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REVIEW PAPER

ACE-Triggered Hypertension Incites Stroke: Genetic, Molecular, and Therapeutic Aspects

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Abstract

Stroke is the second largest cause of death worldwide. Angiotensin converting enzyme (ACE) gene has emerged as an important player in the pathogenesis of hypertension and consequently stroke. It encodes ACE enzyme that converts the inactive decapeptide angiotensin I to active octapeptide, angiotensin II (Ang II). Dysregulation in the expression of ACE gene, on account of genetic variants or regulation by miRNAs, alters the levels of ACE in the circulation. Variable expression of ACE affects the levels of Ang II. Ang II acts through different signal transduction pathways via various tyrosine kinases (receptor/non-receptor) and protein serine/threonine kinases, initiating a downstream cascade of molecular events. In turn these activated molecular pathways might lead to hypertension and inflammation thereby resulting in cardiovascular and cerebrovascular diseases including stroke. In order to regulate the overexpression of ACE, many ACE inhibitors and blockers have been developed, some of which are still under clinical trials.

Keywords Stroke · Genetic variants · miRNAs · Neurons · Glial cells · Vascular smooth muscle cells

Introduction

Stroke is the second largest cause of death worldwide (Benjamin et al. 2017). It is defined as the focal dysfunction of brain, spinal cord, and retina, lasting more than 24 h or till death, demonstrated from objective evidence of imaging and pathological signs confirming ischemic injury (Sacco et al. 2013). Pathogenic alterations in various genes involved in different physiological pathways, predispose individuals to stroke (Munshi and Kaul 2010; Kaul and Munshi 2012; Munshi et al. 2015). Demographic and clinical studies have established hypertension to be a major risk factor in the development of ischemic stroke. The blood pressure in the circulation is maintained by the orchestration between the various components of renin–angiotensin–aldosterone system (RAAS) pathway. RAAS is a complex system for regulation of blood pressure and fluid hemostasis. Angiotensin converting enzyme-1 (ACE) gene plays a significant role in the regulation of vascular tone and smooth muscle cell proliferation resulting in the development of hypertension and cerebrovascular diseases including stroke (Jacob et al. 1991; Villard and Soubrier 1996; Das et al. 2015). In circulation (Endocrine or classical RAAS), systemic hypotension induces juxtaglomerular cells in kidneys to secrete renin, which further hydrolyses angiotensinogen to angiotensin I (Ang I). ACE is a key player in the RAAS, where it catalyzes the conversion of Angiotensin I to Angiotensin II (Weir and Dzau 1999). In addition to circulatory RAAS, local synthesis of Ang II comprising tissue RAAS system also exists in other organs like kidney and brain. Endocrine RAAS and functional interaction between various tissue RAAS along with counter regulatory peptides on multiple levels adds to the inherent complexity of the RAAS system. Ang II initiates the signaling cascade of proinflammatory molecules and is a potent vasoconstrictor leading to increased blood pressure. It acts on transmembrane angiotensin II receptor type 1 (AT1R) which through certain signal transduction pathways, including kinases and Gq/PLC, promote events like release of aldosterone from adrenal glands, sodium and water reabsorption from kidneys leading to increased blood flow and hypertension, a major risk factor for stroke. ACE inhibitors and blockers are given to patients with vascular disorders for the regulation of hypertension so as to prevent a secondary ischemic stroke.

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The genetic alterations in the ACE gene that influence the level of circulating ACE enzyme and thereby increase the risk of ischemic stroke have been studied in different ethnic groups. These studies have provided compelling evidence of the involvement of ACE gene variants especially Insertion/Deletion (I/D) polymorphism in intron 16, with the activity of ACE enzyme as well as development of stroke (Martínez-Rodríguez et al. 2013; Kumar et al. 2014; Malueka et al. 2018). We have already established the association of ACE I/D polymorphism with susceptibility to ischemic stroke and also found that higher levels of circulating ACE result in increased risk of ischemic and hemorrhagic stroke in patients from Andhra Pradesh (South India) (Das et al. 2015).

Besides the standard components of RAAS like renin, angiotensin I, angiotensin II, ACE and the two receptors (AT1&AT2), some novel players including peptides like Ang (1–7), heptapeptide ACE2 enzyme and receptor of Ang (1–7) and Mas have also been included in the RAAS (Santos et al. 2003). ACE2 converts angiotensin I to Ang (1–9) and Ang II to antagonist Ang(1–7). However, this arm of RAAS pathway has been demonstrated to play a protective role in animal models of ischemic stroke. ACE2 exerts the protective effects by the production of Ang (1–7) which in turn stimulates the Mas receptor. In brain, the ACE2/angiotensin (1–7)/Mas receptor axis induces the protective effect independent of hypertension (Peña-Silva and Heistad 2015). This axis was reported to be associated with oxidative stress and neuroinflammation by downregulating malondialdehyde (MDA), nicotinamide adenine dinucleotide phosphate (NADPH), and upregulating super oxide dismutase (SOD) which reduces the brain damage after stroke. This axis has a stimulatory effect on the production of prostaglandin and NO, which are potent vasodilators thus has antithrombotic and anti-proliferative effects (Ferrario et al. 2011; Jiang et al. 2013).

In humans, ACE gene is located on the short arm of chromosome 17 (17q23.3), spanning 21 kilobases, and bears 26 exons and 25 introns. It encodes ACE which is chemically a dipeptidyl carboxypeptidase and a member of zinc metallopeptidase family. (Hubert et al. 1991). The somatic ACE protein (1306 residue) is transcribed from a promoter, upstream of a tandem duplication. This results in incorporation of two active domains i.e., N domain and C domain within the ACE protein. Both of these domains are functional, but exhibit different biochemical properties. Specific inhibitors for specific domains exist revealing that the inhibitor affinity profiles of both the domains vary. The functional elements in both domains consist of a M2-type zinc metallopeptidase motif, an HisGluxxHis with a Glu-positioned 23–24 residues. The two histidines and the downstream glutamate are ligands for the zinc cofactor, required for the peptidase catalytic activity (Dive et al. 1999).

Previous studies have established that different variants in this gene that alter the ACE levels are risk factors in the development of stroke (Munshi et al. 2008; Das et al. 2015). Dysregulation in expression of ACE gene affects the levels of ACE in the circulation which in turn leads to altered levels of Ang II. Ang II acts through two G protein-coupled receptors (GPCRs), AT1 and AT2. Under normal conditions, Ang II maintains sodium–potassium balance, and fluid volume to modulate blood pressure (Frauman et al. 2001). However, under pathophysiological conditions, overexpression of Ang II and enhanced signaling of its type1 receptor induces vascular remodeling leading to the proliferation of vascular smooth muscle cells and vasoconstriction, which gets translated in increased oxidative stress, inflammation, migration, hyperplasia, hypertrophy, hypertension, restenosis, and atherosclerosis (Lyle and Griendling 2006; Higuchi et al. 2007; Lassègue and Griendling 2010). ACE is also involved in the break down or inactivation of bradykinin, which plays a role in inducing vasodilation through prostacyclin and nitric oxide. The inactivation of bradykinin results in vasoconstriction (Pera et al. 2006; Taddei and Bortolotto 2016).

The present review has been complied with an aim to give an overview of the factors especially genetic variation and microRNAs (miRNAs) regulating the levels of ACE and other components of RAAS pathway leading to dysregulation of Ang II, in the pathogenesis of hypertension and consequently ischemic stroke. In addition, the role of Ang II in promoting stroke pathogenesis and therapeutic strategies centered on targeting ACE have also been reviewed.

