Review

The renin-angiotensin system in central nervous system tumors and degenerative diseases

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1. Abstract

Despite their differences, central nervous system (CNS) tumors and degenerative diseases share important molecular mechanisms underlying their pathologies, due to their common anatomy. Here we review the role of the renin-angiotensin system (RAS) in CNS tumors and degenerative diseases, to highlight common molecular features and examine the potential merits in repurposing drugs that inhibit the RAS, its bypass loops, and converging signaling pathways. The RAS consists of key components, including angiotensinogen, (pro)renin receptor (PRR), angiotensin-converting enzyme 1 (ACE1), angiotensin-converting enzyme 2 (ACE2), angiotensin I (ATI), angiotensin II (ATII), ATII receptor 1 (AT_1R), ATII receptor 2 (AT_2R) and the Mas receptor (MasR). The RAS is integral to systemic and cellular pathways that regulate blood pressure and body fluid equilibrium and cellular homeostasis. The main effector of the RAS is ATII which exerts its effect by binding to AT_1R and AT_2R through two competitive arms: an ACE1/ATII/AT_1R axis, which is involved in regulating oxidative stress and neuroinflammation pathways, and an ATII/AT_2R and/or ATII/ACE2/Ang(1-7)/MasR axis that potentiates neuroprotection pathways. Alterations of these axes are associated with cellular dysfunction linked to CNS diseases. The generation of ATII is also influenced by proteases that constitute bypass loops of the RAS. These bypass loops include cathepsins B, D and G and chymase and aminopeptidases. The RAS is also influenced by converging pathways such as the Wnt/β-catenin pathway which sits upstream of the RAS via PRR, a key component of the RAS. We also discuss the co-expression of components of the RAS and markers of pluripotency, such as OCT4 and SOX2, in Parkinson's disease and glioblastoma, and their potential influences on transduction pathways involving the Wnt/β-catenin, MAPK/ERK, PI3K/AKT and vacuolar (H^+) adenosine triphosphatase (V-ATPase) signaling cascades. Further research investigating modulation of the ACE1/ATII/AT_1R and ACE2/Ang(1-7)/MasR axes with RAS inhibitors may lead to novel treatment of CNS tumors and degenerative diseases. The aim of this review article is to discuss and highlight experimental and epidemiological evidence for the role of the RAS, its bypass loops and con-

vergent signaling pathways in the pathogenesis of CNS tumors and degenerative diseases, to direct research that may lead to the development of novel therapy.

2. Introduction

In this review, we discuss the links between the renin-angiotensin system (RAS) and central nervous system (CNS) tumors and degenerative diseases, to highlight the potential role of the RAS in diseases of the CNS. While there is considerable literature on the relationship between the RAS and CNS disorders, there has been a recent resurgence in interest in the shared pathways between CNS tumors and degenerative diseases [1, 2], which suggest the RAS may play a larger role in both disease processes than previously thought.

The systemic role of the RAS in renal and cardiovascular physiology is well recognized, particularly for blood pressure, blood volume and electrolyte homeostasis [3, 4]. Angiotensin II (ATII)—the main effector the RAS, increases arterial pressure by causing vasoconstriction, retention of sodium, and release of the mineralocorticoid aldosterone by the zona glomerulosa of the adrenal cortex in the adrenal gland. RAS inhibitors (RASis) are used in the treatment of hypertension, cardiac failure, diabetic nephropathy, chronic kidney disease and several autoimmune diseases [5]. Despite the widespread use of RASis, the paracrine and autocrine functions of the RAS in organ systems including the CNS are not well understood. The observation that RASis are effective in patients with low or normal plasma renin activity may be explained by autocrine/paracrine RAS acting within the local tissue microenvironment of the CNS [5]. This article discusses the growing evidence demonstrating the universal role of certain components of the RAS in cellular homeostasis and disease pathogenesis [5] of CNS degenerative diseases (Table 1) and CNS tumors (Table 2). The review was undertaken utilizing the key words on the search platform PUBMED. The criteria for inclusion were to demonstrate potential molecular links of the RAS in CNS degenerative diseases including Parkinson's disease and Alzheimer's disease, and CNS tumors including glioblastoma (GB).

3. The renin-angiotensin system

ATII is the main effector hormone produced by the RAS. It is formed by sequential cleavage of angiotensinogen (AGT), which belongs to a family of serpin A_8 proteins and is coded by the *AGT* gene located on chromosome 1, to form angiotensin I (ATI), and ultimately ATII (Fig. 1). AGT is primarily synthesized in hepatocytes, although its synthesis may also occur in adipose tissue, the CNS, heart, kidney, lung, adrenal gland, gastrointestinal tract, ovary, and blood vessels [6]. Oxidation of AGT confers a conformational change in the protein, permitting its cleavage by renin to form ATI. AGT in the brain is found within astrocytes [7, 8]. Renin and AGT are large molecules that are not expected to cross the blood brain barrier (BBB), although they have been detected in the brain [9].

Renin is an aspartyl protease. Its abundant precursor, preprorenin, is coded by a gene located on chromosome 1 [10]. Renin is expressed in neurons, astrocytes, oligodendrocytes and microglia in various regions of the brain [11]. Preprorenin is cleaved to generate (pro)renin, which is then transferred to the Golgi apparatus [12]. Most of the (pro)renin is then cleaved and packaged in dense core secretory granules to be released via regulated exocytosis, with a small proportion of (pro)renin released directly into the general circulation [13]. Brain (pro)renin has a higher affinity for PRR, compared to (pro)renin from other sources, and it cleaves the 10-amino acids from the N-terminus of AGT, to form inactive ATI [14] (Fig. 1). Physiologically, the macula densa (sensory cells) and the renal juxtaglomerular cells within the juxtaglomerular apparatus (JGA), are the primary sources of the PRR and renin in the blood circulation, respectively [15]. Expression and secretion of renin are tightly regulated at the JGA by local baroreceptors and by detection of chloride ion concentrations in the distal tubule fluid by cells in the macula densa [16]. Activation of renin in specialized extrarenal tissues requires binding to vacuolar (H^+) adenosine triphosphatase (V-ATPase), an essential transmembrane proton pump that transports lysosomal accessory proteins, that is equipped with the accessory subunit of the PRR [17] (Fig. 1). V-ATPase is encoded by the *ATP6AP2* gene on Xp11.4 and is critical in CNS development and degeneration [18]. PRR is ubiquitous across most cell types and is highly expressed in certain regions of the brain including the subfornical organ, paraventricular nucleus, nucleus of the solitary tract and the rostral ventrolateral medulla [19]. PRR is essential for cells, allowing them to coordinate other less traditional autocrine RAS functions, such as vesicle transport, protein degradation, and coupled transport [14].

