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**Columns: REVIEW**

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

Naffah-Mazzacoratti MG *et al*. KKS and RAS in neurological diseases

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**Author contributions:** Gouveia TLF actually worked with renin-angiotensin systems in epilepsy, Simões PSR worked with kallikrein and other enzymes related to this system; and Perosa SR worked with kinins and their receptors in CNS.

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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 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 systems diseases such as stroke, Alzheimer, Parkinson, multiple sclerosis, epilepsy and others. Bradykinin and their receptors (B1R and B2R) may exert a role in the pathophysiology of certain central nervous systems diseases. It has been suggested that kinin B1R is up-regulated in pathological condition and has a neurodegenerative pattern, while kinin B2R is constitutive and can act as neuroprotective factor in many neurological conditions. The renin angiotensin system (RAS) is an important blood pressure regulator as well as sodium and water intake controller. AngII is a potent vasoconstrictor molecule and angiotensin converting enzyme is the major enzyme responsible for its release. AngII acts mainly throughout AT1 receptor, with its involvement in several systemic and neurological disorders. Brain RAS has been associated to physiological pathways but is also associated to brain disorders. This review describes topics relating the involvement of both system with several brain dysfunctions and indicates components of KKS ad RAS that have been used as target for several pharmacological approaches.

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

**Core tip:** This review is a widely description concerning to the involvement of kallikrein-kinin and renin-angiotensin systems in neurological disorders. We describe all components of both systems, relating them with several brain diseases such as Alzheimer, Parkinson, epilepsy, multiple sclerosis, blood brain barrier disruption, stroke and inflammation, nominating the involvement of each molecule, their receptor and specific enzymes in individual pathology. We also connected both systems showing that the brain homeostasis depend on a dynamic balance between kallikrein-kinin and renin-angiotensin systems.

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**KALLIKREIN-KININ SYSTEM IN NEUROLOGICAL DISORDERS**

***Components of 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 reports concerning the importance of KKS in mammalians were done in the beginning of the last century, when Abelous *et al*[3] verified that human urine injection in dogs induced reduction of the 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 until now, all components of 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 these 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 negative surface and after that it is able to cleave prekallikrein into the active form of kallikrein. This last enzyme, hydrolysing the high molecular weight kininogen, releases the bradykinin (BK) in circulation, which is an important vasoactive nonapeptide (Arg1-Pro2-Pro3-Gly4-Phe5-Ser6-Pro7-Phe8-Arg9). After C-terminal arginine removal, by circulating and/or tissue kininases, BK is converted in Des-Arg9BK, another potent peptide or in inactive peptides. BK present high affinity for the constitutive kinin B2 receptors (B2R), while Des-Arg9BK shows preference for binding on inductive kinin B1 receptors (B1R)[8].

On tissues, prekallikrein is also converted into kallikrein, which hydrolyses the low molecular weight kininogen, releasing Lys-BK, also denominated as kallidin. After the action of tissue kininases, Lys-Bk is converted in BK or in Des-Arg10-Lys-BK, which also present high affinity for B1R, while its precursor (kallidin) shows more affinity for B2R (Figure 1). All these enzymes involved in 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 central nervous system***

All components of KKS have been localized in the cerebral cortex, brain stem, cerebellum, hypothalamus, hippocampus, pineal gland, among others. They are presented surrounding blood vessels, in neurons and glial cells[9-12]. Kinins are able to stimulate 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 (Ca2+)i levels, inducing brain excitotoxicity. These peptides are also involved in the disruption of blood-brain-barrier (BBB), dilation of parenchymal of cerebral arteries causing edema[13-15]. 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 the classical G-protein activation with generation of different second messengers (Figure 1).

Besides, plasma and tissue enzymes, others 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].

