3] verified that human urine injected into dogs induced a reduction in blood pressure. After that, several authors identified a great number of molecules, with biological activity, involved in this bioactive cascade[4-8]. Thus, since 1900 to date, all components of the KKS were sequentially identified in plasma and/or in tissue as part of a complex enzymatic process linked to several biological and pathological events.

Due to the effects of kinins in blood vessels and tissues, their formation and degradation are tightly controlled. In plasma, the coagulation factor XII (Hageman factor XII) is activated to XIIa by the negative surface and is then able to cleave prekallikrein into the active form of kallikrein. This latter enzyme hydrolyzes high molecular weight kininogen and releases bradykinin (BK) into the circulation, which is an important vasoactive nonapeptide (Arg^1-Pro^2-Pro^3-Gly^4-Phe^5-Ser^6-Pro^7-Phe^8-Arg^9). After C-terminal arginine removal, by circulating and/or tissue kininases, BK is converted into Des-Arg^9BK, another potent peptide or to inactive peptides. BK has high affinity for the constitutive kinin B2 receptors (B2R), while Des-Arg^9BK shows preference for binding to inductive kinin B1 receptors (B1R)[8].

In tissues, prekallikrein is also converted into kallikrein, which hydrolyzes the low molecular weight kininogen, releasing Lys-BK, also known as kallidin. After the action of tissue kininases, Lys-Bk is converted into BK or Des-Arg^{10}-Lys-BK, which also have high affinity for B1R, while its precursor (kallidin) shows more affinity for B2R (Figure 1). All these enzymes involved in the KKS are serine-proteases. Plasma kallikrein and tissue kallikrein 1 (KK1) are the main enzymes involved in kinin release in blood and tissue, respectively.

KKS in the central nervous system

All components of the KKS have been localized in the cerebral cortex, brain stem, cerebellum, hypothalamus, hippocampus, and pineal gland, among others. They are found surrounding blood vessels, in neurons and glial cells[9-12]. Kinins are able to stimulate the production and release of inflammatory mediators such as eicosanoids, cytokines, nitric oxide (NO) and free radicals. Kinins also induce the release of excitatory amino acids, increasing intracellular (Ca^{2+})i levels and inducing brain excitotoxicity. These peptides are also involved in disruption of the blood-brain-barrier (BBB) and dilation of the parenchyma of cerebral arteries causing edema[13-15]. The mitogen-activated protein kinase pathway, which culminates in the transcription of many genes involved in later responses[16] is also activated by B1R. Stimulation of both B1R and B2R leads to classical G-protein activation with the generation of different second messengers (Figure 1).

In addition, plasma and tissue enzymes, other serinoproteases, similar to chymo/trypsin-like proteases, have been described and they are also known as kallikreins (KK1 to KK15). According to Sotiropoulou *et al*[17], this family of 15 enzymes has been related to diseases such as hypertension, renal dysfunction, inflammation, neurodegeneration and several types of cancer[18].

The KKS influences multiple players in the immune system acting on targets such as macrophages, dendritic cells, T and B lymphocytes modulating the activation, proliferation, migration and the effector function of these cells[19]. Thus, kallikreins have been associated with several pathologies, supporting new insights related to the KKS, which could be useful as targets in the treatment of pathological conditions.

KKS in inflammation

In neurodegenerative disorders, inflammation is considering a primary response to injury or to infection, repairing and healing the injured tissue[20]. Vascular permeability and blood flow increases in the first stage of inflammation and substances produced by mast cells and by platelets such as histamine, BK, leukotrienes, prostaglandins and serotonin are released during the initial inflammation process[20]. Blood vessel walls change their permeability allowing the entry of proteins and small molecules, which are important to the recruitment of defense cells. At this stage, leukocytes, adhesion molecules, cytokines and chemotactic factors are recruited to the injured site. Indeed, the release of BK may participate in this process and several authors have studied KKS targets to improve the delivery of drugs through the blood-tumor barrier[21-23].

KKS and cerebrovascular alterations

According to Kung *et al*[24], patients with traumatic brain injury, subarachnoid hemorrhage, intracerebral hemorrhage and ischemic stroke have increased BK levels in CSF and these high levels correlate with the intensity of edema formation. In addition, patients with aneurysmal subarachnoid hemorrhage have low levels of serum KK6 and KK6 levels in blood could predict early complications of this disease. Thus, Martinez-Morillo *et al*[25] suggested that KK6 could be a useful prognostic marker in this pathological condition. Similarly, cerebral hematoma expansion induced by hyperglycemia is mediated by plasma KK[26].