Angiotensin-converting enzyme 1 (ACE1; originally known as ACE), cleaves 2 amino-acids from the C-terminus of ATI, to form ATII (Fig. 1). ACE1 is a dipeptidyl-carboxypeptidase found predominantly in lung endothelium [20]. ACE1 is also expressed by endothelial cells in the intestine [21], placenta [22] and the brush border membrane in the kidney [23]. It is also expressed in areas of the brain that regulate blood pressure, and other areas that perform homeostatic functions including the choroid plexus, organum vasculosum of the lamina terminalis, subfornical organ, and area postrema [24]. In addition to the C-terminus cleavage of ATI to form ATII (Fig. 1), ACE1 also degrades bradykinin to an inactive form, which may impart secondary vasoactive effects by inhibiting the vasodilatory and natriuretic properties of bradykinin [25]. ATII can be converted to angiotensin III (ATIII), and then angiotensin IV (ATIV) by aminopeptidases. ATIII binds to AT_1R with
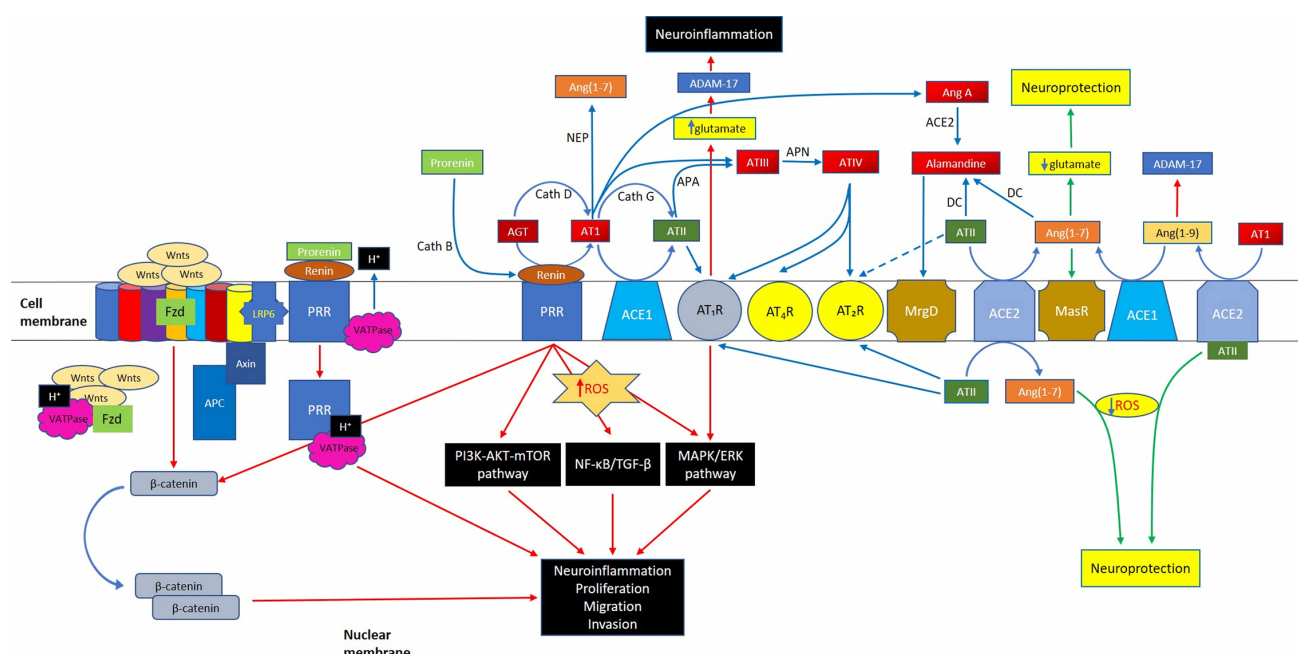
Fig. 1. Schematic diagram of the cellular RAS pathway in neuroprotection, neuroinflammation, neurogenic hypertension and cellular proliferation (see text). ACE1, angiotensin-converting enzyme 1; ACE2, angiotensin-converting enzyme 2; ADAM-17, a member of the disintegrin and metalloprotease adamalysin family; AGT, angiotensinogen; AKT, protein kinase B; APA, aminopeptidase A; APC, adenomatosis polyposis coli; APN, aminopeptidase N; AT1, angiotensin 1; ATII, angiotensin II; ATIII, angiotensin III; ATIV, angiotensin IV; AngA, angiotensin A; Ang(1-7), angiotensin(1-7); Ang(1-9), angiotensin(1-9); AT_1R, angiotensin II receptor 1; AT_2R, angiotensin II receptor 2; AT_4R, angiotensin II receptor 4; Cath B, cathepsin B; Cath D, cathepsin D; Cath G, cathepsin G; DC, decarboxylase; ERK, extracellular signal-regulated kinase; Fzd, Frizzled; LPR6, lipoprotein receptor-related protein 6; MAPK, mitogen-activated protein kinase; MasR, Mas receptor; MrgD, Mas-related-G protein coupled receptor; mTOR, mammalian target of rapamycin; NEP, neural endopeptidase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B-cells; PIK3, phosphoinositide 3-kinase; PRR, (pro)renin receptor; ROS, reactive oxygen species; TGF-β, transforming growth factor-β; VATPase, vacuolar adenosine triphosphatase; Wnts, wingless-related integrations sites. The processes leading to overall detrimental effects and the beneficial effects of the RAS are indicated by red arrows and by green arrows, respectively.