KKS influences on multiple players of the immune system acting in targets as macrophages, dendritic cells, T and B lymphocytes modulating the activation, proliferation, migration and the effector function of these cells[19]. Thus, kallikreins now have been associated with several pathologies, supporting new insights related to KKS system, which could be useful as targets for 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 initial inflammation process[20]. Blood vessel walls change its permeability allowing the entrance 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 local. Indeed, the release of BK may participates in this process and several authors have been studying 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 present increased BK levels in CSF and this high levels correlates with the intensity of edema formation. In addition, patients with aneurysmal subarachnoid hemorrhage present low levels of KK6 in serum and its levels in blood could predict early complication of this disease. Thus, Martinez-Morillo *et al*[25] suggested that KK6 could be useful as prognostic marker in this pathological condition. In the same line, cerebral hematoma expansion induced by hyperglycemia is mediated by plasma KK[26].

Kininogen deficient mice show less severe blood-brain barrier 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 absence of kininogen, mice are completely unable to produce BK. This lack underlies 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 those obtained by a pharmacological approach, using 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 blood brain barrier disruption are also features of Alzheimer disease (AD)[28,29]. BK activity affects cerebrovascular tone and blood-brain barrier permeability, both of which are abnormal in AD[30]. According to Ashby *et al*[30], frontal cortex of patients with AD, frontal and temporal cortex of patients with vascular dementia showed high levels of plasma kallikrein as well as its proper mRNA. In addition, this enzyme also presented 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 CSF of patients with AD and with frontotempral dementia. KK6, KK7 and KK10 were decreased in CSF of patients with frontotemporal dementia, while KK10 increased in CSF of subjects with AD. These differences could be useful in the diagnosis of both diseases[31]. An increased expression of KK6 was also observed in CSF, plasma and whole blood of patients with AD[32], showing strong relationship between this 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. Likewise, the blockage of this receptor, using specific antagonists, decreased amyloidosis plaque deposit in the somatosensory/cingulate cortex and dorsal hippocampus[33]. These authors also showed improvement of learning and memory after B1R blockage in APP mice. Thus, according to Lemos *et al*[34] during aging process B1R could be involved in memory degeneration, while B2R could be acting as 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 in memory tasks and showed the involvement of his enzyme with the phosphorylation GluR1 subunit of AMPA receptors, linked with LTP and with memory acquisition. All together, these data show that KKS should participate 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 correlates positively with expanded disability status scale (EDSS) scores and KK6 with future prognostic and worsening in EDSS scale, in relapsing remitting patients. These authors also showed that the exposure of kallikrein to murine cortical neurons promotes neurite retraction and neuronal death[36].

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

***KKS and epilepsy***

As already known the brain inflammatory process is able to initiate seizures[39] and this event is accompanied by an immune mediated leakage in the blood brain barrier. The first evidence linking KKS with epilepsies was done by several authors around seventies[40,41]. After that, a large number of works have been emerged localizing in KKS cascade more specific targets that could help the understanding of epilepsy´s 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-Arg9BK, an agonist of B1R, increase the overflow of glutamate after electrical stimulation, in hippocampal and cortical slices of rats submitted to kindling. This effect was visualized also in rats submitted to kainite model of epilepsy but, in less extension. Authors associated B1R with a condition of latent epileptic hyperexcitability[42]. These data were confirmed by Mazzuferi *et al*[43] when they showed increased release of glutamate after B1R stimulation, induced by Lys-des-Arg9-BK in kindled animals.

Studying the expression of B1R and B2R in the hippocampus of rats submitted to the pilocarpine model of epilepsy our group[44] found an increased expression of both receptors in this structure. We also found[45] that in knockout mice (B1KO and B2KO) pilocarpine model is modified. This means that absence of B1R (B1KO) decreases pyramidal cell death, decreases mossy fiber sprouting and decreases the number of spontaneous recurrent seizures, during 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 an increased expression of B1R and B2R in the hippocampus of rats but, reported that this increase did not correlate with inflammatory levels since IL1β, COX2 and TNFα were not modified in this tissue.

We also showed[45] that B2R was linked to neuroprotection, since its absence is associated with decreased pyramidal cell survival and increase of 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 was recently reported concerning to B2R role in epileptogenesis. Rodi *et al*[49] found that B2R are 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, authors concluded that this excitatory phenomenon is B2R dependent. In addition, these authors also described that kainic acid-induced seizures are attenuated by B2R antagonist, supporting the hypothesis that B2R is involved in an early event that leads a normal brain to epileptic conditions.