ACE Gene Variants

National Center for Biotechnology Information (NCBI) records > 160 polymorphisms in ACE gene. Most of these are single nucleotide polymorphisms. Thirty-four single nucleotide polymorphisms (SNPs) have been documented in the coding region of the gene, and two quantitative trait loci (QTLs) in the 3′ region, affecting the ACE levels have also been well defined (Villard et al. 1996; Sayed-Tabatabaei et al. 2006; Mengesha et al. 2019). Different studies have evaluated variation in ACE gene in association with development of the ischemic stroke, its subtypes as well as hemorrhagic stroke in various ethnic groups. Although the functional significance of some of these variants has not been reported, there are some variants found to affect ACE levels. Among the various reported variants of ACE gene, only the functional outcome in terms of its affect on ACE expression/activity of some variants is known (Tables 1, 2). In addition, certain missense variants affecting the structural and functional aspects of ACE protein have also been associated with the development of ischemic stroke. However, the mechanism by which the intronic and synonym

Table 1 Role of ACE gene variants in association with stroke development in different ethnic groups

S. no.	Variant	Variant type	Allele	Ethnicity	Sample size	Molecular consequences	Stroke	Outcomeme	References
1	rs4309	SNV	C > T	Caucasian	Cases 359 Controls 328	Upstream transcript variant	IS	ACE hyper activity	(Dennis 2008)
2	rs4311	SNV	T > C	European	Cases 60	Upstream transcript variant	Primary Lobar ICH	No change in ACE levels/activity	(Domingues-Montanari et al. 2011)
3	rs4329	SNV	A > C,G	European	1st study: Cases 890 Controls 594 2nd study: Cases 710 Controls 3751	Intronic variant	IS	No change in ACE levels/activity	(Matarin et al. 2009)
4	rs4333	SNV	T > C	Caucasian	Cases 359 Controls 328	Intronic variant	IS	ACE hyper activity	(Dennis 2008)
5	rs1799752	INDEL		Asian, Caucasian, European	Cases 3355 Controls 4722, European: Cases 60	Intronic variant	ICH and primary lobar ICH	Increased ACE activity in D allele	(Chen et al. 2018; Domingues-Montanari et al. 2011)
6	rs4353	SNV	A > G	Mexican	Cases 239 Controls 371		IS	Increased ACE serum levels	(Martínez-Rodríguez et al. 2013)
7	rs4267385	SNV	C > T			Intronic variant	IS	Higher ACE serum activity	(Peck et al. 2008)
8	rs12451328	SNV	C > A	European	1st study: Cases 890 Controls 594 2nd study: Cases 710 Controls 3751		IS	No change in ACE levels/activity	(Matarin et al. 2009)
9	rs4646994	INDEL	D allele	Indians, Multiethnic, Indonesian	Indians: Cases 104 Controls 198 Multiethnic: Cases 2806 Controls 3612; Cases 744 Controls 1411 Indonesian: Cases 61 Multiethnic: Cases 10,070 Controls 22,103		HS (ICH) IS (SVD)	Varied ACE concentration with DD	(Huang et al. 2014; Kalita et al. 2011; Malueka et al. 2018; Malueka et al. 2017; Zhang et al. 2012)
10	NG011648	INDEL		North Indian North west Greece	Indian: Cases 224 Controls 224 Greece: Cases 176 Controls 178	Intronic variant	Associated with SVD, IS onset in female	Higher ACE serum activity	(Kumar et al. 2014; Markoula et al. 2011)

Table 2 Variants of ACE gene not associated with stroke

S. no.	Variant	Variant type	Allele	Ethnicity	Sample size	Molecular consequences	Stroke	Outcomeme	References
1	rs4295	SNV	C > G	Danish, European	Dansih: Cases 176 Controls 498 European: Cases 60	Upstream transcript variant	No significant association with (SAH) HS	Low expression of ACE-mRNA with I allele	(Domingues-Montanari et al. 2010; Staalsø et al. 2011)
2	rs4305	SNV	A > G	Danish	Cases 176 Controls 498	Upstream transcript variant	No significant association with (SAH) HS	Low expression of ACE-mRNA with I allele	(Staalsø et al. 2011)
3	rs8066276	SNV	T > C, G	Greek and Polish	Greek: Cases 250 Controls 250 Polish: Cases 190 Controls 322	Intronic variant	No profound relation with ICH	Regulate ACE level	(Dardiotis et al. 2011)
4	rs4291	SNV	T > A, C	Danish, Caucasian	Danish: Cases 176 Controls 498 Caucasians: Cases 238 Controls 476	Upstream transcript variant	No significant association with HS (SAH) and SVD	Low expression of ACE-mRNA with I allele	(Gormley et al. 2007; Staalsø et al. 2011)
5	rs4343	SNV	G > A	Greek and Polish, Danish	Greek: Cases 250 Controls 250 Polish: Cases 190 Controls 322, Danish: Cases 176 Controls 498	Synonymous variant	No association with ICH and SAH	Regulate ACE level	(Dardiotis et al. 2011; Staalsø et al. 2011)
6	rs4331	SNV	A > G	Danish	Cases 176 Controls 498	Synonymous variant	No significant association with (SAH) HS	Low expression of ACE-mRNA with I allele	(Staalsø et al. 2011)
7	rs7221780	SNV	C > T	Greek and Polish	Greek: Cases 250 Controls 250 Polish: Cases 190 Controls 322	Intronic variant	No profound relation with ICH	Regulate ACE level	(Dardiotis et al. 2011)
8	rs1800764	SNV	C>G, T	Caucasian	Cases 238 Controls 476	Functional variant, upstream transcript variant	NO association with SVD	No change in ACE levels/activity	(Gormley et al. 2007)
9	rs4290	SNV	C>A, T	Caucasian	Cases 238 Controls 476	Functional variant, upstream transcript variant	NO association with SVD	No change in ACE levels/activity	(Gormley et al. 2007)

variants affect the disease development without affecting ACE expression are not understood well. The association studies of ACE variants with hypertension have not been included in this section as it has been reviewed previously by other authors (Mengesha et al. 2019).

Ischemic Stroke

Based on the results of various association studies carried out in ischemic stroke patients, it has been found that some variants had a protective effect in certain populations while in other cohorts these variants contribute to the pathogenesis of the disease. These studies have evaluated different variants (I/D polymorphism, haplotypes, quantitative trait loci, and several other SNPs) of ACE gene. ACE I/D variant is the major functional variant of ACE gene which has been widely explored. The results of some previous studies have reported a positive association of D allele with ischemic stroke (Munshi et al. 2008; Wei et al. 2017). D allele of ACE gene is not only associated with the risk of ischemic stroke in a Polish population but also subsequent case–control studies conducted on Greece and Turkish community by Tuncer et al. 2006 and Karagiannisa et al. confirmed similar findings (Celiker et al. 2009). The increase in ACE level due to DD genotype leads to an enhanced level of Ang II that eventually add up to the infarct size and increases the oxidative stress and inflammation worsening the brain damage and also the functional outcome of ischemic stroke (Ferrari 2004). In a study including eighteen thousand two hundred fifty-eight multiethnic cases, Zhao et al. (2014) reported the increased risk of ischemic stroke among Asians bearing I/D polymorphism. Significant heterogeneity was observed among all genetic samples considering the whole of the population, the increased risk was hypothesized due to interaction with other risk factors like intercellular adhesion molecule 1 (ICAM) and monocyte chemo attractant protein-1 (MCP-1) (Zhao et al. 2014). On the contrary, in a study conducted to assess the association of ACE haplotypes and I/D polymorphism with the disease, no interdependence of D allele with other polymorphism was found (Tascilar et al. 2009). Minimal number of studies have also speculated the role of ACE gene polymorphism in males and females. One such study was conducted by Markoula et al. (2011) involving 176 Northwest Greece cases, and reported the greater risk of lacunar and large artery atherosclerosis in females due to the effect of gonadal steroids, testosterone, and estrogen, on the levels on ACE and Ang II (Markoula et al. 2011). Various other variants that have been explored in different ethnic groups include rs4295, rs4353, rs4309, rs12451328, rs4968591, NG011648, rs4290, rs1800764, rs4646994, rs4329, rs4333, and rs4353 (Table 1).

