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REVIEW ARTICLE

The Potential Therapeutic Capacity of Inhibiting the Brain Renin–Angiotensin System in the Treatment of Co-Morbid Conditions in Epilepsy

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Abstract
Epilepsy is one of the most prevalent neurological diseases and although numerous novel anticonvulsants have been approved, the proportion of patients who are refractory to medical treatment of seizures and have progressive co-morbidities such as cognitive impairment and depression remains at about 20–30%. In the last decade, extensive research has identified a therapeutic capacity of the components of the brain renin–angiotensin system (RAS) in seizure- and epilepsy-related phenomena. Alleviating the activity of RAS in the central nervous system is considered to be a potential adjuvant strategy for the treatment of numerous detrimental consequences of epileptogenesis. One of the main advantages of RAS is associated with its modulatory influence on different neurotransmitter systems, thereby exerting a fine-tuning control mechanism for brain excitability. The most recent scientific findings regarding the involvement of the components of brain RAS show that angiotensin II (Ang II), angiotensin-converting enzyme (ACE), Ang II type 1 (AT_1) and type 2 (AT_2) receptors are involved in the control of epilepsy and its accompanying complications, and therefore they are currently of therapeutic interest in the treatment of this disease. However, data on the role of different components of brain RAS on co-morbid conditions in epilepsy, including hypertension, are insufficient. Experimental and clinical findings related to the involvement of Ang II, ACE, AT_1, and AT_2 receptors in the control of epilepsy and accompanying complications may point to new therapeutic opportunities and adjuvants for the treatment of common co-morbid conditions of epilepsy.

Key Points

There is a link between the brain renin–angiotensin system (RAS) and seizure activity, behavioral changes and neuropathology, hypertension and epilepsy, and possible treatment of co-morbid conditions in epilepsy.

Overexpression of RAS components in the central nervous system is considered a risk factor for seizure and epilepsy development and the accompanying complications.

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II type 1 (AT_1) receptor antagonists have anticonvulsant, anti-inflammatory, antioxidant, behavioral, and neuroprotective properties in the epileptic state.

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1 Introduction

As a multifactorial neurological disorder, epilepsy is characterized by spontaneous epileptiform activity and accompanying complications such as depression, cognitive impairment, autism, and attention deficit and hyperactivity disorder [1–4]. In patients with temporal lobe epilepsy (TLE), hippocampal formation is the most affected brain structure with detected histopathological changes in the hilus of the dentate gyrus (DG) and CA1 and CA3 subfields, as well as altered expression and function of different neuropeptide receptors [5, 6]. Antiepileptic drugs (AEDs) mainly suppress the symptoms of epilepsy but are unable to prevent epileptogenesis or the development of a chronic epileptic state, characterized by detrimental neurochemical, morphological and behavioral consequences, comprising oxidative stress, disturbed equilibrium between excitatory and inhibitory neurotransmitter systems, inflammation and neuronal loss in the limbic system [2, 7–11].

In addition to the renin–angiotensin system (RAS), the components of which are found in most organs and tissues

and are crucial for cardiovascular control, the discovery of an independent RAS in the central nervous system (CNS) expanded the functions of this system beyond its classical physiologies, including seizure susceptibility, learning and memory, stress, and depression [12, 13]. The role of brain RAS in the regulation of neuronal plasticity and its beneficial impact in neurological disorders such as epilepsy, Alzheimer s disease, Parkinson s disease, and Huntington s chorea has been the subject of research and interpretation during the last decade [12–15]. The octapeptide angiotensin II (Ang II), generated by angiotensin-converting enzyme (ACE) or tonin, is the main biologically active peptide, acting as a neuromodulator in the CNS with dual effects on neuronal excitability: excitatory, mediated by Ang II type 1 (AT_1) receptors, and inhibitory, mediated by Ang II type 2 (AT_2) receptors [16–18].

Over the last few years, accumulated scientific evidence has provided strong support for the involvement of brain RAS components in seizure- and epilepsy-related phenomena. Recent studies from several laboratories, including ours, have reported altered levels of angiotensin peptides and receptor expression in limbic brain regions characterized by low seizure threshold, both in experimental models and in patients with TLE [19–22]. Most of the findings demonstrated that inhibition of RAS components, in particular Ang II and AT_1 receptors, attenuated seizure susceptibility [20, 23–26]. Currently, data on the role of different components of brain RAS on co-morbid conditions in epilepsy, including hypertension, are insufficient. This review summarizes experimental and clinical findings related to the involvement of Ang II, ACE, AT_1, and AT_2 receptors in the control of epilepsy and accompanying complications, which might point to new therapeutic opportunities and adjuvants for the treatment of common co-morbid conditions of epilepsy.