Kininogen-deficient mice show less severe BBB damage, edema and inflammation formation after thrombosis and ischemic stroke. According to some authors, kininogen deficiency is able to reduce thrombosis after stroke, without increasing the risk of intracerebral hemorrhage. In the absence of kininogen, mice are completely unable to produce BK. This lack of kininogen underlies

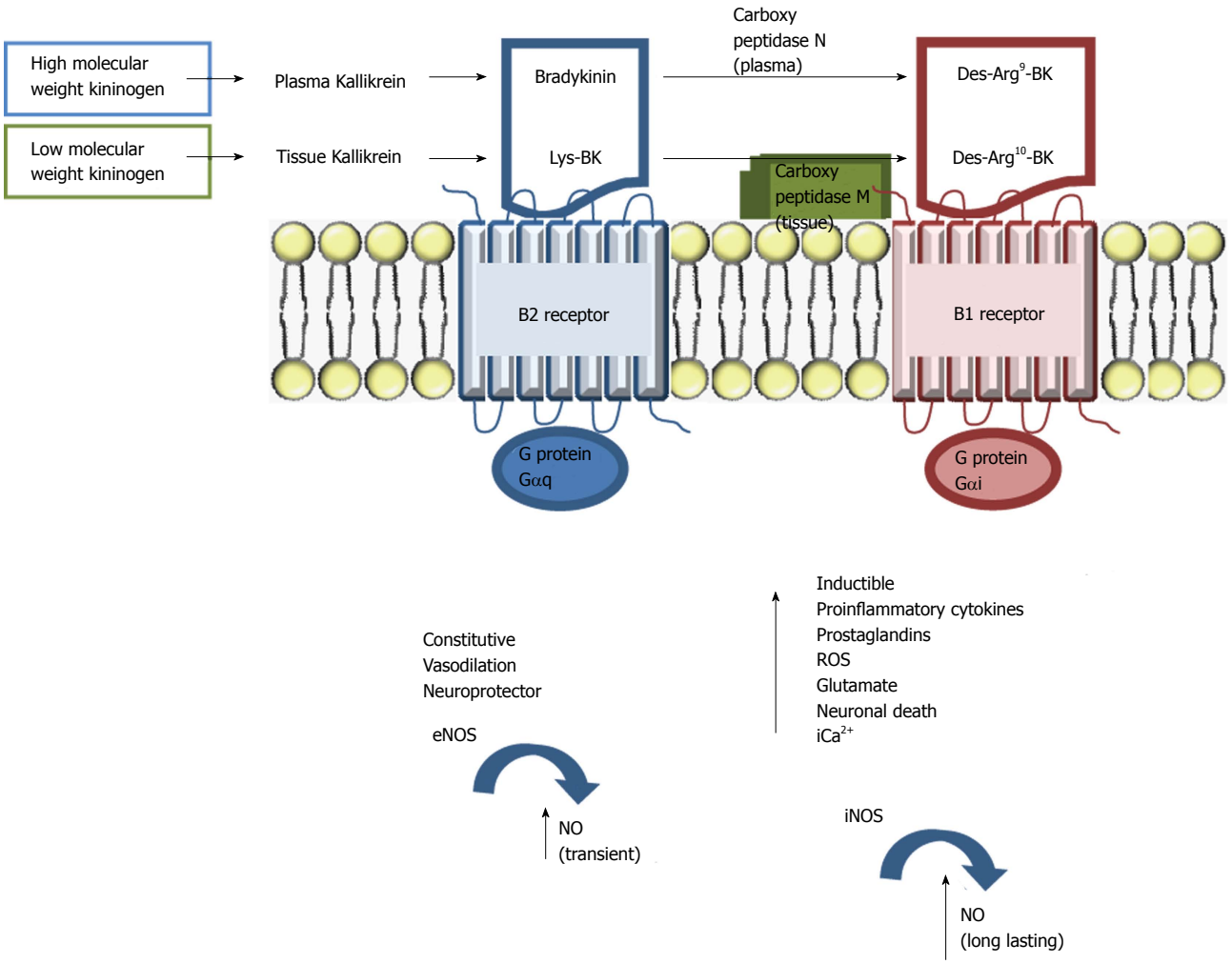

Figure 1 Schematic representation of the kallikrein-kinin system. Bradykinin and Lys-bradykinin (BK), generated by the action of plasma or tissue kallikrein on the precursor (high or low molecular weight kininogen) are the main bradykinin and its receptor (B2R) agonists. These peptides can be converted to B1R agonists after removal of C-terminal-Arg. Both peptidases, membrane-bound carboxypeptidase M, linked to B1R at the C-terminal domain or the soluble carboxypeptidase N are able to remove Arg from the C-terminal portion of BK. B2R is constitutively expressed, showing physiological effects such as vasodilation, transient nitric oxide (NO) production by endothelial nitric oxide synthase (eNOS), whereas B1R expression is induced by injury or inflammatory conditions, with long-lasting NO production, resulting in a neurotoxic environment with reactive oxygen species (ROS) production and increased release of glutamate with excitoxicity-induced neuronal death.

the strong anti-inflammatory phenotype observed in the context of brain ischemia in these animals[27]. Moreover, genetic depletion of B1R improves functional outcome after focal head injury in mice. This effect is similar to that obtained by a pharmacological approach, using a selective B1R antagonist[8]. Thus, mice with B1R depletion show minor axonal damage, reduced apoptosis, astrocyte activation and less inflammation. In contrast, blockage of B2R had no effect on brain protection.