less affinity compared to ATII, and to AT_2R with more affinity than ATII. ATIV binds to ATIV receptor (AT_4R). Ang(1-7) can be produced by cleavage of ATI or ATII by ACE2, which can then bind Mas receptors (MasRs). ATI is also cleaved by ACE2 to form Ang(1-9), which can be converted to Ang(1-7) by ACE, that can bind MasRs and AT_2R. Ang(1-9) also binds to Mas-related-G protein coupled receptors (MrgDs), a recently discovered component of the RAS. Alamandine, an Ang(1-7) analog formed by decarboxylation of Ang(1-7), is the main ligand for MrgDs. ATII may also be converted to alamandine by decarboxylation of ATII into an angiotensin A (AngA) precursor (an ATII analog). Lastly, ACE2 cleaves AngA to form alamandine [26] (Fig. 1).

ACE2, a monocarboxypeptidase, is a transmembrane protein found on cells in many tissues, including brain endothelium [27]. ACE2 preferentially cleaves ATII to form Ang(1-7) in the cerebrospinal fluid (CSF), a ligand for the MasR, where the ACE2/Ang(1-7)/MasR axis opposes the effect of ATII (Fig. 1), and is neuroprotective — an effect enhanced by vitamin D in hypertensive rats [28]. Conversely, ACE2 also acts in a minor manner on ATI, to re-

lease Ang(1-9), which can contribute to neurogenic hypertension with neuronal upregulation of ADAM-17 (Fig. 1), also known as tumor necrosis factor (TNF) converting enzyme, a member of the disintegrin and metalloprotease (ADAM) family. ADAM-17 cleaves the ectodomain of ACE2 resulting in its release from the plasma membrane, leading to RAS overactivity [29].

The end effects of ATII are mediated by its binding to AT_1R and AT_2R (Fig. 1) found in many organs, including the brain [30]. AT_1R and AT_2R belong to a large family of G-protein-coupled 7 trans-membrane receptors. Most of the classically recognized detrimental effects of the RAS, such as neurogenic hypertension, are mediated by AT_1R [3] (Fig. 1). The downstream effects of ATII on AT_1R are complex. They include activation of receptor tyrosine kinases and several small G-proteins, stimulation of nicotinamide adenine dinucleotide phosphate oxidase (NOX) subunits to produce reactive oxygen species (ROS), and functional crosstalk with other signaling pathways. This results in endothelial dysfunction and organ damage [31].

Table 1. Epidemiological and experimental evidence for the association between RASis and CNS neurodegenerative diseases.

Authors and year	RASi used	Study type	Participant number	Neurodegenerative disease(s)	Outcome(s)
Scotti et al. (2021) [138]	ACEis and ARBs	Meta-analysis of 15 studies	3,307,532	Any dementia, AD and VD	ARBs are associated with a significant decrease in risk for dementia (pRR 0.78, 95% CI: 0.70–0.87) and AD (pRR 0.73, 95% CI: 0.60–0.94). Compared to ACEis, ARBs reduce the risk of any dementia (pRR 0.86, 95% CI: 0.79–0.94)
Harrison et al. (2021) [139]	Specific RASis studied not stated	Retrospective cohort	181,495	Dementia, AD, MD and PD	Compared to RASis, CCBs are associated with an increased likelihood of dementia (OR 1.24, 95% CI: 1.18–1.32), MDs (OR 1.21, 95% CI: 1.16–1.28). The OR for AD and PD both also have increased likelihood
Oscanoa et al. (2020) [140]	ARBs	Meta-analysis of 10 studies	Patients were derived from 10 studies (1 RCT, 2 case-control and 7 cohort studies)	AD	ARBs are associated with a reduced risk of incident AD (HR 0.72, 95% CI: 0.58–0.88, $p < 0.001$). In the sole RCT included, the incidence of AD is also decreased (HR 0.31, 95% CI: 0.14–0.68)
Dong et al. (2011) [141]	ACEi (perindopril)	*In vivo* experimental study on a mouse model of AD	N/A	Mouse model of AD	Prevented cognitive impairment and brain injury caused by glial activation and oxidative stress induced by Aβ injection
Li et al. (2010) [142]	ARBs and ACEis	Prospective cohort analysis	819,491	Dementia, including AD	The HR for incident dementia in the ARB group was 0.76 (95% CI: 0.69–0.84) compared with a cardiovascular comparator. Those taking ARBs with pre-existing AD have a significantly lower risk of admission to a nursing home (0.51, 95% CI: 0.36–0.72) and death (0.83, 95% CI: 0.71–0.97) ACEis were associated with a reduced risk of incident dementia (0.54, 95% CI: 0.51–0.57) and admission to a nursing home (0.33, 95% CI: 0.22–0.49)
Yamada et al. (2010) [143]	ACEi (perindopril)	*In vivo* experimental study on a mouse model of AD	N/A	Mouse model of AD	Reversal of cognitive impairment
Stegbauer et al. (2009) [144]	Renin inhibitor (aliskiren), ACEi (enalapril), ARB (losartan)	*In vivo* experimental study	N/A	MOG-EAE, a model that mimics several aspects of MS	Significantly ameliorated course of MOG-EAE
Ohrui et al. (2004) [145]	ACEi (perindopril)	Randomized, prospective, parallel group trial	161	AD	The mean 1-year decline in mini-mental state examination scores in the group taking a brain penetrating ACEi is lower than the 1-year decline in those taking non-brain penetrating ACEis or CCBs
Iwasaki et al. (2003) [146]	ACEi (temocapril)	*In vitro* experimental study on organotypic spinal cord culture	N/A	Post-natal organotypic culture model of motor neuron degeneration, induced by glutamate	Temocapril prevents motor neuron death from glutamate-induced neurotoxicity
Reardon et al. (2000) [137]	ACEi (perindopril)	Pilot study	7	PD	Enhances the effect of levodopa without inducing dyskinesia