2 Experimental Findings: The Brain Renin–Angiotensin System (RAS) and Epilepsy

The experimental findings regarding the effects of RAS components in epilepsy are summarized in Table 1.

2.1 Seizure Activity

Initial studies, launched by our team, demonstrated that the biologically active angiotensin peptides Ang II, Ang III, and Ang IV exhibited anticonvulsant activity, both in acute seizure tests in naïve mice and in pentylenetetrazol-kindled mice [27–31]. However, long-term intracerebroventricular (ICV) infusion of Ang II, starting after kainate-induced status epilepticus (SE) in rats, exacerbated epileptogenesis, shortened the latent period and increased the number of spontaneous motor seizures (SMS) [32]. These findings suggest that, depending on whether the brain is in a physiological or pathophysiological state, Ang II can exert dual effects on seizure susceptibility: anticonvulsant in acute seizure tests in naïve animals or proconvulsant in epileptogenesis. The latter is associated with complex plastic phenomena and network reorganizations leading to a decrease in the seizure threshold and impaired balance between the classical excitatory and inhibitory neurotransmitter system. The increased seizure susceptibility is closely linked with neuronal loss in limbic structures and γ-aminobutyric acid (GABA)-ergic interneurons in the hilus of the DG, recruitment of new synapses, and axonal sprouting in glutamatergic neurons [33–36]. Epileptogenesis is also associated with aberrant neurogenesis, severe inflammation (activated microglia and destroyed astrocyte function), and altered expression and function of important receptors closely related to seizure susceptibility [37]. Experimental results in models of epilepsy revealed that the levels of RAS components were increased in the brain. Thus, upregulation of Ang II levels, ACE, and AT_1 receptors was reported in rat hippocampus both in a genetic-based model [20] and in an acquired model of TLE induced by pilocarpine [21, 24]. In accordance with these findings, we recently reported that upregulation of the AT_1 receptors is a common pathway associated with epileptogenesis in normotensive Wistar and spontaneously hypertensive rats (SHRs) [22]. The proconvulsant effect of Ang II in epileptogenesis might involve excitatory influences via AT_1 receptors related to facilitated release of glutamate and activation of excitatory *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in brain structures such as the hippocampus [38, 39], the paraventricular nucleus of the hypothalamus [40], as well as the basolateral complex and the central and cortical amygdala [41].

2.2 Anticonvulsant Activity

During the last decade, data were accumulated in support of the hypothesis that inhibition of RAS exerts anticonvulsant effects in both naïve animals and models of epilepsy, which confirm the proconvulsant action of Ang II in the brain. In the maximal electroshock (MES) test in mice, enalapril and losartan potentiated the anticonvulsant activity of AEDs without affecting their plasma and brain concentrations, thereby exhibiting pharmacodynamic effects [42–44]. Similarly, two ACE inhibitors, fosinopril and zofenopril, not only potentiated the effect of AEDs, but exerted direct effects on seizures in the DBA/2 (Dilute Brown Non-Agouti) mice model of generalized tonic–clonic seizures [45]. Further, the new-generation antihypertensive drug aliskiren, as well as the AT_1 receptor antagonists telmisartan and olmesartan, had an anticonvulsant effect against pentylenetetrazol-induced

Table 1 Effects of renin–angiotensin system components in experimental models of epilepsy