KKS and dementias

Decreased cerebral flow and BBB disruption are also features of Alzheimer's disease (AD)[28,29]. BK activity affects cerebrovascular tone and BBB permeability, both of which are abnormal in AD[30]. According to Farrall *et al*[30], the frontal cortex of patients with AD, the frontal and temporal cortex of patients with vascular dementia showed high levels of plasma kallikrein as well as its mRNA. In addition, this enzyme also had high activity showing that kinin production could influence cerebral blood flow and vascular permeability related to AD. Other types of KK are also modified in the CSF of patients with AD and with frontotemporal dementia. KK6, KK7 and KK10 were decreased in the CSF of patients with frontotemporal dementia, while KK10 increased in the CSF of subjects with AD. These differences could be useful in the diagnosis of both diseases[31]. Increased expression of KK6 was also observed in CSF, plasma and whole blood of patients with AD[32], showing a strong relationship between the KKS and brain degeneration. Furthermore, mice expressing human amyloid precursor protein (APP), carrying familial AD gene mutations, showed increased expression of B1R in astrocytes of the hippocampal formation. Similarly, blockage of this receptor, using specific antagonists, decreased amyloidosis plaque deposits in the somatosensory/cingulate cortex and dorsal hippocampus[33]. These authors also showed improvements in learning and memory after B1R block-

age in APP mice. Thus, according to Lemos *et al*[34] during the aging process, B1R could be involved in memory degeneration, while B2R could act as a neuroprotective factor.

Kallikrein 8 also known as neuropsin participates in extracellular proteolysis involved in long-term potentiation (LTP), necessary for the establishment of memory acquisition in the hippocampus[35]. According to these authors, KK8 knockout mice were impaired, failed memory tasks and showed the involvement of this enzyme in phosphorylation of the GluR1 subunit of AMPA receptors, linked with LTP and with memory acquisition. Taken together, these data show that the KKS participates in these degenerative diseases.

KKS and neuromuscular diseases

Kallikreins are also associated with secondary progressive multiple sclerosis and promote neurodegeneration[36]. According to these authors, high levels of KK1 and KK6 may serve as biomarkers of multiple sclerosis progression. KK1 levels correlate positively with expanded disability status scale (EDSS) scores and KK6 with future prognostic and worsening of the EDSS scale, in relapsing remitting patients. These authors also showed that exposure to kallikrein promoted neurite retraction and neuronal death in murine cortical neurons[36].

Recent work showed that deletion of the *KK6* gene affected the number of oligodendrocytes and the amount of myelin in the developing spinal cord, in particular the myelin basic protein[37]. These data suggest that KK6 has an important function in promoting oligodendrocyte development in the spinal cord as well as in damaged spinal cords. In addition, KK6 has also been associated with hypertrophic astrocytes in human pathological conditions, promoting astrocyte stellation, stimulating inflammatory cytokine (IL-6) secretion and suppressing GFAP mRNA expression[38]. Undoubtedly, KK6 seems to be very important for the homeostasis of CNS cells, participating in several events during physiological and pathological conditions.

KKS and epilepsy

It is already known that the brain inflammatory process is able to initiate seizures[39] and this event is accompanied by an immune-mediated leakage in the BBB. The first evidence linking the KKS with epilepsies was demonstrated by several authors around the 1970s[40,41]. Since then, a large number of studies have emerged localizing more specific targets in the KKS cascade that could help in understanding epilepsy physiopathology. In 1999, Bregola *et al*[42] showed changes in hippocampal and cortical B1R in two experimental models of epilepsy. These authors reported that Lys-des-Arg^{9}BK, an agonist of B1R, increased the overflow of glutamate after electrical stimulation, in hippocampal and cortical slices of rats submitted to kindling. This effect was also visualized in rats submitted to the kainate model of epilepsy, but to a lesser extent. The authors associated B1R with the condition of latent epileptic hyperexcitability[42]. These data were confirmed by Mazzuferi *et al*[43] when they showed the increased release of glutamate after B1R stimulation, induced by Lys-des-Arg^9-BK in kindled animals.

When studying the expression of B1R and B2R in the hippocampus of rats submitted to the pilocarpine model of epilepsy, our group[44] found increased expression of both receptors in the hippocampus. We also found[45] these alterations in knockout mice (B1KO and B2KO) in the pilocarpine model. This means that the absence of B1R (B1KO) decreases pyramidal cell death, decreases mossy fiber sprouting and decreases the number of spontaneous recurrent seizures, during the chronic phase, showing that B1R is proconvulsant. These data were confirmed by Silva *et al*[46]. However, using the model of audiogenic kindling with limbic recruitment, Pereira *et al*[47] found increased expression of B1R and B2R in the hippocampus of rats, but reported that this increase did not correlate with inflammatory levels as IL1β, COX2 and TNFα were not modified in this tissue.