Studies evaluating association of ACE I/D polymorphism with different stroke subtype have also been carried out. Kumar et al. (2014) including an equal number of cases and controls found that D allele is a risk factor for the small vessel disease (SVD) in North Indians. Increased level of ACE accelerates vasoconstriction that supplements fibrinoid necrosis is reported to be involved in the etiology of SVD. In our previous study carried out in a South Indian population we have found an association of ACE I/D polymorphism with intracranial large artery atherosclerosis (Munshi et al. 2008). A meta-analysis by Zhang et al. (2014) involving 10,070 cases of different ethnicity reported D allele as a low susceptibility penetrance marker, and found its association with 37% higher risk of SVD in Asians and just a borderline significance in Europeans (Zhang et al. 2012). Contrary to the above findings, a study conducted on 200 South Indian cases outlined a positive association of II allele with large vessel disease (LVD).

Hemorrhagic Stroke

The studies focussing on the association of ACE I/D polymorphism with hemorrhagic stroke has not been carried out at length. However, few studies evaluating this association have showed conflicting results. Some of the studies have established a strong association of ACE I/D with hemorrhagic stroke. Apart from increasing ACE serum levels that promotes hypertension [a significant risk factor for intracerebral hemorrhage (ICH)], DD genotype is also manifested in inflammatory vasculitides of blood vessel. Sun et al. (2014) found that Asians are at higher risk of developing primary intracerebral hemorrhage (PICH) comparison to Caucasians, which may be attributed to different genetic backgrounds and environmental factors (Sun et al. 2014). In Asians, DD genotype has been reported to be hemorrhagic stroke promoting (Das et al. 2015). In addition, increased ACE levels were found to promote early arteriolar proliferation of smooth muscle cells which consequently lead to death of these cells resulting in hemorrhagic stroke (Chen et al. 2018; Sun et al. 2014). Kumar et al. (2014) reported an increased risk of ICH in Asians (North Indians) bearing the D allele (Kumar et al. 2014).

In a study carried out in a European population [East Anglian and Polish], the reduced ACE level (I allele and II genotype) were found to be associated with intracranial aneurysm leading to subarachnoid hemorrhage (Keramatipour et al. 2000; Slowik et al. 2004). A meta-analysis conducted on 6359 cases and 13,805 healthy controls belonging to multiethnicity found I allele to be a risk factor for the developmental of all subtypes of hemorrhagic stroke (Peck et al. 2008). Three other case–control studies conducted on Caucasians reported no significant association between ACE variants including tag SNPs and the I/D polymorphism and risk of developing haemorrhagic stroke (Pannu et al. 2005; Dardiotis et al. 2011; Staalsø et al. 2011).

Domingues-Montenari conducted a study on 60 Spanish hemorrhagic stroke patients and reported that five variants [rs4311 (T), rs1799752 (D), rs4295 (G), rs4461142 (T), rs8066114 (G)] had a positive association with cerebral amyloid angiopathy (CAA)-related primary lobar ICH recurrence. Association of specific haplotypes and D allele was also reported to be in association with primary lobar intracerebral hemorrhage (Domingues-Montanari et al. 2010). The information about genetic variation reported in ACE gene along with molecular consequences and functional outcomes implicated in the pathogenesis of ischemic and hemorrhagic stroke have been summed up in Tables 1, 2 and Fig. 1. There are some variants that alter the ACE level thereby promoting the development of stroke (Table 1). On the contrary, certain variants altering ACE levels did not show any significant association with the development of the disease (Table 2). These variants need to be explored further for their functional validation before coming to a conclusion.

miRNAs Regulating Components of ACE Pathway

miRNAs are ~ 22 nucleotide long single stranded non-coding RNAs which regulate heterogeneous biological processes by RNA-mediated gene silencing mechanisms (Kim 2005; Bátkai and Thum 2012). They regulate the expression of protein-coding genes through a cascade of reticulated molecular events (Lee et al. 2004). Different miRNAs have been reported which target RAAS components or get regulated by different players involved in RAAS pathway. Many of these miRNAs affect the different pathophysiological processes like hypertension, hypertrophy, and inflammation thereby leading to stroke. Details about the functional implication, targeted and targeting molecules of different miRNAs have been summed up in Tables 3, 4 and Fig. 2.

Understanding Mechanistic Pathways of Ang II Using Different Model Systems

The ACE levels get altered on account of various factors as discussed previously. This in turn influences the levels of Ang II affecting the downstream signal transduction pathways in neurons, glial cells, and vascular smooth muscle cells (VSMCs) and thereby resulting in the development of hypertension and inflammation, the two major risk factors for stroke (Saavedra 2005).

Neurons

Ang II contributes to the development of neurogenic hypertension through several pathways including NADPH oxidase/ROS (Braga et al. 2011; Biancardi et al. 2017), ERK1/2-RSK-nNOS signaling (Sharma and Patel 2017), MAPK-AP1/NFκB pathway (Biancardi et al. 2017), COX-1-derived PGE2 and EP1R signal pathway (Sriramula et al. 2015), and BDNF/TrkB-UCP2 signaling pathway (Carmichael and Wainford 2015). The signaling cascade varies in neurons from different regions of the brain e.g., unique pathways have been reported in neurons from nucleus tractus