Aβ, amyloid beta; ACEi, angiotensin-converting enzyme inhibitor; AD, Alzheimer's disease; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CI, confidence interval; HR, hazard ratio; MD, movement disorder; MOG-EAE, myelin-oligodendrocyte glycoprotein-induced experimental autoimmune encephalomyelitis; MS, multiple sclerosis; N/A, not applicable; OR, odds ratio; PD, Parkinson's disease; pRR, random effect pooled relative risks; RAS, renin-angiotensin system; RASis, RAS inhibitors; RCT, randomized controlled trial; VD, vascular dementia.

Table 2. Epidemiological and experimental evidence of the association between RASis and CNS tumors.

Authors and year	RASis used	Study type	Participant number	CNS tumor	Outcomes
Happold et al. (2018) [157]	ACEi and ARBs	Retrospective cohort study	810	Newly diagnosed GB	The OS for patients taking ACEis is 20.4 months versus 22.6 months for those taking the control (HR 1.25, 95% CI: 0.96–1.62, p = 0.10) The OS for patients taking ARBs is 21.7 versus 22.3 for those taking the control (HR 0.86, 95% CI: 0.61–1.21, p = 0.38) There is no association between survival outcomes and RASi usage in patients with GB
Levin et al. (2017) [159]	RASis in patients receiving chemotherapy and/or bevacizumab	Retrospective study	2 cohorts: 1186 glioma patients, and 181 patients with recurrent GB	WHO grade 2–4 glioma and recurrent GB	In glioma patients receiving chemotherapy, RASi exposure improves OS (HR 0.82; 95% CI: 0.71–0.93; p = 0.003) In patients with recurrent GB who receive bevacizumab in varying doses, RASis improve OS (0.649; 95% CI: 0.46–0.92; p= 0.0016)
Carpentier et al. (2016) [160]	ARBs	Cross sectional study	11 ARB treated patients with 11 matched controls	GB patients treated with ARBs for hypertension, who had pre-operative MRI without steroids	Decreased volume of peri-tumoral hyper T2-FLAIR signal (vasogenic edema)
Januel et al. (2015) [161]	ACEi and ARBs	Retrospective study	81	GB patients treated with RT and TMZ	The number of patients who remain functionally independent at 6 months after RT is higher in the patient group treated with ATII inhibitors, compared to those who were not (85% vs 56%, p = 0.01) Patients treated with ATII have a PFS of 8.7 months (vs. 7.2 months in other patients), and their OS is 16.7 months (vs. 12.9 months). The use of ATII inhibitors is a statistically significant prognostic factor for both PFS (p = 0.04) and OS (p = 0.04)
Kast et al. (2014) [158]	Captopril and celecoxib as part of the CUSP9 treatment protocol (apretitant, auranofin, captopril, celecoxib, disulfiram, itraconazole, minocycline, quetiapine and sertraline combined with TMZ)	In vivo	N/A	Recurrent GB	Using CUSP9 with TMZ, 50% of patient-derived GB stem cells display high sensitivity to the drug combination, demonstrated by a decrease in percentage cell survival Decreased Wnt-activity
Carpentier et al. (2012) [162]	ACEi and ARB	Retrospective study	87	Glioma	Decrease in steroid dosage required

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ATII, angiotensin II; CI, confidence interval; GB, glioblastoma; HR, hazard ratio; RCT, randomized controlled trial; OS, overall-survival; PFS, progression-free survival; RAS, renin-angiotensin system; RASi, RAS inhibitor; RT, radiotherapy; T_2-FLAIR, T_2-fluid-attenuated inversion recovery; TMZ, temozolomide.

AT$_2$R is found in abundance during fetal development, however, its expression in adult humans is generally limited to the kidney, adrenal gland, ovary, and brain [32]. AT$_2$R stimulation generally counteracts the actions of AT$_1$R, to facilitate vasodilation and natriuresis which mitigates hypertension, inflammation, and neoplasia [3] (Fig. 1). Yet these opposing actions of ATII, through AT$_1$R and AT$_2$R, are diverse. For example, ATII binding to AT$_1$R promotes endothelial cell proliferation, angiogenesis, and inflammation through the upregulation of vascular endothelial growth factor (VEGF) [33]. In contrast, ATII binding to AT$_2$R can induce activation of nuclear factor κB (NF-κB), an important regulator of immune responses through its mediation of chemokine transcription, to cause inflammation [34] (Fig. 1). Binding of ATII to AT$_1$R has been shown to inhibit glutamate transporters in paraventricular astrocytes resulting in increased extracellular glutamate levels that contribute to enhanced pre-sympathetic neuronal activity and sympatho-excitatory outflow leading to hypertension [35]. Glutamate excitotoxicity, known to play a role in neurological disorders and neuronal damage, has also been linked to the upregulation of ADAM-17, reduced activity of ACE2, and downregulation of the compensatory function of the ACE2/Ang(1-7)/MasR axis [36] (Fig. 1).

AT$_2$R activation in conjunction with the compensatory ACE2/Ang(1-7)/MasR axis has anti-oxidative and anti-inflammatory properties [37] (Fig. 1). Nuclear AT$_2$R activation leads to increased nitric oxide (NO) production, with its signaling resulting in hyperpolarization via decreased activity of calcium and potassium channels providing a neuroprotective mechanism in brain injury [38]. Ang(1-7) is more abundant than ATII, binds to MasR [39], and is abundant on cell, mitochondrial and nuclear membranes, as well as being associated with AT$_2$R and Mas related G-protein coupled receptors. Binding of Ang(1-7) to MasR increases NO and reduces ROS, which may limit oxidative stress in the normal brain pathways [40] (Fig. 1). During aging, the levels of AT$_2$R and MasR decrease and the levels of AT$_1$R increase, suggesting that AT$_2$R may play a neuroprotective role [11].