We also showed[45] that B2R was linked to neuroprotection, as its absence is associated with decreased pyramidal cell survival and increased mossy fiber sprouting. Confirming these data, other authors have shown that BK triggers a neuroprotective cascade *via* B2R activation, which conferred protection against NMDA-induced excitotoxicity[48]. However, different data were recently reported concerning the role of B2R in epileptogenesis. Rodi *et al*[49] found that B2R was overexpressed in limbic areas and that slices prepared from B1R knockout mice (B1K0) were more excitable than those from wild-type mice. This effect was abolished using B2R antagonists. Due to this result, the authors concluded that this excitatory phenomenon was B2R dependent. In addition, these authors also demonstrated that kainic acid-induced seizures are attenuated by a B2R antagonist, supporting the hypothesis that B2R is involved in an early event that leads a normal brain to epileptic conditions.

When studying patients with temporal lobe epilepsy (TLE) and hippocampal sclerosis we also showed increased levels of B1R and B2R in the hippocampus[50], when compared with autopsy-control tissues. These receptors were visualized in pyramidal neurons of the hilus and in CA1 and CA3 regions of the hippocampal formation. The hippocampus of these patients also showed overexpression of KK1 by astrocytes, which were co-localized with GFAP protein, confirming participation of the KKS[51].

Together, these data show effective participation of the KKS system in TLE and Figure 2 shows our suggestion concerning a possible cross-talk between hippocampal neurons and astrocytes in the KKS in epileptic diseases.