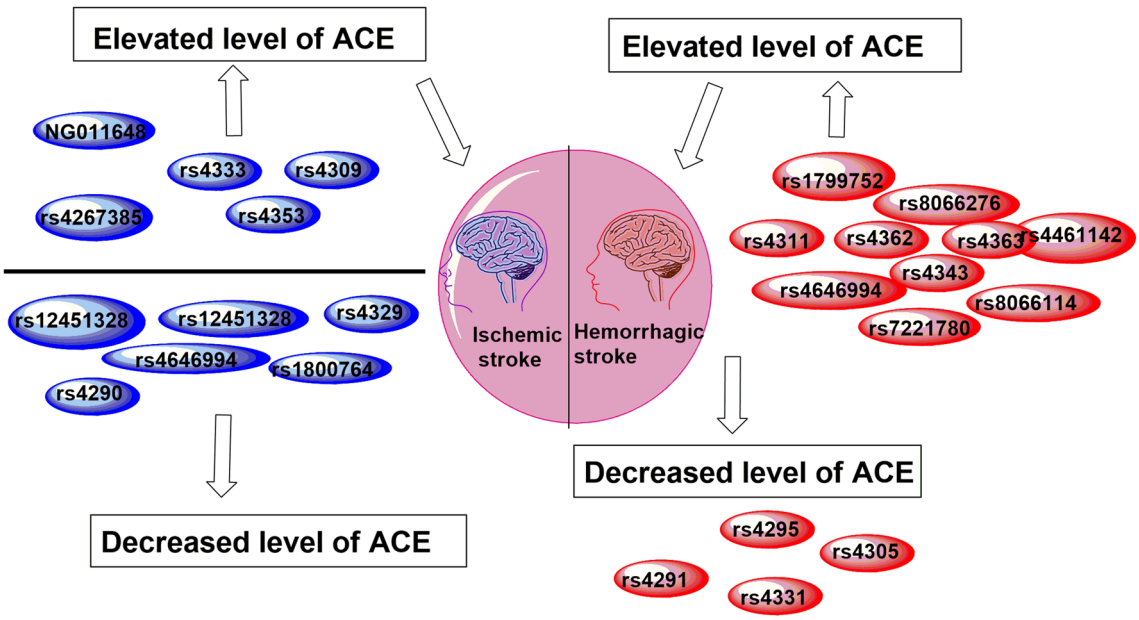

Fig. 1 Genetic variants affecting ACE levels in ischemic and hemorrhagic stroke

Table 3 miRNAs regulating RAAS pathway

S. no.	Targeted RAAS component	miRNA involved	Functional outcome	References
1	AT1R	miR-155 (Human umbilical vein endothelial cells (HUVECs)	Regulation of endothelial cell inflammation and migration	(Zhu et al. 2011)
2	ACE; ACE2	miRNA-27a and 27b; microRNA-143 (Wistar rat cardiomyocyte; VSMCs; mouse fetus)	Ventricular hypertrophy	(Boettger et al. 2009; Fernandes et al. 2011; Goyal et al. 2010)
3	ATIR	miR-155 (rat aortic adventitial fibroblasts)	Vascular remodeling	(Zheng et al. 2010)
4	AT1R	miR-155 (Primary cultured VSMCs from the aorta of C57/BL6 mice)	VSMC proliferation	(Yang et al. 2014)
5	AGT, ACE and AGTR2	miR-483-3p NT and TG mice; y human aortic smooth muscle cells (HASMC), rat aortic smooth muscle cell (RAASMC) line (SV40-LT, CRL-2018)	Affect cellular signaling in RAAS pathway	(Kemp et al. 2014)
6	ACE	miR-143 and miR-145 (Invitro, invivo)	Increased Angiotensin II production in the vessel wall	(Boettger et al. 2009)
7	ACE2	miR-421 primary human cardiac myofibroblasts	Post-transcriptional regulation of ACE2	(Lambert et al. 2014)
8	ACE	miR-143/145 cultured endothelial cells	Vascular complications associated with diabetes mellitus.	(Kohlstedt et al. 2013)
9	ATR1	miR-155 Rat H9C2 cardiomyocyte	Cardiac hypertrophy	(Yang et al. 2016)
10	Greater activity of the RAAS	decreased microRNA-181a Schlager BPH/2 J mice genetic model of hypertension	Hypertension	(Jackson et al. 2014)
11	Ang II	miR-384 Human umbilical vein endothelial cells	Prevents Ang II- induced ER stress and apoptosis	(Lin et al. 2017)

solitarius (NTS), catecholaminergic (CATH.a) neuron, and neurons of paraventricular nucleus (PVN).

Ang II induces the prohypertensive condition in neurons by nuclear translocation of nuclear factor kappa-B (NFkB) which further acts to regulate transcription of several genes resulting in the overexpression of proinflammatory cytokines, reactive oxygen species (ROS), superoxide, peroxynitrite, and circulating norepinephrine and decreased neuronal nitric oxide synthase (nNOS) and thereby leading to hypertension and in turn stroke (Allen 2002; Barnes and Karin 1997; Campese et al. 2005; Cardinale et al. 2012; Kang et al. 2009). Increased superoxide levels convert the intrACEllular nitric oxide to peroxynitrite, and modify the Na^+ and K^+ ion channels of the cell membrane. Calcium/calmodulin kinase II (CaMKII), a redox-sensitive kinase, activated by superoxide also acts on these ion channels (Yin et al. 2010). Affected ion channels trigger an altered neuronal firing that enhances the sympathetic nerve activity leading to increased hypertension (Chengzhi et al. 2012). All these mechanisms have been discussed in detail in previous publications (Agarwal et al. 2013; Braga et al. 2011; Cheng et al. 2010; Chengzhi et al. 2012; Peterson et al. 2009; Zimmerman et al. 2002, 2004). Another study reported a unique pathway in which Ang II modulates the pressor effect through AT_1R-dependent ROS-SAPK/JNK signaling in glutamatergic neurons in the rostral ventrolateral medulla (RVLM) of stress-induced hypertensive rats (Jiang et al. 2018).

Glial Cells

Glial cells assist neurons by carrying out several fundamental functions like neurotransmitter trafficking and recycling, release of transporters, transmitter (glutamate), energy substrates, neurosteroids, purines, cytokines, growth factors, mediate ion metabolism, and provide protection against oxidative stress. These cells are of five types including schwann cells, oligodendrocyte, microglial cells, ependymal cells, and astrocytes. Dysfunctional glial cells have a huge impact in contributing to neuroinflammation, neuronal excitability, and loss leading to the development of various neurological disorders including stroke (Booth et al. 2017; Brambilla et al. 2013; Di Malta et al. 2012; Khakh et al. 2017).

Table 4 RAAS components regulating various miRNAs

S. no.	RAAS component	miRNA regulated	Functional outcome	References
1	Ang II	miR-132 and miR-212	Hypertension	(Eskildsen et al. 2013)
2	Ang II	miR-205	Activation of matrix metalloproteinases (MMPs) and inflammation leading to abdominal aortic aneurysm	(Kim et al. 2014)
3	Ang II	MiR-133a, miR-29b (Sprague–Dawley rats cardiocytes)	Myocardial fibrosis	(Castoldi et al. 2012)
4	Ang II	miR-98 (cultured cardiomyocytes)	Cardiac hypertrophy	(Yang et al. 2011)
5	Ang II	miR-29b, -129-3p, -132, -132* and -212 (Cardiac fibroblast cell culture)	Regulation of cardiac cells	(Jeppesen et al. 2011)
6	Ang II	miR-132,-125b-3p and miR-146b, miR-300-5p,-204 and miR-181b (Adult rat cardiac fibroblast)	Cardiac fibrosis and hypertension	(Jeppesen et al. 2011)
7	Ang II	miR-130a (SHRs) and Wistar -Kyoto rats (WKYs) VSMC cell culture from sprague- Dawley rats	Proliferation of VSMCs	(Wu et al. 2011)
8	Ang II	miR-29b NRK-52E cells; (SHRs) and Wistar–Kyoto rats (WKYs)	Epithelial mesenchymal transition leading to renal fibrosis	(Nemecz et al. 2016)
9	Ang II	miR-29b mouse model of hypertension and cultured cardiac fibroblast	Cardiac remodeling and fibrosis	(Zhang et al. 2014)
10	Ang II	miR-132 rat vascular smooth muscle cells (VSMC)	Regulation of genes related to cell-cycle and motility	(Jin et al. 2012)
11	Ang II	miR-224 (adult rat cardiocytes)	Cardiac fibrosis	(Ning and Jiang 2013)
12	ACE	miR-145 HASMC	Modulation of VSMCs	(Hu et al. 2014)
13	Ang II	miR-19b cultured cardiomyocytes	Overexpression of connective tissue growth factor (CTGF) in cultured cardiomyocytes	(Gao et al. 2014)
14	Ang II	miR-30 Ang II-induced podocyte injury mouse model	Ang II-induced podocyte injury through calcium/calcineurin signaling	(Zhao et al. 2017)
15	Ang II	miR-29a-3p	Renal fibrosis	(Castoldi et al. 2016)

Ang II acts on Angiotensin 1 receptor and activates non-receptor tyrosine kinase JAK/STAT (Janus kinases/signal transducer and activator of transcription proteins) pathway triggering the release of interleukin-6 (IL-6) (Kandalam and Clark 2010). IL-6 further increases the plasma C-reactive protein (CRP) levels, initiating a low grade inflammation (Abeywardena et al. 2009). A study performed on astrocytes cultured from the brainstem and cerebellum reported that Ang II promotes the phosphorylation of Src and Pyk2 that sends an activation signal to ERK1/2 leading to growth of astrocytes (Clark and Gonzalez 2007b). Src is also involved in Ang II-induced activation of protein serine/threonine kinase c-Jun N-terminal kinase (JNK) that triggers astrocyte proliferation in cultured astrocytes from brain stem (Clark et al. 2008). Overactive brain RAAS leads to an increase in sympathetic nervous system activity leading to hypertension (Tsuda 2012).