Model	Treatment	Effects of treatment	References
PTZ kindling	Losartan (100 µg/mouse) + Ang II (0.05 µg/mouse), ICV	Decreases seizure intensity in mice	[30]
	Ang II (1 µg/mouse), single ICV	Suppresses kindling in mice	[27, 28]
ivPTZ seizure threshold test	Ang II (1 µg/mouse), single ICV	Increases seizure threshold in mice	[29]
	Aliskiren (75 mg/kg), single IP injection	Increases seizure threshold in mice	[46]
PTZ seizure test	Olmesartan (2.5 and 5 mg/kg), oral	Increases seizure latency in mice	[50]
	Losartan (10 mg/kg), SC	Anticonvulsant effect in rats	[49]
MES test	Aliskiren (75 mg/kg), IP	Enhances the anticonvulsant effect of AEDs in mice	[47]
	Losartan (30–50 mg/kg), IP Enalapril (30 mg/kg), IP	Potentiates anticonvulsant effect of AEDs in mice	[42–44]
	Telmisartan (5 and 10 mg/kg), oral	Anticonvulsant effect in mice	[50]
Auditory model of generalized tonic–clonic seizures	Repeated acoustic stimulation for 2 weeks Losartan (50 mg/kg/day) or enalapril (10 mg/kg/day), oral for 21 days, starting 7 days before the acoustic stimulation	Upregulation of ACE and AT_1 receptors in Wistar audiogenic rat (genetic-based model) Reduces seizure intensity in Wistar audiogenic rat (genetic-based model)	[20]
	Fosinopril (10 mg/kg), IP injection Zofenopril (15 mg/kg), IP	Potentiates anticonvulsant effect of AEDs in DBA/2 mice	[45]
Albumin-induced vascular injury model of epilepsy	Losartan (100 mg/kg), IP; 2 g/L oral for 3 weeks in Wistar rats	Anticonvulsant effect	[23]
KA-induced SE	Losartan (10 mg/kg/day), chronic SC infusion for 14 days before SE	Prevents oxidative stress and neurotoxicity in Wistar rats and SHRs	[84]
	ZD7155 (5 mg/kg), IP	Suppresses the noradrenaline and dopamine increases in the hippocampus in WKY rats and SHRs	[51]
Pilocarpine-induced post-SE model of TLE	Pilocarpine (350 mg/kg), IP	Increases Ang II levels in the hippocampus in rats	[21]
Lithium pilocarpine-induced post-SE model of TLE	Lithium chloride (127 mg/kg), IP 24 h prior to pilocarpine (30 mg/kg), IP Losartan (100 µg/5 µL), ICV starting 1 h before lithium chloride and administered for 12–21 days	Increases expression of Ang II and AT_1 receptors in activated microglia in rats Anti-inflammatory and neuroprotective effect; improves cognition in rats	[24]
KA-induced post-SE model of TLE	Losartan (10 mg/kg/day), chronic oral administration for 28 days, starting 2 h after SE	Anticonvulsant and neuroprotective effects; positively affects behavioral changes in rats	[25]
	Ang II (1.52 µg/µL/day), chronic ICV infusion for 28 days	Proconvulsant and neuroprotective effects; exacerbates behavioral changes in rats	[32]
	Losartan (10 mg/kg/day), chronic oral administration for 28 days, starting 2 h after SE	Anticonvulsant and neuroprotective effect in SHRs	[26]
	Losartan (10 mg/kg/day), chronic oral administration for 28 days, starting 2 h after SE	Strain-dependent effects on memory in Wistar rats and SHRs	[73]
	KA (5 or 2.5 mg/kg), IP until SE Losartan (10 mg/kg/day), chronic oral administration for 28 days, starting 2 h after SE	Upregulation of AT_1 receptor in the dorsal hippocampus in Wistar rats and SHRs and the basolateral amygdala in SHRs Stronger suppression of upregulated AT_1 receptors in SHRs than Wistar rats	[22]
Amygdala kindling model of TLE	Enalapril (10 mg/kg/day), chronic oral pretreatment for approximately 3 months	Prevented development of small vessel disease; normalized kindling process in SHRs	[48]
Traumatic brain injury	Candesartan (1 mg/kg/day), chronic SC administration, starting before the injury	Anti-inflammatory and neuroprotective effect; improves motor and memory functions in mice	[59]

ACE angiotensin-converting enzyme, *AEDs* antiepileptic drugs, *Ang II* angiotensin II, AT_1 angiotensin II type 1, *DBA/2* Dilute Brown Non-Agouti, *ICV* intracerebroventricular, *IP* intraperitoneal, *ivPTZ* intravenous pentilenotetrazol, *KA* kainite, *MES* maximal electroshock, *PTZ* pentylenetetrazol, *SC* subcutaneous, *SE* status epilepticus, *SHRs* spontaneously hypertensive rats, *TLE* temporal lobe epilepsy, *WKY* Wistar-Kyoto

clonic seizures and in the MES test in mice [46, 47]. Another study showed that long-term treatment with either enalapril or losartan significantly reduced seizure intensity, the effect being accompanied by a blood pressure decrease in a genetic model of epilepsy Wistar audiogenic rats [20]. Russo et al. [48] showed that long-term enalapril pretreatment in SHRs inhibited the occurrence of small-vessel disease and concurrently stabilized the rapid kindling process. Our results are in