RENIN-ANGIOTENSIN SYSTEM AND NEUROLOGICAL DISORDERS

Components of the renin-angiotensin system

The renin-angiotensin system (RAS) was initially consid-

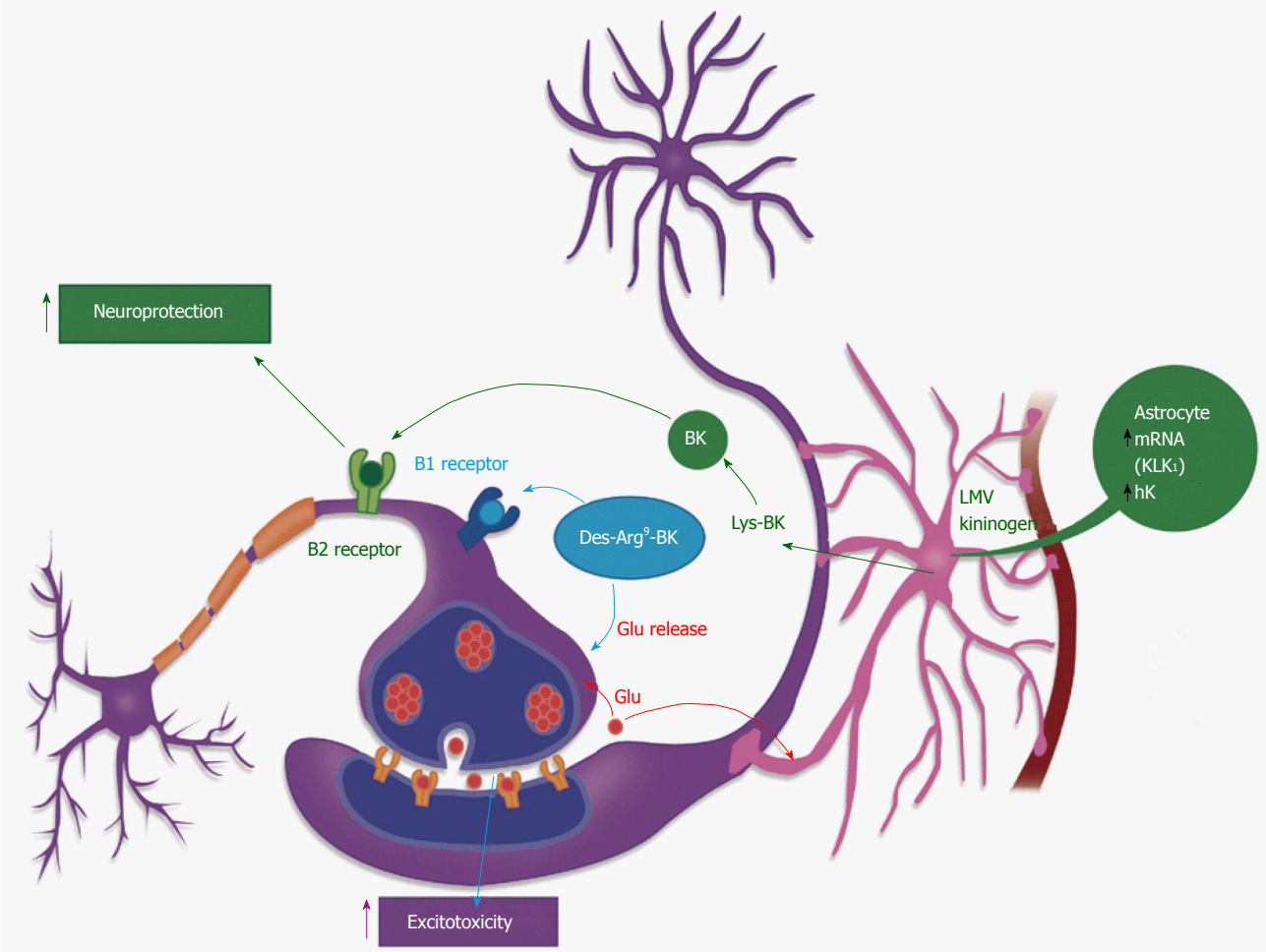

Figure 2 Cross-talk between glial and neural cells related to the kallikrein-kinin system. An adaptation based on the image found at the following site: http://learn.genetics.utah.edu/units/addiction/reward/images/neuronsAstrocyte.jpg. Kallikrein 1 (KK1) in the hippocampus, acts on its main substrate, the low molecular weight kininogen, to release Lys-bradykinin (BK) which can be hydrolyzed to BK, Des-Arg9BK or des-Arg10-Lys-BK by kininases, localized in astrocytes or at the extracellular matrix. These short-living peptides will act on the neuronal surface: binding to kinin B1R they will induce an increase in glutamate release, thus increasing neuronal excitability. Acting on kinin B2R these peptides will produce neuroprotection[42-45].

ered to be a circulating humoral system, involved in blood pressure regulation and the control of both sodium and water intake. Molecules formed by this system are associated with vasoconstriction and the release of aldosterone from the adrenal cortex and antidiuretic hormone from the neurohypophysis. RAS components act in the vasculature to promote vasoconstriction and at sites within the central nervous system to stimulate sympathetic outflow, impair the baroreflex sensitivity for heart rate control, promote release of catecholamines and aldosterone, and sodium retention, which have an important role in the development and maintenance of hypertension and insulin resistance during aging[52].

Renin is the rate-limiting enzyme of the RAS and acting on its precursor, angiotensinogen, releases angiotensin I , Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu (Ang I). After dipeptide His-Leu removal by angiotensin converting enzyme (ACE), Ang Ⅱ is produced (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe). Ang Ⅱ is the main effector peptide in this system. Binding to Ang Ⅱ type 1 receptor (AT1R), Ang Ⅱ stimulates vasoconstriction, aldosterone and steroid hormones release, which are involved in sodium reabsorption and water retention. AT1R activity is also related to hypertension, heart dysfunction, brain ischemia, abnormal stress responses, BBB breakdown and inflammation in several species[53]. The second receptor involved in Ang Ⅱ activity is AT2R. However, the function of AT2R is more elusive and controversial. AT2R is expressed during fetal development, decreasing after birth and remaining at a low concentration during adulthood. It has been linked to cell proliferation, differentiation, apoptosis and regeneration of several tissues[54] (Figure 3).

RAS in CNS

In addition to the well-known humoral RAS, in the last decades a tissue RAS has been described, particularly in the CNS. Thus, all components of the RAS have been found in the brain. However, as this tissue has a low level of renin, it remains controversial as to how Ang I is generated by this system. Recently[55], the presence of a prorenin receptor (PRR) was reported, which has a high