The recent spotlight on COVID-19 has also highlighted the role of ACE2 in inflammation, as it also functions as a receptor for SARS-CoV-1 and SARS-CoV-2 [41]. The entry of SARS-CoV-2 into cells downregulates ACE2 receptors, accentuating the adverse effects via the ATII/ACE1/AT$_1$R axis and reducing the protective effects of the ACE2/Ang(1-7)/MasR axis. In the lungs, the viral infection leads to clinical worsening with progression of the inflammatory and thrombotic processes. AT$_1$R blockers (ARBs) have been touted to be of therapeutic value in patients with SARS-CoV-2 infection [42], and potentially aid in reducing delirium due to neuroinflammation in advanced cases that require intensive care [43]. The disease processes of inflammation associated with COVID-19 in critically ill patients has been positively treated with systemic steroids [44]. Steroids are a mainstay treatment of vasogenic neuroinflammation associated with CNS tumors, such as glioblastoma (GB), meningioma and metastatic melanoma to the brain. Neuroinflammation worsened by COVID-19 has also been reported to cause worsening of patients with neurodegenerative diseases such as Alzheimer's disease [45], Parkinson's disease [46], multiple sclerosis [47] and psychiatric disorders [48]. Therefore, it is interesting to speculate that the ACE2/Ang(1-7)/MasR axis of the RAS influences neuroinflammation in many CNS diseases. The RAS interacting with the immune system is also implicated in the pathogenesis of CNS tumors. Given the significance of the immune system in both CNS tumors and degenerative diseases, it is interesting to speculate that the RAS may exert deleterious effects by modulating the neuroinflammatory response through the ATII/ACE1/AT$_1$R axis.

4. Bypass loops of the RAS

The neurogenic blood pressure response via the action of angiotensin on the CNS was first discovered in 1961 [49]. Since then, cellular ATII has been recognized to have both paracrine and autocrine actions with diverse physiological effects including functional modification of the autonomic nervous system [50]. The subsequent discovery of bypass loops of the RAS which include cathepsins B, D and G, chymase, and aminopeptidases playing a supplementary role (Fig. 1), have been demonstrated in the pineal and pituitary glands [51], human amniotic fluid and kidney [52], human neutrophils [53], and in rat pituitary gland cells [54]. Under physiological conditions, cathepsins B, D and G found in neurons and glia and CSF, cleave neuropeptide Y (NPY), an abundant conserved neuropeptide that partly modulates communication between the CNS and the immune system [55]. NPY has been shown to inhibit microglial phagocytosis induced by IL-1β [56] and in cultured rat cortical neurons induced by IL-1β and TNF-α [57], thus reducing neuroinflammation [56].

Amongst the many functions of the CNS, the circumventricular organs (CVOs), which have a partial or absent BBB, may play pivotal roles in cardiovascular control, body fluid equilibrium, food intake, immune response, temperature regulation, energy metabolism, stress response and the vomiting reflex [58]. This is achieved by regulating the bioavailability of NPY by peptidases such as cathepsin D at the interface between the CNS and the periphery [58]. The sensory CVOs comprise the subfornical organ, organ vasculosum of the lamina terminalis and area postrema, and the neurosecretory CVOs comprise the neurohypophysis, median eminence, subcommisural organ and the pineal gland [59]. Tanycytes, specialized epithelial ependymal cells located in the CVOs, detect neuroendocrine signals from the circulating blood, CSF, and perivascular interstitial spaces, and convey signals through dendrites and axons in the median eminence [60] and the sensory CVOs [61]. Cathepsin

D and NPY are localized in the CVOs, especially at the apex of the ependymal cells and tanycytes located at the floor of the third ventricle, above the median eminence [58]. Ordinarily, cathepsin D can cause lysosomal degradation of NPY, but the increased level or potency of cathepsin D results in a reduction of cellular and perivascular NPY, and neuroinflammation [58].

Cathepsin B is a lysosomal cysteine protease that catalyzes (pro)renin to form active renin [54, 62], which can therefore function in the absence of the PRR (Fig. 1). Cathepsin D is an aspartic lysosomal protease with some homology to renin that can convert AGT to ATI, in the absence of renin [63] (Fig. 1). Cathepsin G is a serine protease that catalyzes ATI to form ATII, and by adopting the role of ACE1, it can also convert AGT directly to ATII [64] (Fig. 1). The cathepsins are expressed in several diseases, including keloid disorder [65, 66], Dupuytren's disease [67], vascular tumors [68], vascular malformations [69] and benign and malignant solid tumors including meningioma [70], GB [71], metastatic colon adenocarcinoma to the liver [72], and cutaneous [73] and oral cavity [74] squamous cell carcinoma (SCC). Similarly, chymase—a ubiquitous serine protease with a strong ability to catalyze the formation of ATII, is found in many disorders [75].

5. CNS degenerative diseases

The role of the endocrine RAS in the CNS remains to be fully elucidated. However, the existence of an intrinsic RAS within the brain, and its contribution to neurogenic hypertension [76, 77] and CNS degenerative diseases, such as Alzheimer's disease and Parkinson's disease [40], is now better recognized in the neuroscience literature [78]. Although each component of the RAS has been detected in the CNS, no single cell type within the brain contains all its components. This suggests that localized synthesis is required given the endocrine RAS can only access the brain via the CVOs with fenestrated capillaries [79]. Loosely attached astrocytes and tanycytes in the CVOs can act as a neuroendocrine bridge [80] between the brain and the endocrine RAS within the circulation to access renin. Increased activity of neuronal AT_1R and ACE1 leads to cell death and inflammation combined with blunted compensatory mechanisms that utilize downregulation of Ang(1-7) and AT_2R, which may contribute to the cognitive impairment seen in aging and cognitive disorders [11].