The other well-established cellular activator of Ang II in astrocyte is mitogen-activated protein kinase (MAPK). Ang II mediates astrocyte growth-promoting effects mainly via the stimulation of extrACEllular receptor kinase1/2(ERK1/2) which are terminal serine threonine kinases in MAPK cascade, in a dose- and time-dependent manner (Clark et al. 2001). Previous studies have shown that transactivation of AT1 receptor and the membrane-bound tyrosine kinase platelet-derived growth factor (PDGF) receptor and epidermal growth factor (EGF) receptor activate the ERK1/2 phosphorylation and stimulate astrocyte growth and proliferation. Increase in number of astrocytes may further lead to an increase in central Ang II levels since astrocytes contain high levels of Angiotensinogen, the precursor molecule for Ang II. This may be an endogenous regulatory mechanism to control central Ang II levels and its effects (Clark and Gonzalez 2007a). In a study carried out in astrocytes, cultured from the brain stem, Ang

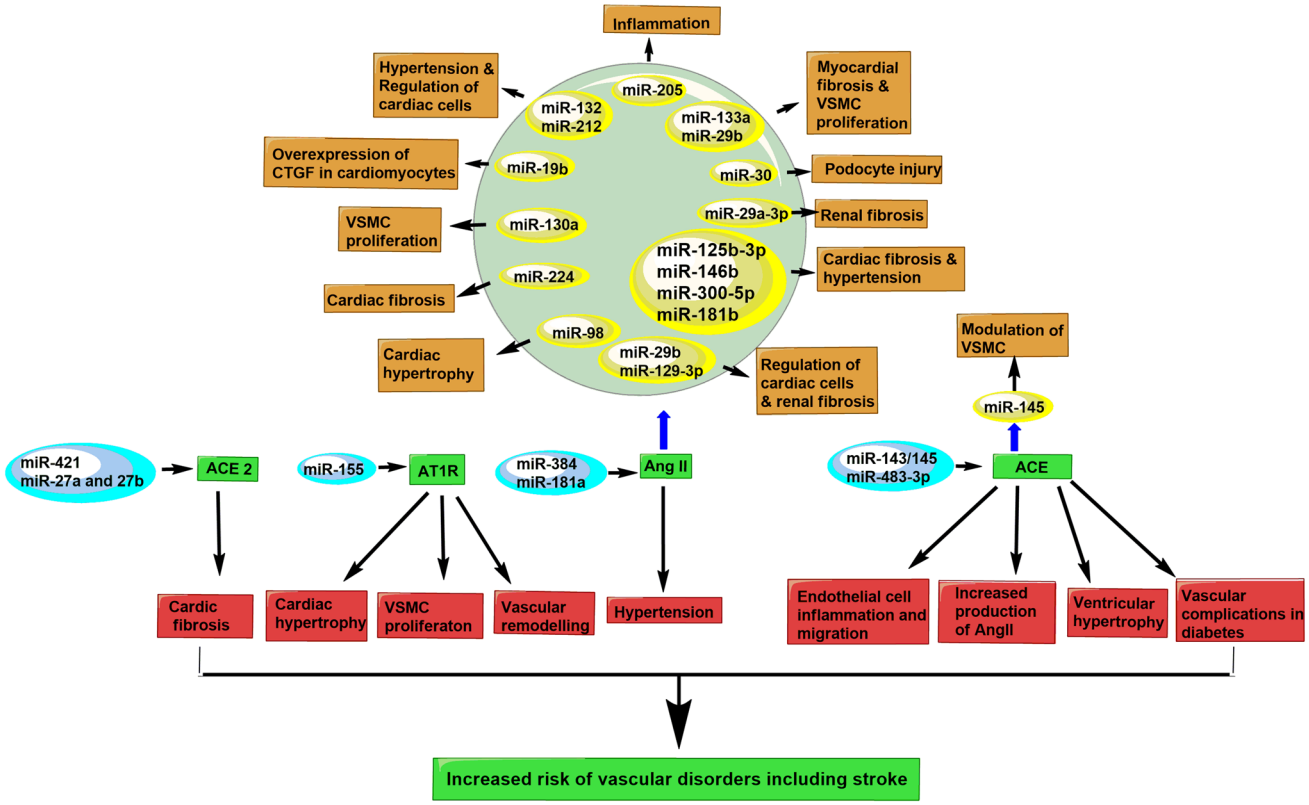

Fig. 2 Various miRNAs targeting or getting targeted by components of RAAS pathway

II-mediated activation of ERK1/2 increased the expression of early response genes, namely c-fos, c-jun, and c-myc in a dose- and time-dependent manner. Further, overexpression of c-fos, c-jun, and c-myc contributes to the dysregulation of many other genes which are otherwise normally expressed within the cell (Delaney et al. 2008). c-fos and c-jun are the essential components in reducing the baroreflex response which enhances the sympathetic tone during hypertension (Chan et al. 1998; Wang and Abdel-Rahman 2004). Both c-fos and c-jun have been implicated in the molecular mechanisms leading to cardiac hypertrophy induced by Ang II and other mitogens (Kim-Mitsuyama et al. 2006).

Transforming growth factor β1 (TGF- β1), a multifunctional regulator that performs several functions such as inhibition of cell growth, induces apoptosis, extracellular matrix production, proliferation, and migration of endothelial and vascular smooth muscle cells; proliferation, differentiation, and activation of immune cells. Excessive and prolonged TGF- β1 signaling has been implicated in various human diseases including vascular disorders (Krupinski et al. 1996). Experiments in transgenic mice overexpressing a constitutively active form of TGF-β1 in astrocytes suggest the pivotal role of Ang II in TGF-β1-induced cerebrovascular dysfunction and neuroinflammation through AT1R-mediated mechanisms. AT1R inhibitor, losartan, significantly reduced the astrogliosis and also diminished the cerebrovascular levels of pro-fibrotic protein connective tissue growth factor while raising levels of anti-fibrotic enzyme matrix metallopeptidase-9 (Prabhakar et al. 2014). Transfection experiments demonstrate that Ang II mediates the activation of TGF-β1 through AT1 receptor via protein kinase C (PKC) and MAPK that activates transcription factors, activator protein 1 (AP-1) box A and B (Weigert et al. 2002). TGF- β1 triggers its biological effects by inducing the formation of a heteromeric transmembrane serine/threonine kinase receptor complex. These receptors then initiate intrACEllular signaling through activation of Smad proteins, followed by phosphorylation of specific Smads which in turn associate with other Smads. These heteromeric Smad complexes accumulate in the nucleus, where they form functional transcriptional complexes in the nucleus at the promoter sites of target genes and modulate their expression (Kretzschmar and Massagué 1998; ten Dijke and Hill 2004). Regulation of various genes like bone morphogenetic protein type II receptor gene (BMPR2) implicated in the pathogenesis of hypertension and vascular diseases have been reported to be controlled by TGF- β1 through Smad proteins (Peterson 2005; Yang et al. 2005).

Ang II promotes neuroinflammation in both astrocytes and microglia. Stimulation by Ang II leads to an increase

in the production of TGF-β1 microglial cells, wheRAAS in astrocytes it mediates an increase the secretion of TGF-β1-activating protease, thrombospondin-1(TSP-1). TSP-1 activates TGF-β1 in the brain and creates a permissive niche allowing T cells to obtain a more inflammatory phenotype. Inhibition of AT1R by candesartan (CA) and blockade of binding between TSP-1 and TGF-β1 by LSKL (Leu-Ser-Lys-Leu); a peptide antagonist of TGF-β1 activation blocks the upregulation of TGF-β1 in both astrocytes and microglia. The data suggest that use of AT1R antagonists (frequently prescribed antihypertensives) may also be useful to interrupt the CNS-specific proinflammatory pathway leading to decreased inflammation in brain (Lanz et al. 2010).

Vascular Smooth Muscle Cells (VSMCs)

Ang II has been reported to activate JAK/STAT pathway in VSMCs also, triggering the release of IL-6 and Angiotensinogen. Ang II can signal the generation of IL-6 independent of JAK/STAT pathway also via nuclear factor-κB-(NFKB) and/or ROS. In VSMCs, a crosstalk between Ang II and membrane-bound tyrosine kinases mediates several important effects of Ang II including protein synthesis of growth-promoting molecules (Daub et al. 1996; Eguchi and Inagami 2000). Transactivation of AT1 receptor and membrane-bound tyrosine kinase platelet-derived growth factor receptor (PDGFR) and epidermal growth factor receptor (EGFR) stimulates VSMC growth and proliferation (Saito and Berk 2001). Moreover, Ang II-induced gene expression mediated through c-Fos at the downstream of the ERK cascade has also been reported in VSMC. The protein synthesis was found to confer through p70 S6 kinase involving both the phosphatidylinositol 3-kinase (PI3 K)/Akt and the ERK cascades (Eguchi and Inagami 2000). The aberrant VSMC remodeling and proliferation contributes to hypertension, plaque formation, and consequently stroke.