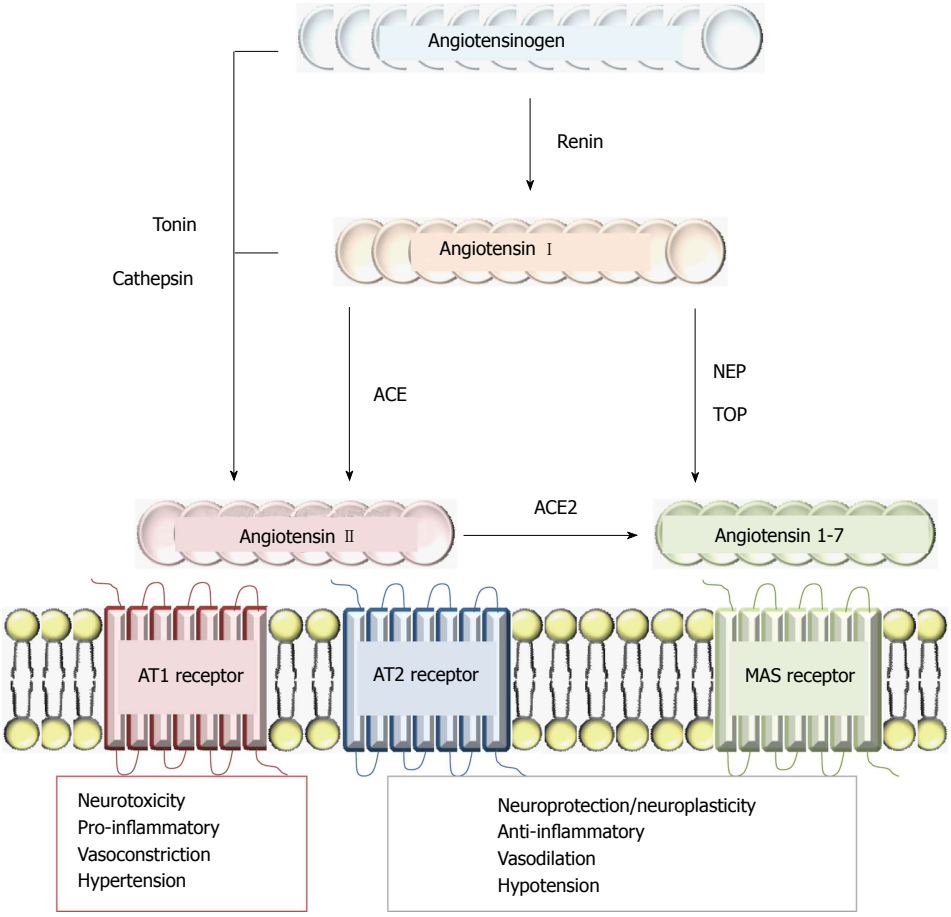

Figure 3 Schematic representation of the renin-angiotensin system and its physiopathological effects. Ang Ⅱ may be generated in the brain *via* the classical pathway, through renin and angiotensin converting enzyme (ACE) action (through Ang Ⅰ cleavage) or can be directly released from angiotensinogen by cathepsin G or tonin actions. Ang1-7 is active in several organs including the brain and several endopeptidases such as thimet oligopeptidase (TOP) or neutral endopeptidases (NEP) may metabolize Ang Ⅰ, generating Ang1-7. Ang Ⅱ may also be hydrolyzed by ACE2 to generate Ang1-7. Binding to Ang Ⅱ type 1 receptor (AT1R), Ang Ⅱ stimulates vasoconstriction, aldosterone and steroid hormones release, which are involved in sodium reabsorption and water retention. AT1R activity is also related to hypertension, heart dysfunction, brain ischemia, abnormal stress responses, blood-brain barrier breakdown and inflammation. The second receptor involved in Ang Ⅱ activity is AT2R and is expressed during fetal development, decreasing after birth and remaining at a low concentration during adulthood. It has been linked to cell proliferation, differentiation, apoptosis and the regeneration of several tissues. Ang1-7 is a Mas receptor agonist, which is related to neuronal plasticity and changes in cellular phenotype that are produced by neuronal activity such as synaptic rearrangements and mossy fiber sprouting in the hippocampus.

level of expression in the brain by neurons and astrocytes. Prorenin binds to its receptors without proteolytic activation and this binding initiates the rate-limiting step in angiotensin formation in the CNS. PRR also acts as an accessory protein for vesicular ATPase, linked to vesicular acidification.

Further to ACE, some homologue components of the RAS have been described such as ACE2 and chymase. Furthermore, peptides such as angiotensin 1-7 (Ang1-7), angiotensin Ⅲ (Ang Ⅲ) and Ang Ⅳ are involved in RAS function. Ang Ⅳ acts at AT4R and Ang1-7 at the Mas receptor. Another enzyme involved in Ang Ⅱ generation is Tonin, which is able to hydrolyze angiotensinogen releasing Ang Ⅱ in tissue, without ACE intervention (Figure 3).

Connection between the KKS and RAS

There is a connection between the KKS and RAS (Figure 4), which is produced by ACE linking both of these important systems. ACE is considered to be the most potent kininase in the blood and in several tissues, such as lung and liver. This enzyme, removes the dipeptide His-Leu from Ang Ⅰ, generates Ang Ⅱ, removes Phe-Arg dipeptide from BK, and inactivates this hypotensor peptide. This is a very important link and it is through the balance between RAS and KKS, that blood pressure can be controlled. This balance is also very important in the brain due to control of BBB permeability.

RAS and inflammation

Despite its action in important physiological processes, RAS has also been associated with pathological conditions. In a recent review[53], authors showed a relationship between the RAS and inflammatory brain disorders, focusing attention on the actions of AT1R in diseases such as stress-induced disorders, anxiety and depression, stroke, brain inflammation, traumatic brain injury and DA. These authors reported that AT1R activation up-regulates common pro-inflammatory mechanisms, activating transcription factors such as NF-κB, triggering an inflammatory cascade with the production of adhe-