The demonstration of higher expression of components of the RAS by dopaminergic neurons in the substantia nigra of monkeys and humans indicates a contributing role in Parkinson's disease [81]. AT_1R, AT_2R and PRR are located on the surface of dopaminergic neurons and glial cells, which is not an unexpected finding for a functional tissue paracrine RAS. Interestingly, AGT, AT_1R, AT_2R and PRR are also found in the cytoplasm and nuclei of neurons, astrocytes, and microglia, implicating an intracrine

RAS in monkey and human substantia nigra [81]. Furthermore, a neuroprotective role of the intracrine ACE2/Ang(1-7)/MasR axis (Fig. 1) appears more relevant in Parkinson's disease, as MasR has been detected in the mitochondria and nuclei of dopaminergic neurons, and within glial cells in the substantia nigra of rats, monkeys and humans [40]. ARBs, which inhibit neuroinflammation and oxidative stress, have been shown to reduce the extent of downregulation of the ACE2/Ang(1-7)/MasR axis that is apparent with aging in rats [39]. Activation of the ACE1/ATII/AT_1R axis leads to a cascade of events resulting in an increase in oxidative stress, apoptosis and neuroinflammation (Fig. 1), which may contribute to neurodegenerative disease pathogenesis [82].

ATII via AT_1R activates oxidative stress by producing ROS mediated by NOX, which stimulates superoxide generation that causes death of neurons in CNS trauma [83] and Parkinson's disease [84]. Induction of AT_1R and ROS also stimulates NF-κB that is reported to cause neuronal death in Parkinson's disease. Conversely, activation of the ATII/AT_2R and/or the ATII/ACE2/Ang(1-7)/MasR axis is seen to be neuroprotective [82] with preservation of dopaminergic neurons [85] (Fig. 1). Upregulation of the protective arm of the RAS in demyelinating diseases such as multiple sclerosis, is associated with a slowing of the pathological disease process in early stages of the disease [86]. Neuroinflammation can be triggered by the RAS through release of ROS and inflammatory mediators in glial cells that can lead to neurodegeneration [87], and elevated levels of ACE1 and ATII have been reported in neuroinflammation seen in Alzheimer's disease models [88]. ATII via AT_1R is also reported to trigger apoptosis by stimulating ROS [89], as seen in a Parkinson's disease rat model where the level of caspase 3 is reported to increase abruptly when given ATII resulting in dopaminergic neuronal death [90].

ACE inhibitors and ARBs inhibit the ACE1/ATII/AT_1R axis, increase ACE2 and enhance the ATII/ACE2/Ang(1-7)/MasR axis, to provide protection against neuroinflammation and neurodegeneration [39]. ARBs and curcumin, an inhibitor of cathepsin B, have been shown to have beneficial effects on Parkinson's disease [90, 91], Alzheimer's disease [92–94], and multiple sclerosis [95]. Both, stroke-prone spontaneously hypertensive rats with reduced ACE2 mRNA levels, and mice treated with ADAM-17 mediating a loss of ACE2 activity, have a much greater tendency to develop neurogenic hypertension [96]. ARBs which block the ACE1/ATII/AT_1R axis limit the formation of ATII, potentiate the effect of ACE2, and increase ACE2 mRNA expression. These events provide a neuroprotective effect via a positive feedback loop for cerebral ischemia [97], in addition to the anti-hypertensive and anti-inflammatory effects that may have a restorative role in traumatic brain injury [98]. The plethora of biochemical connections of the RAS and the potential value of RASis in the treatment of CNS degenerative diseases [40], underscores the need for randomized multi-center

clinical trials by simultaneously targeting different steps of the RAS using multiple repurposed drugs, in combination with the standard treatment.

6. CNS tumors

The understanding of carcinogenesis has evolved markedly over the past two decades due to advances in molecular and genetic profiling. The six hallmarks of cancer first reported by Hanahan and Weinberg in 2000 [99] are less relevant today, as the same authors revised the changes in 2011 to describe further emerging hallmarks that enable characteristics of cancer cells, which are features of a heterogenous tumor microenvironment [100]. Reprogramming of cellular metabolism to support cell growth and proliferation and active evasion of cancer cells from elimination by immune cells, underscore the complexity of the genetic mutations, the role of cancer stem cells (CSCs) defined in the concept of upstream limitless replicative potential, and the vast downstream molecular interactions that contribute to neoplastic transformation and plasticity [100]. In their landmark paper, Yamanaka *et al.* [101] demonstrated that mouse embryonic and adult fibroblasts could be induced to form pluripotent stem cells, with the supplementation of the essential core transcription factors OCT4, SOX2, c-MYC and KLF4. These Yamanaka factors are important pluripotency regulators linked to the regulation of cellular reprogramming pathways with recognized connections to downstream signaling pathways. These include Wnt/β-catenin, Notch, Hedgehog, NF-κB, JAK-STAT, TGF/SMAD, PI3K/AKT/mechanistic target of rapamycin (mTOR), and PPAR pathways, highlighting the multiple complex hurdles and controversy that need to be overcome, to target defined CSCs [102, 103].