agreement with the reports revealing that long-term losartan administration exerted an anticonvulsant effect in the acute pentylenetetrazol seizure test in naïve rats [49]. In support of our finding, the AT_1 receptor antagonists telmisartan and olmesartan in a dose-dependent manner decreased the seizure duration in the MES test and increased the seizure latency in the pentylenetetrazol test in mice [50]. Bar-Klein et al. [23] reported that treatment with losartan reduced the frequency and intensity of seizures, accompanied by transforming growth factor (TGF)-β in a model of albumin-induced vascular injury in Wistar rats, resulting in vessel damage and subsequent epileptiform activity. Long-term treatment with losartan alleviated the frequency of SMS in a kainate-induced post-SE model of TLE in Wistar rats [25]. In contrast, the AT_1 receptor antagonist ZD7155 injected only once was unable to suppress SE both in SHRs and in Wistar-Kyoto (WKY) rats [51]. Thus, continuous treatment was superior over a single administration in the prevention of seizure-related consequences of SE. More recently, we found that losartan was able to blunt the SE-induced protein expression increase of AT_1 receptors in the CNS [22]. These findings confirmed the putative role of the AT_1 receptors and ACE inhibitors in seizure phenomena and epilepsy. It is well-known that the AT_1 receptors are distributed mostly in brain regions that are responsible for the control of the cardiovascular functions, such as the hypothalamus, brain stem, and anterior pituitary [52]. However, although found in low levels, these receptors were co-expressed with $GABA_A$ receptor complexes in limbic brain structures vulnerable to epileptiform activity such as the hippocampus, the amygdala, and the piriform cortex [53]. The close link of RAS with the classical inhibitory neurotransmission was also supported by the fact that the GABAergic pathway had an inhibitory regulatory influence on specific neuronal networks related to important functions of Ang II in brain, such as thirst and blood pressure, as well as control of the hormonal release involved in these phenomena [54, 55].

2.3 Behavioral Changes

Ang II, the main effector peptide of RAS, has been reported to exert effects on motor activity, anxiety, depressive-like behavior, and memory consolidation in experimental rats [13, 53].

Several laboratories demonstrated that rats with spontaneous seizures are characterized by lack of anxiety and fear along with hyperlocomotion, which suggests increased emotionality and impulsivity [3, 56–58]. This inadequate behavior correlated with impaired links between crucial limbic regions such as the amygdala, ventral hippocampus, and entorhinal cortex [57]. Recently, we reported that continuous exposure to Ang II impaired some of the concomitant behavioral changes in epileptic rats [32]. In contrast, AT_1 receptor blockade attenuated epilepsy-enhanced locomotion and affected the emotional state of anxiety in a phase-dependent manner, suggesting that activation of the AT_1/AT_2 receptors underlies the diurnal behavioral variations in kainate-treated normotensive Wistar rats [25]. Similarly, Villapol et al. [59] found that candesartan improved motor and spatial memory functions in a mouse model of traumatic brain injury (TBI). While AT_1 receptor antagonists and ACE inhibitors exhibit anxiolytic effects [50, 60–63], the anxiogenic effect of long-term infusion of Ang II was suggested to be under the control of the AT_1 receptor [32, 64].

Long-term Ang II administration evoked depression-like behavior in naïve rats [32]. In epileptic rats, Ang II exacerbated the co-morbid depression [32], while losartan treatment alleviated this emotional disturbance [25]. These findings are in line with numerous experimental and clinical data, suggesting that suppression of Ang II AT_1 receptor signaling pathways leads to antidepressant-like activity [65–69].

In general, many reports have demonstrated that Ang II is able to alter spatial memory in naïve animals. Although endogenous Ang II was stated as being a non-participant in spatial memory formation [70], short- or long-term administration of the octapeptide impaired the hippocampus-dependent spatial memory in intact mice and rodents tested in the Morris water maze test [71]. Moreover, most of the reports indicated that Ang II worsened the cognitive processes via AT_1 receptor stimulation [71, 72]. In accordance with the literature data, we showed that long-term ICV infusion of Ang II delayed the learning capacity of naïve rats in the radial arm maze test [32]. It could be speculated that damage to some specific limbic circuits, with a key role in memory impairment, could be affected by Ang II. However, this octapeptide had no impact on the epilepsy-induced deficit in spatial memory, which could be due to the exacerbating effect of Ang II on impulsive-like behavior with increased locomotion.