Studying patients with temporal lobe epilepsy (TLE), presenting 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 hilus and CA1, CA3 regions of hippocampal formation. The hippocampus of these patients also showed an overexpression of KK1 by astrocytes, which were co-localized with GFAP protein, confirming the participation of KKS in human phenomenon[51].

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

**RENIN-ANGIOTENSIN SYSTEM AND NEUROLOGICAL DISORDERS**

***Components of renin-angiotesin system***

The renin-angiotesin system (RAS) was initially considered as a circulating humoral system, involved in the blood pressure regulation as well as in sodium and water intake control. Molecules formed by this system are associated with vasoconstriction and release of aldosterone from adrenal cortex and antidiuretic hormone from neurohypophysis. RAS components act in 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, sodium retention, having an important role in development and maintenance of hypertension and insulin resistance during aging[52].

Renin is the rate-limiting enzyme of RAS and acting on its precursor, angiotensinogen releases angiotensin I, Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu (AngI). After the dipeptide His-Leu removal by angiotensin converting enzyme (ACE), AngII is produced (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe). AngII is the main effector peptide of this system. Binding to Ang II type 1 receptor (AT1R), AngII stimulates vasoconstriction, aldosterone release and steroid hormone, 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 in several species[53]. The second receptor involved in AngII activity is AT2R. However, AT2R function remains more elusive and controversial. AT2R is expressed during the fetal development, decreasing after birth and remaining in 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 and, with particular attention, in CNS. Thus, all components of RAS have been found in the brain. However, as this tissue presents low level of renin, remains very controversial how AngI is generated by this system. Recently[55], it has been reported the presence of a prorenin receptor (PRR), which has a high level of expression in the brain by neurons and astrocytes. Prorenin binds on its receptors without proteolytic activation and this binding initiate the rate-limiting step for angiotensin formation in CNS. PRR also acts as an accessory protein for vesicular ATPase, linked to vesicular acidification.

Furthermore to ACE, some homologue components of RAS have been described such as ACE2 and Chymase. Furthermore, peptides as angiotensin 1-7 (Ang1-7), angiotensin III (AngIII) and AngIV have been involved in RAS function. AngIV acts at AT4R and Ang1-7 at Mas receptor. Another enzyme involved in AngII generation is named Tonin, which is able to hydrolyze angiotensinogen releasing AngII on tissue, without ACE intervention (Figure 3).

***Connection between KKS and RAS***

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

***RAS and inflammation***

Despite its action on important physiological processes, RAS also has been associated to pathological conditions. A recent review[53], authors showed a relationship between RAS and inflammatory brain disorders, calling attention to the actions of the 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 as NF-ĸB, triggering an inflammatory cascade with production of adhesion molecules, cytokines, reactive oxygen species (ROS), prostaglandins and NO. It was also proposed that circulating AngII stimulates brain vascular endothelial target cells, producing blood-brain barrier breakdown, allowing macrophage infiltration into brain parenchyma, increasing microglia and astrocytes activation[53]. AngII 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 AngII has been related to stroke protection, mediated by AT2R, AT4R and Ang1-7/Mas receptor. However, this author also indicates that recent clinical trials that blockade RAS have a potential role in stroke prevention. These data show that RAS may have dual function in the brain, depending on different peptides action and their proper 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 said, AngII acts on an inflammatory cascade, *via* AT1R, producing high levels of ROS by activating NADPH oxidase complex[60], which are the early processes that lead to dopaminergic cell death, into the nigrostriatal system, in Parkinson disease[61]. These data reported that AT1R blockage reduces dopaminergic neurons loss as well as lipid peroxidation in Parkinson model (injection of 6-OHDA in rats). These authors also concluded that RAS is present in dopaminergic neurons with high vulnerability into nigrostriatal system. Interaction of dopamine/AngII may be a major factor in aging-related dopaminergic vulnerability, that could be the result between increased AT1R expressions, 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 to the treatment of Parkinson disease. In addition other authors[62,53] 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 RAS. Longitudinal studies have suggested an association between high blood pressure and dementia, 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 during 4 years and dementia and/or cognitive decline were reduced in treated group, showing a connection between these dual pathologies[63]. Captopril (ACE inhibitor) improves cerebrovascular structure of hypertensive subjects. Indeed, benefit was found when ACE inhibitor is able to cross the blood brain barrier, 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]. In this view, Yamada *et al*[65] have shown that perindopril ameliorated the cognitive performance of rats submitted to Alzheimer´s disease models, through inhibition of brain ACE.