GB is one of the most aggressive and lethal brain cancers, with a median overall survival of 14.6 months, despite the current standard of care involving surgery, radiotherapy and temozolomide [104]. The aggressive behavior and cellular pleomorphism in GB has various possible proposed mechanistic hierarchies. These multiple mechanisms include (1) the ability for GB CSC clones to show mesenchymal differentiation to generate chondrogenic cells associated with reduced growth rate [105], and (2) aberrant expression of *EGFR*, *NF1* and *PDGFRA/IDH1* genes in GB which define the classical, mesenchymal and proneural subtypes [106]. The proneural subtype shows the least benefit from aggressive therapies [106]. The mechanistic relevance of GB cell subpopulations that express OCT4 and SOX2 as being potentially more aggressive in GB carcinogenesis is yet to be proven [107, 108]. GB single cell RNA sequencing confirms the four distinct cellular states of GB with dynamic changes in the tumor microenvironment and plasticity [109]. Furthermore, endothelial cells in human GB have been shown to carry the same genomic alteration as tumor cells, suggesting the endothelial cells have a neoplastic

origin. When these GB stem-like cells were injected subcutaneously into immunocompromised mice, the xenograft vessels were composed of human endothelial cells, properties highly suggestive of a plastic subpopulation of CSCs [110]. GB rarely present with distant metastasis, but the presence of circulating tumor cells [111] implicates a role for epithelial-to-mesenchymal transformation, and the necessity for a selective tumor microenvironmental *niche* that is essential for local tumor recurrence [112].

OCT4 is the master regulator for stem cell pluripotency [113], and the only Yamanaka factor that cannot be replaced to generate induced pluripotent stem cells (iPSCs). There is greater expression of OCT4 in higher grade gliomas [113, 114]. Similarly, SOX2 has also been recognized as a critical upstream transcription factor which maintains self-renewal of GB CSCs. This is supported by the observation that knockout of SOX2 inhibits GB cell proliferation [115]. Furthermore, SOX2 activity has been associated with the maintenance of glioma stem cells and the ability to reprogram differentiated glioma cells into stemlike cells which may contribute to chemoresistance and tumor recurrence [116]. Recent studies have demonstrated the presence of cell populations expressing primitive transcription markers in CNS tumors such as GB that exhibit abundant expression of SOX2 [108], and components of the RAS: PRR, AT$_1$R, and AT$_2$R [117], although a mechanistic link has yet to be demonstrated.

SOX2 is known to be critical in lung development, and in promoting lung SCC as an oncogene [118]. PRR is also essential in the development of the lung through the Wnt/β-catenin pathway [119], suggesting a possible role of the PRR in cancers with higher expression of *ATP6AP2* in various cancer types including GB [120]. PRR has been linked to the Wnt/β-catenin pathway (Fig. 1), functioning in a renin independent manner, acting as an adaptor between Wnt receptors and the V-ATPase complex (Fig. 1), mediating Wnt signaling during early CNS development [121]. Wnt/β-catenin signaling, essential for the neural differentiation of neural stem cells [122], is activated in olfactory ensheathing cells (OECs), which are special glial cells that secrete neurotropic factors promoting the migration and growth of glial-derived cells like neurons [123] and astrocytes [124]. Conditioned medium isolated from Wnt activated OECs from neonatal mice has been observed to increase the percentage of cells co-expressing Ki67 and SOX2, in addition to maintaining expression of nestin and promoting differentiation of neural stem cells to neurons [125]. Further investigation into whether there is a functional link is warranted.

PRR appears to play a role in the development of human glioma by aberrant activation of the Wnt/β-catenin signaling pathway [120]. Increased PRR expression in GB compared to normal brain or low-grade glioma has been demonstrated, irrespective of isocitrate dehydrogenase (IDH) status [126]. There is a positive correlation be-

tween the degree of PRR expression and a higher WHO grade of astrocytoma, with increased glioma cell proliferation and inhibition of apoptosis through decreased caspase 3 activation driven by the Wnt/β-catenin pathway in GB cells [126].

Components of the RAS: AGT, renin, ACE, ATI and ATII are synthesized and expressed by human GB and GB cell cultures [127]. Renin has been detected in GB cells, particularly in perivascular GB astrocytes [128]. The possible importance of the RAS in GB may be highlighted by the demonstration of podocalyxin, a highly glycosylated transmembrane protein present in hematopoietic stem cells, endothelial cells, glomerular podocytes and some neural progenitors, in promoting GB cellular proliferation and invasion. This occurs via elevation of soluble β-catenin and increased Wnt/β-catenin signaling [129]. Furthermore, podocalyxin can downregulate the expression of MasR and Ang(1-7) through a PI3K dependent mechanism enhancing the proliferative and invasive potential of GB cells [130]. Glutaminergic neurogliomal synapses formed by presynaptic neurons and postsynaptic glioma cells located on tumor microtubules, have emerged as a mechanism whereby calcium ion dependent communication in the microtubules can drive GB invasion and progression [131]. Whether this is mechanistically linked to glutamate excitotoxicity-induced downregulation of the ATII/ACE2/Ang(1-7)/MasR axis observed in neuroinflammation [36] and the upregulation of neuronal ADAM-17 (Fig. 1) that leads to an increase in pre-sympathetic activity in glutaminergic neurons [132], requires further investigation. Using positive feedback mechanisms, glutaminergic neurogliomal synapses in gliomas increase neuronal excitability and appear to positively mediate activity-regulated glioma invasion and growth [133].

Current evidence suggests the RAS plays a role in CNS diseases such as GB, but mechanistic links have yet to be demonstrated. Underscoring the recent molecular advances using the IDH mutation to classify gliomas [134], GB has the established pathognomonic central necrosis, perivascular cellular palisading, endothelial proliferation within the outer and inner margins of the active tumor bulk, and vasogenic white matter edema at the growing front on the outer margin of the tumor [135]. We speculate that the RAS may play a role in all these characteristic features. This includes the neoplastic endothelium involved in capillary breakdown at the BBB that results in vasogenic edema, and the formation of tumor microvessels that feed the maturing tumor cells within the tumor bulk before their resultant apoptosis and necrosis within the central region of the active tumor. Many questions have arisen, especially since PRR is upregulated in CVOs and tanycytes, such that there may be a progenitor subpopulation in the areas of endothelial proliferation around the loose astrocytes and endothelium closer to the outer margins of tumors that have upregulated PRR expression, and co-express OCT4 and SOX2. Using the OCT4+ and/or SOX2+ cell subpop-