In an experiment carried out by Moore et al. (2015), it was found that Ang II promotes overexpression of macrophage (CD68) and leukocyte (CD45+) in mice aorta. CD-206-expressing M2 macrophages were more than the inducible nitric oxide synthase-expressing M1 macrophage. Real-time PCR data also confirmed the above finding. The markers of M1 macrophage (iNOS, chemokine (C-X-C motif) ligand (CXCL)2 and tumor necrosis factor (TNF) were found to be downregulated in comparison with M2 macrophage markers (CD206), arginase (Arg)-1, and Fc receptor-like S scavenger receptor (Fcrls). Chemokine receptor (CCR2) was also highly expressed in mice aorta along with its ligands including CCL2, CCL7,CCL8. Flow cytometry identified that Ly6Chi monocytes were the main CCR2-expressing cell type. Intervention with a CCR2 antagonist (INCB3344) reduced the aortic macrophage numbers as well as aortic collagen deposition, elastin loss, and BP in Ang II-treated mice, thus, suggesting that Ang II-dependent hypertension in mice is attributed by Ly6Chi monocyte and M2 macrophage accumulation in the aorta. Inhibition of macrophage accumulation with a CCR2 antagonist might provide a preventive strategy for BP in Ang II-induced vessel fibrosis (Moore et al. 2015).

Ang II activates the Smad pathway via AT1 receptor and MAPK activation, independently of TGF-β in cardiac myocytes. Following the lead of MAPK pathway Ang II signals fibrosis via connective tissue growth factor (CTGF) promoter expression, and extrACEllular matrix (ECM) proteins like fibronectin and type-1 procollagen overexpression, leading to hypertension and cardiac remodeling (Chen et al. 2000).

Treatment Strategies Targeting ACE

Since ACE is the major component of hypertension in stroke patients, several antihypertensive drugs like ACE inhibitors and angiotensin receptor blockers targeting Ang II have been developed (Arnold et al. 1998). These antagonists have become the first line of treatment for patients who are at a higher risk of stroke occurrence or recurrence (Sica 2016).Various studies have interpreted the use of antihypertensive drugs for primary prevention of stroke but they are still under check for their role to prevent a secondary stroke (Lonn et al. 2016).

ACE Inhibitors (ACEIs)

ACEIs competitively inhibit the activity of ACE to prevent formation of the active octapeptide, angiotensin II, from the inactive decapeptide, angiotensin I. The first orally active ACE inhibitor drug captopril was commercially released in 1981 (Ohkuma et al. 2019). Following the release of captopril, enalapril, and lisinopril in the early to mid-1980s, the progress in the field of ACE inhibitors remained relatively dormant on account a developmental perspective until 1991 when four ACE inhibitors namely fosinopril, quinapril, benazepril, and ramipril were released in the market (Miller and Arnold 2019). This was followed by the entry of other ACE inhibitors like perindopril, moexipril, and trandolapril in the market between 1993 and 1996 (Sica 2010). In the previous section of this study, the mechanism by which ACE inhibitor works has been mentioned. Studies involving animal models suggested that ACE inhibitors promote angiogenesis and reverse cerebrovascular remodeling. However, the pro-angiogenic effect of ACE inhibition is not clear. The mechanism is hypothesized to be mediated by gradual increase in bradykinin subsequent NO production. ACE inhibition also helps in downregulation of fibrinoid necrosis, inhibition of atherosclerotic plaque progression,

and also reverting of periarteriolar fibrosis and obstructing mains steps of hyperplasia after a vascular injury (Vaughan and Pfeffer 1994; Yazawa et al. 2011). Thus, ACE inhibition plays a crucial role in improving functional outcome after stroke. Smeda et al. (1999) demonstrated that captopril efficiently autoregulates the cerebral blood flow and cerebrovascular constriction in testing stroke prone hypertensive rats (SHRsp) (Smeda et al. 1999).

The FDA-approved ACEIs for high blood pressure include Captopril, Benazepril, Enalapril, Fosinopril, Lisinopril, Perindopril, Quinapril, Ramipril, and Trandolapril (www.fda.gov). Recently, qbrelis has been added to the list and approved by FDA as an ACE inhibitor for lowering blood pressure. The clinical trial of ACEIs like lisinopril, enalapril, perindopril, and ramipril have been completed for stroke and for some inhibitors the trials are still ongoing (Table 5). In Heart Outcome Prevention Evaluation (HOPE) trial, ramipril conferred a 32% decreased relative risk of stroke (Arnold et al. 2003). Another study, perindopril protection against recurrent stroke study (PROGRESS), determined the effect of Perindopril in lowering the blood pressure in both hypertensives and normotensives elucidating its effectiveness and even better results when used along with diuretic indapamide (Chalmers and MacMahon 2003).

ACE Receptor Blockers (ARBs)

ARBs block the action of angiotensin II by preventing angiotensin II from binding to angiotensin II receptors over the surface of cells (Ferrario 2002). As a result, blood vessels dilate and blood pressure is reduced. Reduced blood pressure makes it easier for the heart to pump blood and can prevent heart failure. The AT1R in the brain is involved in vasopressin release and regulation of sympathetic drive, and its overexpression might result in decreased blood flow in the neuronal region which is the consequence of increased vasoconstriction and cerebrovascular remodeling (Sriramula et al. 2011). Some of the FDA-approved ARBs include Atacand, Avapro, Benicar, Cozaar, Diovan, Micardis, and Teveten (www.fda.gov). Losartan, a non-peptidergic antagonist of AT1R, has been demonstrated to reduce blood pressure with high efficacy in a high-renin hypertensive rat model. As a result, it prevents the pressor effect generated by systemic Ang II. The systemic administration of losartan (3 mg/kg) significantly diminished the pressor effect generated by the electrical stimulation of subfornical organ. In addition, it was found that the systemic administration of losartan significantly reduces neuronal excitation of PVN neurons to SF0 stimulation or microinjection of Ang II by 58.8% and 88.9% of PVN cells, respectively. These observations suggest that systemic losartan crosses the blood–brain barrier (BBB) and acts at AT1 receptors within the PVN. Inhibition of AT1 receptor signaling is useful as an anti-inflammatory as well as immunosuppressive therapy (Li et al. 1993). Several clinical trials have been conducted to evaluate the efficacy of this drug in stroke patients. A trial called LIFE (Losartan Intervention for Endpoint reduction in Hypertension study) which allocated the use of Losartan versus Atenolol, Ang II receptor blocker for lowering blood pressure, revealed a 25% lessened relative reduction in risk for stroke (Dahlöf et al. 2002). Another study, Morbidity and Mortality after Stroke Eprosartan compared with Nitrendipine for Secondary Prevention Study (MOSES), examined the use of Eprosartan (ARB) with Nitrendipine (Calcium antagonist) and found the use of ARBs to be more effective in preventing secondary stroke outcome (Schrader et al. 2005).