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

***RAS and epilepsy***

However, 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 between 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 was 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 RAS system 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 RAS is inwardly associated with this brain disorder. AT1Rs were colocalized with NeuN protein, labeling pyramidal neurons of more vulnerable areas. We also found that a common mutation, that 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 did not treat with carbamazepine showed increased ACE activity[71].

Trying to understand the alteration of RAS components in the epileptogenic process we studied AngI, AngII and Ang1-7 levels in the hippocampus of rats submitted to pilocarpine-induced TLE. We found decreased levels of AngI in acute (status epilepticus), silent (seizure-free period) and chronic (spontaneous recurrent seizures) phases. In contrast, AngII was increased into the chronic phase, while Ang-1-7 was increased in acute and silent periods. These data showed that during epileptogenic process AngI was converted in AngII or in Ang1-7. However, ACE expression was decreased in all phases, showing that other enzymes of RAS system may participate of 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 spontaneous seizures period (chronic phase)[71], in accordance with data found in patients with TLE[70], supporting the involvement of this receptor in seizure generation. Silent phase was characterized by an increase of Ang1-7 levels as well as its proper Mas receptor. Interestingly, during the silent phase of this model occurs an intense hippocampal reorganization, which has been related to Ang1-7/Mas induced plasticity.

**CONCLUSION**

In conclusion, peptides generated by RAS or KKS are deeply involved in several neurological diseases and an improvement in the knowledge about its function and in releasing peptides on tissues and blood could be useful to develop new targets and drugs to treat these pathologies.

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

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**Figure 2 Cross-talk between glial and neural cells related to kallikrein-kinin system**. An adaptation based on the image found at the site: <http://learn.genetics.utah.edu/units/addiction/reward/images/neuronsAstrocyte.jpg>. Kallikrein 1 (KK1) on the hippocampus, acting on its main substrate, the low molecular weight kininogen, release Lys-bradykinin (BK) that could 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 neuronal surface: binding to kinin bradykinin and their receptors (B2R they will induce increase in glutamate release, thus increasing neuronal excitability[42-45].

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**Figure 3 Schematic representation of the renin-angiotensin system and its physiopathological effects.** AngII 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 AngI, generating Ang1-7. AngII also may be hydrolyzed by ACE2 to generating Ang1-7. Binding to Ang II type 1 receptor (AT1R), AngII stimulates vasoconstriction, aldosterone release and steroid hormone, 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 AngII activity is AT2R and is expressed during the fetal development, decreasing after birth and remaining in a low concentration during adulthood. It has been linked to cell proliferation, differentiation, apoptosis and regeneration of several tissues. Ang1-7 is a Mas receptor agonist that 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.

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**Figure 4 Schematic representation of angiotensin converting enzyme roles on the renin-angiotensin and kallikrein-kinin systems**. A: Conversion of AngI into AngII 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, 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 receptors (B2R) receptor also include vasodilation and hypotension, *via* release of nitric oxide (NO), prostacyclins and endothelium-derived hyperpolarizing factor (EDHF). Is important to emphasize that in human pathological conditions, when is necessary the use of ACE inhibitors, all production of AngII is downregulated. In this sense, all kallikrein-kinin system is upregulated and the physiological effects of kinins are potentiated, since all kinin-related peptides were less hydrolyzed by inhibited-ACE.

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