In the kainate model of TLE, losartan treatment had beneficial effects on memory in both SHRs and Wistar rats [73]. Likewise, spatial learning and memory were improved by losartan in the Morris water maze following pilocarpine-induced SE in rats [24]. Interestingly, naïve and epileptic SHRs showed better performance in the radial maze test than normotensive rats [73, 74], which might be explained by increased motor activity and impulsive-like behavior, typical for this strain. However, clinical data revealed a close relationship between hypertension and memory deficit in middle-aged patients [75]. Thus, experimental data from our laboratory and those of others [73, 76] suggest that SHRs are not an appropriate strain to study deficits in cognition associated with co-morbid hypertension in epilepsy.

2.4 Neuropathology Changes

Although Ang II exacerbated epileptogenesis and behavioral co-morbidities, this octapeptide exerted a strong neuroprotection mostly in the CA1 field of the dorsal hippocampus in epileptic rats [32]. The beneficial effect of Ang II on SE-induced neuronal damage might be mediated by the AT_2 receptors. In support of this assumption are results from other investigators who used different paradigms and also reported the neuroprotective effect of Ang II via stimulation of the AT_2 receptors [77, 78]. Alternatively, as a modulator of classical neurotransmitters, Ang II might act indirectly via stimulation of classical inhibitory GABAergic neurotransmission [38, 39, 79].

In addition to the anticonvulsant activity and favorable behavioral outcomes, several studies disclosed anti-inflammatory and neuroprotective effects of RAS inhibition in chronic epileptic conditions. The AT_1 receptor antagonists were reported to exert strong anti-inflammatory and neuroprotective effects in a TBI model in mice. Thus, while candesartan was able to activate peroxisome proliferator-activated receptor (PPAR)-γ and reduced the TGF-β1 cytokine expression in cortical and hippocampal astrocytes, candesartan mitigated TBI provoked neuronal loss and activated microglia in mice [59]. In the pilocarpine model of TLE, Sun et al. [24] showed that losartan attenuated inflammatory responses through inhibition of tumor necrosis factor-α in activated glial cells. Furthermore, neuroprotection was demonstrated in the CA1 and CA3 areas of the hippocampus and in the hilus of the DG after long-term treatment with losartan. Recently, we demonstrated that long-term treatment with losartan during epileptogenesis exerted strong neuroprotection in the CA1 area of the hippocampus in rats [25]. Interestingly, long-term ICV infusion of Ang II after SE also reduced the kainate-induced damage in the CA1 area of the hippocampus in rats [32]. We can speculate that this specific neuroprotection mainly in the CA1 area of the hippocampus exerted by either losartan or Ang II treatments during epileptogenesis could be attributed to the response of the endogenous Ang II as a result of AT_2 receptor subtype activation. While the latter is known to be negligible in physiological conditions, it was upregulated both in a rat model of epilepsy [20] and in patients with epilepsy [19].

3 Clinical Findings of Brain RAS and Epilepsy

Clinical findings regarding the activity of RAS components in human epilepsy are summarized in Table 2. Argañaraz et al. [19] originally reported that the expression and synthesis of AT_1 receptors are increased in the cortex and hippocampus of patients with TLE. These authors also observed elevated levels of AT_2 receptors in the hippocampus of epileptic patients, but without an increase in the messenger RNA (mRNA), proposing involvement of both receptor subtypes in the pathophysiology of TLE. The anticonvulsant drug carbamazepine was found to inhibit ACE in TLE patients, confirming the relationship between epilepsy and RAS [80].

A recent study revealed that losartan failed to suppress human epileptiform activity in brain slices from patients with pharmacoresistant TLE [81]. A possible reason for this lack of efficacy was attributed to the mechanisms involved in seizure generation used in the in vitro experimental approach, which could not reflect the real situation under in vivo conditions. This issue warrants the need for further detailed clinical investigations, which could allow us to better understand the link between epilepsy and RAS.

4 Co-Morbid Hypertension and Epilepsy

Few studies consider the bidirectional relationship between hypertension and epilepsy. Hypertension predisposes to lower seizure threshold and is thereby is a high-risk factor that can trigger epileptogenesis and development of epilepsy [82, 83]. In support of this presumption are our results showing that the kainate-induced seizure activity and neurotoxicity are more severe in hypertensive conditions [84]. A similar electroencephalogram (EEG) profile was observed between rats with congenital hypertension and kainate-treated normotensive rats [85].