ulations that express components of the RAS, there may be distinct characteristics of pluripotent cells identifiable by measuring single cell glutamate excitotoxicity together with single cell RNA sequences at the penumbra of GB. Furthermore, given podocalyxin promotes GB invasion and proliferation linked to upregulation of the Wnt/β-catenin signaling and down-regulation of MasR and Ang(1-7), there may be concomitant upregulation of ADAM-17 and glutamate excitotoxicity at the neurogliomal synapses in the carcinogenesis of GB. Lastly, cathepsin D and NPY are co-localized to the CVOs, there is the distinct possibility of activation of the RAS bypass loops involving cathepsin D with upregulation of AT_1R, ADAM-17 and glutamate excitotoxicity in GB. This suggests cathepsin D may be a potential regulator in GB. The speculation that co-expression of components of the RAS and upstream transcriptions factors hold functional significance requires intensive investigation with both *in vitro* and *in vivo* experiments. The vast array of genetic and molecular anomalies linked to cells in brain tumors, underscore the need for clinical trials investigating customized targeted molecular therapies [136].

7. Therapeutic potential of RASis and future perspectives

The role of RASis in degenerative neurological disorders remains unclear (Table 1, Ref. [137–146]), although an early proof-of-concept double-blind placebo-controlled study shows perindopril, an ACE inhibitor, enhances the effect of levodopa without inducing dyskinesia [137]. Multiple review articles discuss the theoretical benefit of RASis for neurodegenerative diseases, but to date these drugs are not routinely used clinically for these disorders [40, 78, 82, 147, 148].

The use of RASis in the treatment of cancer may mitigate adverse effects of cytotoxic agents experienced by cancer patients, hence improving their overall quality of life [149]. A meta-analysis of 17 observational studies by Shen *et al.* [126] show RASis are associated with a reduced risk of cancer [150]. A prospective population-based study also shows long-term (>3 years) administration of RASis is associated with a decreased risk of cancer with a DD genotype, which is linked with high levels of ACE1 [151]. Other epidemiological studies have shown a protective benefit of RASis against the risk of colorectal cancer [152, 153] and an overall reduced risk of cancer [154]. RASis have also been shown to improve the overall survival of patients with aggressive non-metastatic pancreatic ductal adenocarcinoma [155]. Based on observational data, RASis may be broadly protective against cancer. However, further functional studies and large randomized controlled trials are required to conclusively demonstrate whether RASis reduce cancer risk and improve the overall survival of cancer patients [156].

A recent retrospective cohort study analyzed data from 810 patients enrolled in two large multicenter studies to investigate the role of drugs targeting the RAS in GB (Table 2). They challenge the rationale for performing future prospective studies [157], given the paucity of data on multiple drug repurposing purely targeting the RAS pathway. A recent clinical trial using multiple repurposed drugs that target the RAS and converging signaling pathways, including captopril and celecoxib in combination with temozolomide, shows promise as evidenced by the observed maintenance of good quality of life for patients [158]. In addition, RASis in combination with bevacizumab has been shown to improve survival in patients with GB [159] (Table 2, Ref. [157–162]), whereas there is no overall survival benefit of this VEGF inhibitor as a monotherapy for *de novo* or recurrent GB [163]. PRR may be a critical biomarker and therapeutic target for the treatment of cancers including GB, as it influences the Wnt/β-catenin, MAPK/ERK and PI3K/AKT/mTOR pathways [120, 126, 127, 164] (Fig. 1). Several steps of the RAS pathway can potentially be targeted [165] and the effects of a novel approach, targeting the RAS and its bypass loops simultaneously using multiple repurposed drugs, on GB is currently being investigated in a clinical trial [166]. Therapeutic options may be facilitated by augmenting the compensatory mechanisms of the RAS [82, 120, 165, 166].

There is conflicting evidence on the efficacy of RASis in the treatment CNS tumors, and other cancer types [165, 166] (Table 2), which is likely to be multifactorial. The effects of RASis may depend on the cancer type, participant baseline characteristics, the RASi used, study design, and publication bias. Another possible contributing factor is differing levels of antagonism between the pro-inflammatory ACE1/ATII/AT_1R axis and the protective ATII/AT_2R and/or ATII/ACE2/Ang(1-7)/MasR axis, in different CNS tumors. Despite variable findings from retrospective studies, *in vitro* studies investigating the administration of RASis in different tumor models support the efficacy of targeting the RAS using RASis to influence cancer cell survival.

The demonstration of components of the RAS in a spectrum of CNS diseases, such as Parkinson's disease and GB, highlights the need for further research using well-developed experimental models. This includes functional experiments to elucidate the complex pathways linked to the RAS, and its potential role in the pathophysiology of CNS diseases. The recent technological breakthroughs in generating human cerebral organoids [167] from pluripotent cells, combined with genetic engineering [168], mass spectroscopic proteomics [169] and next generation gene sequencing tools [170], will allow more detailed studies to be conducted, to investigate the pathogenesis of CNS tumors and degenerative diseases. This may lead to the development of novel therapeutic approaches by targeting the RAS and its related pathways.

8. Author contributions

SH and EJK drafted the manuscript. PFD, SSS, TM, AHK, SRH, STT and ACW critically revised the manuscript. All authors commented on and approved the manuscript.

9. Ethics approval and consent to participate

Not applicable.

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12. Conflict of interest

PFD and STT are inventors of the patent Cancer Diagnosis and Therapy (United States Patent No. 10281472), provisional patents Cancer Diagnosis and Therapy (PCT/NZ2015/050108) and Cancer Therapeutic (PCT/NZ2018/050006), provisional patent application Novel Pharmaceutical Compositions for Cancer Therapy (US/62/711709). The authors declare that the review article was written in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The authors otherwise declare no conflict of interest.

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