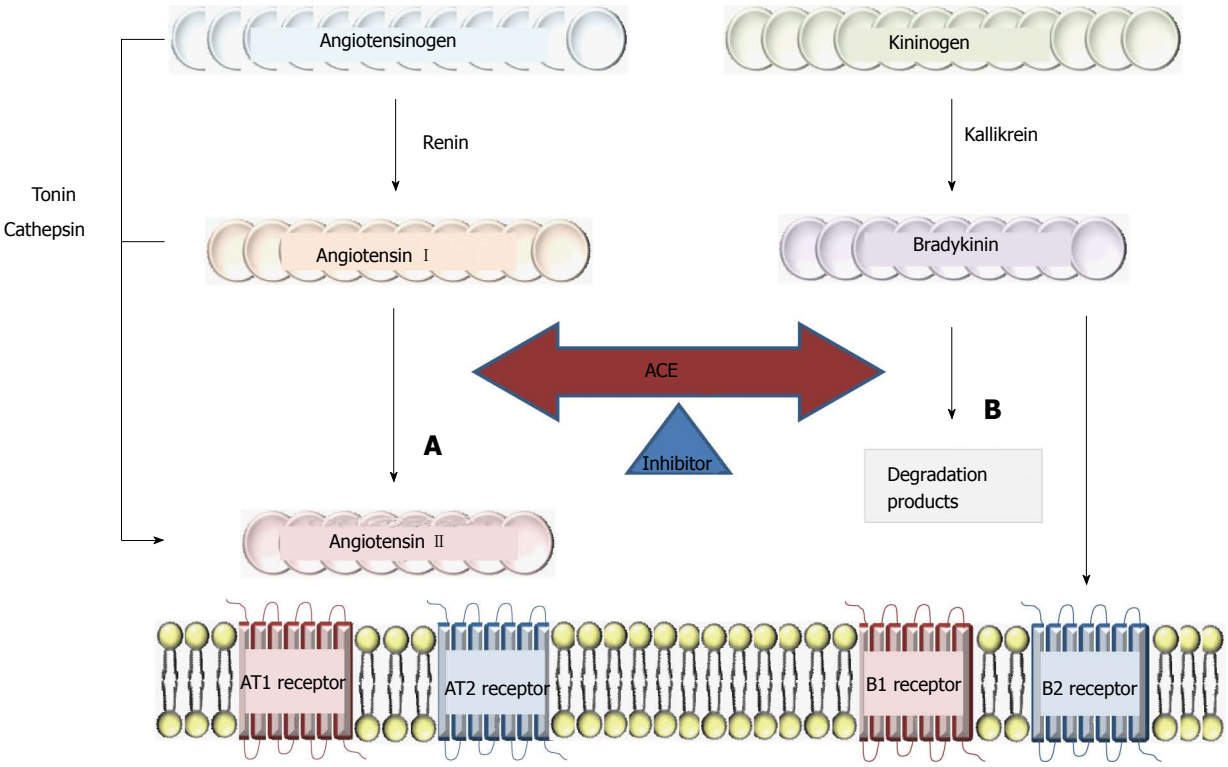

Figure 4 Schematic representation of the role of angiotensin converting enzyme in the renin-angiotensin and kallikrein-kinin systems. A: Conversion of Ang I into Ang II by angiotensin converting enzyme (ACE); B: Bradykinin (BK) degradation by ACE. Physiological effects on the renin-angiotensin system mediated by Ang II type 1 receptor (AT1R) include: vasoconstriction, neuroinflammation, and increased sympathetic nerve activity. Those mediated by Ang II type 2 receptor (AT2R) include cell differentiation and vasodilation. The effects on the kallikrein-kinin system, mediated by kinins, bradykinin and their receptor (B2R) also include vasodilation and hypotension, *via* the release of nitric oxide (NO), prostacyclins and endothelium-derived hyperpolarizing factor (EDHF). It is important to emphasize that in human pathological conditions, the use of ACE inhibitors results in downregulation of Ang II production. In this sense, the kallikrein-kinin system is upregulated and the physiological effects of kinins are potentiated, as all kinin-related peptides are less hydrolyzed by ACE inhibition.

sion molecules, cytokines, reactive oxygen species (ROS), prostaglandins and NO. It was also proposed that circulating Ang II stimulates brain vascular endothelial target cells, producing BBB breakdown, allowing macrophage infiltration into brain parenchyma, increasing microglia and astrocytes activation[53]. Ang II also induces C-reactive protein production by vascular cells as well as by macrophages in culture[56].

RAS and cerebrovascular alteration

Several authors have shown that captopril (ACE inhibitor) improves cerebrovascular structure and function in old hypertensive rats, attenuating eutrophic and hypertrophic inward, remodeling cerebral arterioles. In contrast, Tanahashi *et al*[57] showed that Ang II is related to stroke protection, mediated by AT2R, AT4R and Ang1-7/Mas receptor. However, these authors also indicated that recent clinical trials demonstrated that blockade of the RAS has a potential role in stroke prevention. These data show that the RAS may have dual function in the brain, depending on the action of different peptides and their receptors.