Table 2 Effects of renin–angiotensin system components in human epilepsy

Treatment	Model	Effects	References
Cortico-amygdalohippocampectomy	TLE patients	Upregulation of AT_1 receptors in the cortex and hippocampus and of AT_2 receptors in the hippocampus	[19]
Carbamazepine (400–1200 mg/day)	TLE patients	Inhibition of ACE activity	[80]
Losartan (10 and 50 μmol/L) on brain slices	TLE patients	Fails to suppress human epileptiform activity in the hippocampus and temporal neocortex	[81]

ACE angiotensin-converting enzyme, *AT_1* angiotensin II type 1, *AT_2* angiotensin II type 2, *TLE* temporal lobe epilepsy

The revised investigations identified a common profile of some abnormalities related to epilepsy and hypertension, as shown in Fig. 1.

4.1 Overexpression

Like in normotensive rats, losartan alleviated seizure frequency both during the treatment period and after its discontinuation in SHRs [84]. In general, the AT_1 and AT_2 receptors were missing or expressed in small amounts in limbic structures in mammals [51], but under pathological conditions overexpression of components of RAS was observed in experimental animals and in patients with either epilepsy or hypertension [19, 86]. In agreement with these authors we reported that compared with normotensive Wistar rats, the AT_1 receptors in the hippocampus of SHRs were overexpressed not only under epileptic conditions but also in naïve rats [22] (Table 1). Losartan exerted stronger and more structure-dependent suppression of the upregulated AT_1 receptors in epileptic SHRs than in normotensive rats.

4.2 Blood–Brain Barrier Dysfunction and Vascular Damage

An extreme increase of the arterial blood pressure resulted in blood–brain barrier (BBB) dysfunction [87–89]. On the other hand, seizures predisposed to BBB damage, which caused extravasation of plasma constituents and vasogenic brain edema [88, 90]. Thus, impairment of the BBB might initiate epileptogenesis through direct neuronal depolarization or excessive leakage [90]. Previous reports demonstrated that blood pressure suppression [90, 91] during convulsions enabled the BBB disruption to be avoided. Alongside this, repeated losartan treatment was effective in the prevention of BBB permeability in hypertensive rats [92, 93], suggesting that this drug might be protective against barrier leakage in epileptic conditions, as well as in epilepsy accompanied with hypertension. Still, losartan was shown to decrease central sympathetic nerve activity in hypertensive rats [94].

Other investigations postulated that disregarded hypertension, a cerebrovascular risk factor, could indirectly elicit and accelerate the development of epilepsy. Russo et al. [48] found that in the amygdala kindling model of TLE, SHRs with hypertension-related cerebral small vessel disease attained Racine s stage 5 quicker than controls. Another study reported that vascular damage predisposed to epilepsy and mainly affected the frontal and central lobes in stroke patients, while leukoaraiosis was mostly distributed among patients with TLE [83, 95, 96]. However, at present, the risk factors for leukoaraiosis remain unclear.

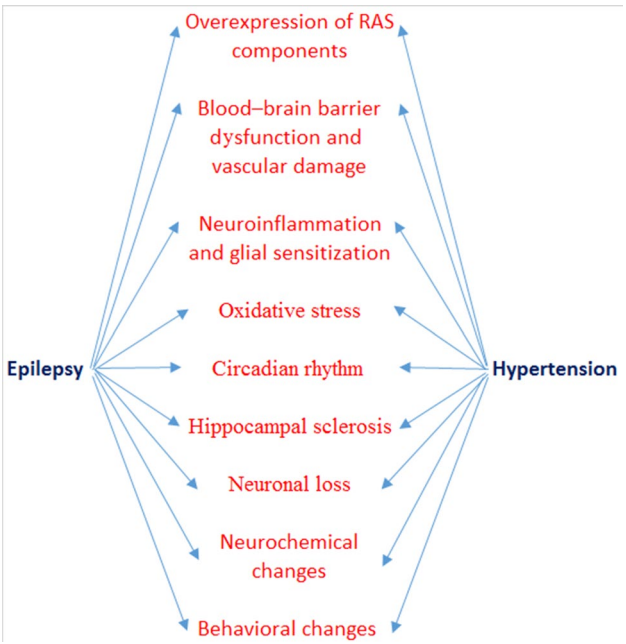

Fig. 1 Abnormalities related to epilepsy and hypertension. *RAS* renin–angiotensin system