Conclusion

Stroke is one of the leading cause of death worldwide. The ACE is an important entity in context of RAAS pathway where it catalyzes the conversion of angiotensin I to angiotensin II. Angiotensin II triggers changes in vascular elasticity leading to vasoconstriction, initiation of plaque formation and consequently atherosclerosis. All these physiological processes hinder the cerebral blood flow, apart from enhanced oxidative stress leading to stroke. Functional genetic variants of ACE gene have been evaluated

Table 5 Clinical trials including ACEIs and ARBs in stroke

S. no	Trials	Cases	Drug	Drug class	Significance	References
1.	HOPE	9297	Ramipril	ACEI	32% reduction in stroke	(Yusuf et al. 2000)
2.	LIFE	9193	Losartan	ARB	25% lower risk of stroke	(Dahlöf et al. 2002)
3.	PROGRESS	6105	Perindopril	ACEI	5% decrease in stroke recurrence, 28% reduction in relative risk	(Group 2001)
4.	MOSES	1405	Eprosartan	ARB	Reduced blood pressure	(Schrader et al. 2005)
5.	ONTARGET	25,620	Telmisartan/ Ramipril + telmisartan	ARB/ACE + ARB	recurrence of stroke reduced in Telmisartan cases	(Ruilope et al. 2007)
6.	ACCESS	500	Candesartan	ARB	52% less incidence of stroke	(Böhm et al. 2017)

by different research groups in various ethnic groups. Some studies found an association of ACE variants with stroke, whereas others reported contradictory findings. In addition, many miRNAs have also emerged as key players in regulation of RAAS pathway and simultaneously certain miRNAs also get regulated by different components involved in the RAAS pathway. Dysregulation of these miRNAs leads to elevated levels of Ang II. Alterations in Ang II levels affect the downstream signal transduction pathways in neurons, glial cells, and VSMCs and thereby result in the development of hypertension and inflammation, the two established risk factors for stroke. The overexpression of ACE is controlled by prescribing inhibitors and blockers that have been developed over the period of time. However, some of these are still under clinical trials.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

References

Abeywardena, M. Y., Leifert, W. R., Warnes, K. E., Varghese, J. N., & Head, R. J. (2009). Cardiovascular biology of interleukin-6. *Current Pharmaceutical Design, 15*(15), 1809–1821.

Agarwal, D., Dange, R. B., Raizada, M. K., & Francis, J. (2013). Angiotensin II causes imbalance between pro-and anti-inflammatory cytokines by modulating GSK-3β in neuronal culture. *British Journal of Pharmacology, 169*(4), 860–874.

Allen, A. M. (2002). Inhibition of the hypothalamic paraventricular nucleus in spontaneously hypertensive rats dramatically reduces sympathetic vasomotor tone. *Hypertension, 39*(2), 275–280.

Arnold, J. M. O., Yusuf, S., Young, J., Mathew, J., Johnstone, D., Avezum, A., … Bosch, J. (2003). Prevention of heart failure in patients in the Heart Outcomes Prevention Evaluation (HOPE) study. *Circulation, 107*(9), 1284–1290.

Barnes, P. J., & Karin, M. (1997). Nuclear factor-κB—A pivotal transcription factor in chronic inflammatory diseases. *New England Journal of Medicine, 336*(15), 1066–1071.

Bátkai, S., & Thum, T. (2012). MicroRNAs in hypertension: Mechanisms and therapeutic targets. *Current Hypertension Reports, 14*(1), 79–87.

Benjamin, E. J., Blaha, M. J., Chiuve, S. E., Cushman, M., Das, S. R., Deo, R., … Isasi, C. (2017). Heart disease and stroke statistics-2017 update: A report from the American Heart Association. *Circulation, 135*(10), e146–e603.

Biancardi, V. C., Bomfim, G. F., Reis, W. L., Al-Gassimi, S., & Nunes, K. P. (2017). The interplay between Angiotensin II, TLR4 and hypertension. *Pharmacological Research, 120,* 88–96.

Boettger, T., Beetz, N., Kostin, S., Schneider, J., Krüger, M., Hein, L., et al. (2009). Acquisition of the contractile phenotype by murine arterial smooth muscle cells depends on the Mir143/145 gene cluster. *The Journal of Clinical Investigation, 119*(9), 2634–2647.

Böhm, M., Schumacher, H., Teo, K. K., Lonn, E. M., Mahfoud, F., Mann, J. F., … Sliwa, K. (2017). Achieved blood pressure and cardiovascular outcomes in high-risk patients: Results from ONTARGET and TRANSCEND trials. *The Lancet, 389*(10085), 2226–2237.

Booth, H. D., Hirst, W. D., & Wade-Martins, R. (2017). The role of astrocyte dysfunction in Parkinson's disease pathogenesis. *Trends in Neurosciences, 40*(6), 358–370.

Braga, V., Medeiros, I., Ribeiro, T., França-Silva, M., Botelho-Ono, M., & Guimarães, D. (2011). Angiotensin-II-induced reactive oxygen species along the SFO-PVN-RVLM pathway: Implications in neurogenic hypertension. *Brazilian Journal of Medical and Biological Research, 44*(9), 871–876.

Brambilla, L., Martorana, F., & Rossi, D. (2013). Astrocyte signaling and neurodegeneration: New insights into CNS disorders. *Prion, 7*(1), 28–36.

Campese, V. M., Shaohua, Y., & Huiquin, Z. (2005). Oxidative stress mediates angiotensin II–dependent stimulation of sympathetic nerve activity. *Hypertension, 46*(3), 533–539.

Cardinale, J. P., Sriramula, S., Mariappan, N., Agarwal, D., & Francis, J. (2012). Angiotensin II–induced hypertension is modulated by nuclear factor-κB in the paraventricular nucleus. *Hypertension, 59*(1), 113–121.

Carmichael, C. Y., & Wainford, R. D. (2015). Hypothalamic signaling mechanisms in hypertension. *Current Hypertension Reports, 17*(5), 39.

Castoldi, G., Di Gioia, C. R., Bombardi, C., Catalucci, D., Corradi, B., Gualazzi, M. G., … Condorelli, G. (2012). MiR-133a regulates collagen 1A1: Potential role of miR-133a in myocardial fibrosis in angiotensin II-dependent hypertension. *Journal of cellular physiology, 227*(2), 850–856.

Castoldi, G., di Gioia, C., Giollo, F., Carletti, R., Bombardi, C., Antoniotti, M., … Stella, A. (2016). Different regulation of miR-29a-3p in glomeruli and tubules in an experimental model of angiotensin II-dependent hypertension: Potential role in renal fibrosis. *Clinical and Experimental Pharmacology and Physiology, 43*(3), 335–342.

Celiker, G., Can, U., Verdi, H., Yazici, A. C., Ozbek, N., & Atac, F. B. (2009). Prevalence of thrombophilic mutations and ACE I/D polymorphism in Turkish ischemic stroke patients. *Clinical and Applied Thrombosis/Hemostasis, 15*(4), 415–420.

Chalmers, J., & MacMahon, S. (2003). Perindopril protection against Recurrent Stroke Study (PROGRESS): Interpretation and implementation. *Journal of Hypertension, 21,* S9–S14.

Chan, J. Y., Chen, W.-C., Lee, H.-Y., & Chan, S. H. (1998). Elevated Fos expression in the nucleus tractus solitarii is associated with reduced baroreflex response in spontaneously hypertensive rats. *Hypertension, 32*(5), 939–944.

Chen, Y.-C., Chang, K.-H., & Chen, C.-M. (2018). Genetic polymorphisms associated with spontaneous intracerebral hemorrhage. *International Journal of Molecular Sciences, 19*(12), 3879.

Chen, M. M., Lam, A., Abraham, J. A., Schreiner, G. F., & Joly, A. H. (2000). CTGF expression is induced by TGF-β in cardiac fibroblasts and cardiac myocytes: A potential role in heart fibrosis. *Journal of Molecular and Cellular Cardiology, 32*(10), 1805–1819.

Cheng, W.-H., Lu, P.-J., Ho, W.-Y., Tung, C.-S., Cheng, P.-W., Hsiao, M., et al. (2010). Angiotensin II inhibits neuronal nitric oxide synthase activation through the ERK1/2-RSK signaling pathway to modulate central control of blood pressure. *Circulation Research, 106*(4), 788.