RAS in extrapyramidal diseases

RAS has been identified in the nigrostriatal system and, according to several authors, dopaminergic neurons have an intracellular/intracrine RAS[58,59]. As already mentioned, Ang II acts on the inflammatory cascade, *via* AT1R, producing high levels of ROS by activating the NADPH oxidase complex[60], which are the early processes leading to dopaminergic cell death, in the nigrostriatal system, in Parkinson's disease[61]. These data showed that AT1R blockage reduces dopaminergic neuron loss as well as lipid peroxidation in the Parkinson model (injection of 6-OHDA in rats). These authors also concluded that the RAS is present in dopaminergic neurons with high vulnerability in the nigrostriatal system. The interaction of dopamine/Ang II may be a major factor in age-related dopaminergic vulnerability, that could be the result of increased AT1R expression, decreased AT2R expression, enhanced levels of inflammatory mediators and ROS in dopaminergic pathways[61]. Thus, manipulation of RAS using AT1R antagonists or ACE inhibitors could be helpful in the treatment of Parkinson's disease. In addition, other authors[53,62] also advocate the use of AT1R blockers in the treatment of several inflammatory brain disorders.

RAS and dementias

Other brain pathologies such as AD have also been linked to the RAS. Longitudinal studies have suggested an association between high blood pressure and demen-

tia, showing that hypertension is a risk factor for the development of AD during aging. Patients treated with perindopril (ACE inhibitor) with previous stroke and/or ischemic events were followed for 4 years and dementia and/or cognitive decline were reduced in the treated group, showing a connection between these dual pathologies[63]. Captopril (ACE inhibitor) improves cerebrovascular structure in hypertensive subjects. Indeed, benefit was found when an ACE inhibitor was able to cross the BBB, showing that peripheral action is important, but the effect on cognition is not exclusively due to blood pressure control, but is related to the central action of these drugs[64]. Yamada *et al*[65] showed that perindopril ameliorated cognitive performance in rats submitted to AD models, through inhibition of brain ACE.

In contrast, other authors showed that ACE converts Aβ1-42 (amyloidogenic form) to Aβ1-40 (soluble form), decreasing the Aβ1-42/Aβ1-40 ratio. According to these authors, ACE is also able to degrade Aβ1-42 and Aβ1-40, thus reducing the risk of AD development. They also suggested that treatment with captopril promotes predominant Aβ1-42 deposit in the brain, increasing neuronal vulnerability and death, contradicting the data obtained in patients with hypertension and dementia, treated with this ACE inhibitor. These authors suggest that new strategies could be implemented to improve ACE activity, as novel targets in the treatment of AD[66].

RAS and epilepsy

Other ACE inhibitors such as fosinopril, zofenopril, enalapril and captopril have been associated with the potentiation of antiepileptic drugs[67]. These authors showed that the combination of carbamazepine, lamotrigine, topiramate and valproate with ACE inhibitors decrease audiogenic seizures. Captopril also potentiates the effect of carbamazepine and lamotrigine against electroshock seizures[68]. These data were confirmed in other models of epilepsy. According to Pereira *et al*[69], ACE inhibitor and/or AT1R antagonist were able to reduce the severity of audiogenic seizures. These data link the RAS with generalized seizures and with other types of epilepsies.

In 2008 our group showed, for the first time, an upregulation of AT1R as well as its messenger expression in the cortex and hippocampus of patients with temporal lobe epilepsy, associated with temporal mesial sclerosis[70]. Increased expression of AT2R was also found in the hippocampus showing that the RAS is inwardly associated with this brain disorder. AT1Rs were colocalized with NeuN protein, labeling pyramidal neurons in more vulnerable areas. We also found that a common mutation, which increases ACE activity, occurs in high frequency in the blood cells of patients with TLE and mesial sclerosis. Interestingly, in the hippocampus of these patients, ACE activity was down regulated. Investigating this contradictory data we found that carbamazepine, used to treat seizures was able to inhibit hippocampal ACE activity in these patients. The inhibition of ACE by carbamazepine occurred *in vitro* and *in vivo*, confirming a strong link between TLE and RAS. Patients not treated with carbamazepine showed increased ACE activity[71].

In trying to understand the alteration of RAS components in the epileptogenic process we studied Ang I, Ang II and Ang1-7 levels in the hippocampus of rats submitted to pilocarpine-induced TLE. We found decreased levels of Ang I in acute (status epilepticus), silent (seizure-free period) and chronic (spontaneous recurrent seizures) phases. In contrast, Ang II was increased in the chronic phase, while Ang1-7 was increased in acute and silent periods. These data showed that during the epileptogenic process Ang I was converted into Ang II or Ang1-7. However, ACE expression was decreased in all phases, showing that other enzymes in the RAS may participate in this event such as NEP and Tonin. Indeed, both enzymes were upregulated in the hippocampus of these rats[72]. Our results also showed an upregulation of AT1R during the spontaneous seizure period (chronic phase)[71], in accordance with data found in patients with TLE[70], supporting the involvement of this receptor in seizure generation. The silent phase was characterized by an increase in Ang1-7 levels as well as its Mas receptor. Interestingly, during the silent phase of this model, intense hippocampal reorganization occurs, which has been related to Ang1-7/Mas-induced plasticity.

CONCLUSION

In conclusion, peptides generated by the RAS or KKS are deeply involved in several neurological diseases and an improvement in the knowledge of their function and release in tissues and blood could be useful in the development of new targets and drugs to treat these pathologies.

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