4.3 Neuroinflammation and Glial Sensitization

Both epilepsy and hypertension promoted neuroinflammation, including astrocytes and microglial activation leading to the release of inflammatory cytokines and chemokines [23, 24, 97, 98]. The elevated Ang II levels, observed in epileptic and hypertensive conditions, altered migration, differentiation, and proliferation of neuronal and glial cells and caused dysregulation of the neuronal–microglial signaling and the production of proinflammatory factors [24, 97]. Positive astrocytes were detected in two hypertensive strains: SHRs and deoxycorticosterone acetate-salt-treated rats [98]. Like epileptic rats, naïve SHRs were characterized by increased levels of inflammatory interleukins and decreased levels of anti-inflammatory cytokines [97]. While chronic inflammation promoted the development of epilepsy and essential hypertension, RAS inhibitors could diminish these conditions, illustrating an anti-inflammatory activity [23, 24, 97].

4.4 Oxidative Stress

Hyperactive RAS and AT_1 receptor-mediated Ang II responses, in particular, included increased release of inflammatory and oxidant substances such as leukotrienes, free radicals, C-reactive protein and prostaglandins, and thus initiated oxidative stress with a subsequent disturbance in the antioxidant defense system [99–101]. Hypertension associated with excessive release of free radicals could be a risk factor for the development of epileptogenic foci. Like

hypertension, seizure and epilepsy also lead to excitotoxicity and generation of reactive oxygen/nitrogen species and oxidative stress [84, 102, 103]. In 2014, we tested subchronic losartan infusion before SE in the kainate model of TLE, which prevented oxidative stress and neurotoxicity in normotensive Wistar rats and SHRs [84]. Losartan attenuated the kainate-induced increase in lipid peroxidation both in SHRs and Wistar rats and produced higher expression of heat shock protein 72 in the hippocampus. In agreement with our previous data and those of other researchers, SHRs were characterized by a disturbed oxidative defense system compared with normotensive rats in physiological conditions [11, 101]. Previously, Haugen et al. [104] reported that hyperactivity of RAS triggered oxidative stress in SHRs. In this regard, several studies supported the suggestion that Ang II-dependent generation of superoxide and oxygen species presents a key mechanism of cardiac and renal impairment, secondary to diverse pathologies [105–107]. Yet, some of the beneficial effects associated with RAS inhibition can be linked to the prevention of oxidant-mediated damage [108]. Experimental studies evidenced that antagonists of AT_1 receptors function as free radical-scavenging antioxidants in SHRs. Thus, losartan treatment, at the same dose as in our studies (10 mg/kg/day in drinking water for a period of 14 days), increased superoxide dismutase (SOD) activity and glutathione peroxidase to protect brain, kidney, and liver in SHRs, but did not change these parameters in normotensive WKY rats [101]. We found that losartan pretreatment reduced the kainate-induced adaptive increase in the cytosolic SOD activity in the frontal cortex of both normotensive Wistar rats and SHRs [84]. In the latter, the antioxidant effect was also detected in the hippocampus, which could result from the differences in the antioxidant buffering capacities of both strains in the above-mentioned brain regions. Interestingly, we did not detect any changes in the mitochondrial SOD activity in kainate-induced limbic seizures, which suggests that the cytosolic defense system is more sensitive to the acute kainate seizure model than the mitochondrial antioxidant enzyme system in the two strains. Our results support the presumption of an indirect effect of the AT_1 receptor antagonist on the antioxidant system, since data on a direct interaction between RAS inhibition and ROS are still lacking.

4.5 Circadian Rhythm

Findings in animal models and patients with a family history of hypertension revealed a positive correlation between Ang II production in the CNS and the circadian rhythm of arterial pressure [109, 110]. Disturbed diurnal rhythms of the cerebral and systemic circulation were observed in epileptic patients [111].

4.6 Hippocampal Neuropathology and Neuronal Loss

In addition to the neuropathological changes described in Sect. 2.4, further literature findings suggested that the close relationship between hypertension and epilepsy involved hippocampal neuropathology and neuronal loss [25, 26, 32, 83, 98, 112–114]. Patients with hypertensive encephalopathy were characterized by hippocampal sclerosis, which led to the development of TLE [83]. A reduced number of neurons was observed in the hilus of the DG of SHRs and in hypertensive rats treated with deoxycorticosterone [98]. Neuronal damage is a known feature in experimental [35, 114] and human epilepsy [5, 6]. Our results showed that continuous AT_1 receptor blocking was effective against neuronal loss not only in normotensive rats with epilepsy, but also exerted neuroprotection mostly in the CA3 area of the hippocampus and the septo-temporal hilus of the DG in epileptic SHRs [25, 26, 32].

4.7 Neurochemical Changes

Neurochemical changes in hypertension and epilepsy diseases have been established [3, 112, 115]. Administration of Ang II could influence the levels of central neurotransmitters in rats [116]. Like in epileptic Wistar rats, concentrations of the monoamines serotonin, tryptophan, and dopamine were decreased in the hippocampus of naïve and epileptic SHRs [3]. While epilepsy is associated with noradrenergic, serotonergic, and GABAergic deficits [117], elevated levels of extracellular neurotransmitters in the hippocampus were identified during seizure activity in humans and in animal seizure models, as an adaptive response to reducing seizures [115]. Recently, we reported that the kainate-evoked changes of hippocampal monoamine release distinguished between SHRs and normotensive rats [51]. The kainate-induced increase of the hippocampal monoamine levels in SHRs and WKY rats was abolished by the AT_1 receptor antagonist ZD7155, reflecting the association of the monoamines and RAS in the mechanisms of epilepsy and hypertension.

4.8 Behavioral Changes

Data from the literature showed that both hypertension and epilepsy have various behavioral disturbances (as discussed early, including in Sect. 2.3), and most of them were positively affected by RAS inhibition.

All these data imply that the burden of co-morbidity with epilepsy is high. Inhibitors of AT_1 receptors were proven to be effective not only in the treatment of cardiovascular and metabolic disorders plus hypertension and diabetes mellitus, but also in neurodegenerative disorders such as epilepsy [10, 20, 110]. Moreover, the combination of antihypertensives

and AEDs was reported to be a relatively safe strategy for treatment of epilepsy associated with hypertension [43–47]. We also showed that blocking of the AT_1 receptors was more pronounced in a model of epilepsy with co-morbid hypertension [22, 84].

5 Conclusion and Future Perspectives

Generally, experimental and clinical data confirmed the involvement of the brain RAS in the pathophysiology of epilepsy and its accompanying complications. The alteration of the function and expression of RAS components in many brain structures involved in seizure susceptibility have been crucial for the development of epileptogenesis and its consequences both in animal models of epilepsy and in patients with mesial TLE [19–22, 32], including epilepsy with co-morbid hypertension [26, 84]. The RAS inhibitors have been shown to possess anticonvulsant, anti-inflammatory, antioxidant, behavioral, and neuroprotective properties in an epileptic state [20, 23–26, 59, 84]. The use of AEDs has been shown only to suppress the symptoms but not to influence epilepsy and its concomitant deleterious changes, which warrants the need for developing new therapeutic approaches [118, 119]. Besides, most patients using AEDs are at risk of severe and long-term adverse effects and drug interactions, and develop pharmacoresistance at a later stage, reducing their quality of life [120, 121]. The excessive release of Ang II under pathological conditions exerted proconvulsant properties and aggravated the development of a chronic epileptic phase and its concomitant behavioral changes, including hyperlocomotion and depression, but also elicited neuroprotection [32], which suggests a fine-tuning modulatory mechanism through activation of the AT_1 or AT_2 receptors that might be considered potential drug targets. Thus, RAS inhibitors, commonly used as a strategy for prevention of high blood pressure, alone or in combination with AEDs, have been shown to be effective in the treatment of other neurological disorders, as well as epilepsy and its concomitant alterations, either by direct a decrease in blood pressure or indirect reduction of free radicals and/or proinflammatory cytokines and modulation of the neuronal and vascular circuit [20, 23–26, 43, 44, 46, 47, 59, 84]. Moreover, RAS inhibition, in particular as a result of blockade of the AT_1 receptors, was more pronounced in a model of epilepsy with co-morbid hypertension [22, 26, 84].

These studies suggest that the ACE inhibitors and blockade of the AT_1 receptors may be useful to reduce the detrimental consequences resulting from epilepsy, as an adjunctive treatment in epilepsy with co-morbid hypertension. Yet, these findings highlight the importance of experimental and clinical studies focused on the inhibition of central RAS components to better understand the pathological mechanism of epilepsy under hypertensive conditions.

Compliance with Ethical Standards

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Conflict of interest Natasha Ivanova and Jana Tchekalarova declare that they have no conflicts of interest.

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