Chengzhi, L., Li, W., Essackjee, A., Sherpa, N., & Di, L. (2012). Angiotensin-II induced reactive oxygen species: Implications in neurogenic hypertension. *Journal of Hypertension, 1,* 106.

Clark, M. A., & Gonzalez, N. (2007a). Angiotensin II stimulates rat astrocyte mitogen-activated protein kinase activity and growth through EGF and PDGF receptor transactivation. *Regulatory Peptides, 144*(1–3), 115–122.

Clark, M. A., & Gonzalez, N. (2007b). Src and Pyk2 mediate angiotensin II effects in cultured rat astrocytes. *Regulatory Peptides, 143*(1–3), 47–55.

Clark, M. A., Guillaume, G., & Pierre-Louis, H. C. (2008). Angiotensin II induces proliferation of cultured rat astrocytes through c-Jun N-terminal kinase. *Brain Research Bulletin, 75*(1), 101–106.

Clark, M., Landrum, M., & Tallant, E. (2001). *Angiotensin II activates mitogen-activated protein kinases and stimulates growth in rat medullary astrocytes.* Paper Presented at the Faseb Journal.

Dahlöf, B., Devereux, R. B., Kjeldsen, S. E., Julius, S., Beevers, G., de Faire, U., … Lederballe-Pedersen, O. (2002). Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): A randomised trial against atenolol. *The Lancet, 359*(9311), 995–1003.

Dardiotis, E., Jagiella, J., Xiromerisiou, G., Dardioti, M., Vogiatzi, C., Urbanik, A., … Slowik, A. (2011). Angiotensin-converting enzyme tag single nucleotide polymorphisms in patients with intracerebral hemorrhage. *Pharmacogenetics and Genomics, 21*(3), 136–141.

Das, S., Roy, S., Sharma, V., Kaul, S., Jyothy, A., & Munshi, A. (2015). Association of ACE gene I/D polymorphism and ACE levels with hemorrhagic stroke: Comparison with ischemic stroke. *Neurological Sciences, 36*(1), 137–142.

Daub, H., Weiss, F. U., Wallasch, C., & Ullrich, A. (1996). Role of transactivation of the EGF receptor in signalling by G-protein-coupled receptors. *Nature, 379*(6565), 557.

Delaney, J., Chiarello, R., Villar, D., Kandalam, U., Castejon, A. M., & Clark, M. A. (2008). Regulation of c-fos, c-jun and c-myc gene expression by angiotensin II in primary cultured rat astrocytes: Role of ERK1/2 MAP kinases. *Neurochemical Research, 33*(3), 545–550.

Dennis, G. J. (2008). *A haplotype analysis of the angiotensin converting enzyme gene in ischaemic stroke*. Leicester: University of Leicester.

Di Malta, C., Fryer, J. D., Settembre, C., & Ballabio, A. (2012). Astrocyte dysfunction triggers neurodegeneration in a lysosomal storage disorder. *Proceedings of the National Academy of Sciences USA, 109*(35), E2334–E2342.

Dive, V., Cotton, J., Yiotakis, A., Michaud, A., Vassiliou, S., Jiracek, J., … Corvol, P. (1999). RXP 407, a phosphinic peptide, is a potent inhibitor of angiotensin I converting enzyme able to differentiate between its two active sites. *Proceedings of the National Academy of Sciences USA, 96*(8), 4330–4335.

Domingues-Montanari, S., Fernandez-Cadenas, I., Del Rio-Espinola, A., Mendioroz, M., Ribo, M., Obach, V., … Corbeto, N. (2010). The I/D polymorphism of the ACE1 gene is not associated with ischaemic stroke in Spanish individuals. *European Journal of Neurology, 17*(11), 1390–1392.

Domingues-Montanari, S., Hernandez-Guillamon, M., Fernandez-Cadenas, I., Mendioroz, M., Boada, M., Munuera, J., … Gutierrez, M. (2011). ACE variants and risk of intracerebral hemorrhage recurrence in amyloid angiopathy. *Neurobiology of Aging, 32*(3), 551. e513–551. e522.

Eguchi, S., & Inagami, T. (2000). Signal transduction of angiotensin II type 1 receptor through receptor tyrosine kinase. *Regulatory Peptides, 91*(1–3), 13–20.

Eskildsen, T., Jeppesen, P., Schneider, M., Nossent, A., Sandberg, M., Hansen, P., … Rasmussen, L. (2013). Angiotensin II regulates microRNA-132/-212 in hypertensive rats and humans. *International Journal of Molecular Sciences, 14*(6), 11190–11207.

Fernandes, T., Hashimoto, N. Y., Magalhaes, F. C., Fernandes, F. B., Casarini, D. E., Carmona, A. K., … Oliveira, E. M. (2011). Aerobic exercise training–induced left ventricular hypertrophy involves regulatory MicroRNAs, decreased angiotensin-converting enzyme-angiotensin II, and synergistic regulation of angiotensin-converting enzyme 2-angiotensin (1-7). *Hypertension, 58*(2), 182–189.

Ferrari, R. (2004). Preserving bradykinin or blocking angiotensin II: The cardiovascular dilemma. *Dialogues in Cardiovascular Medicine, 9,* 71–92.

Ferrario, C. M. (2002). Use of angiotensin II receptor blockers in animal models of atherosclerosis. *American Journal of Hypertension, 15*(S1), 9S–13S.

Ferrario, C. M. (2011). ACE 2: More of Ang 1-7 or less Ang II? *Current Opinion in Nephrology and Hypertension, 20*(1), 1.

Frauman, A. G., Johnston, C. I., & Fabiani, M. E. (2001). Angiotensin receptors: Distribution, signalling and function. *Clinical Science, 100*(5), 481–492.

Gao, S., Liu, T.-W., Wang, Z., Jiao, Z.-Y., Cai, J., Chi, H.-J., et al. (2014). Downregulation of MicroRNA-19b contributes to angiotensin II-induced overexpression of connective tissue growth factor in cardiomyocytes. *Cardiology, 127*(2), 114–120.

Gormley, K., Bevan, S., & Markus, H. (2007). Polymorphisms in genes of the renin-angiotensin system and cerebral small vessel disease. *Cerebrovascular Diseases, 23*(2–3), 148–155.

Goyal, R., Goyal, D., Leitzke, A., Gheorghe, C. P., & Longo, L. D. (2010). Brain renin-angiotensin system: Fetal epigenetic programming by maternal protein restriction during pregnancy. *Reproductive Sciences, 17*(3), 227–238.

Group, P. C. (2001). Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. *The Lancet, 358*(9287), 1033–1041.

Higuchi, S., Ohtsu, H., Suzuki, H., Shirai, H., Frank, G. D., & Eguchi, S. (2007). Angiotensin II signal transduction through the AT1 receptor: Novel insights into mechanisms and pathophysiology. *Clinical Science, 112*(8), 417–428.

Hu, B., TaoSong, J., YanQu, H., LongBi, C., ZhenHuang, X., Xin-Liu, X., et al. (2014). Mechanical stretch suppresses microRNA-145 expression by activating extracellular signal-regulated kinase 1/2 and upregulating angiotensin-converting enzyme to alter vascular smooth muscle cell phenotype. *PLoS ONE, 9*(5), e96338.

Huang, Y., Li, G., Lan, H., Zhao, G., & Huang, C. (2014). Angiotensin-converting enzyme insertion/deletion gene polymorphisms and risk of intracerebral hemorrhage: A meta-analysis of epidemiologic studies. *Journal of the Renin-Angiotensin-Aldosterone System, 15*(1), 32–38.

Hubert, C., Houot, A.-M., Corvol, P., & Soubrier, F. (1991). Structure of the angiotensin I-converting enzyme gene. Two alternate promoters correspond to evolutionary steps of a duplicated gene. *Journal of Biological Chemistry, 266*(23), 15377-15383.

Jackson, K. L., Marques, F. Z., Nguyen-Huu, T.-P., Stevenson, E. R., Charchar, F. J., Davern, P. J., & Head, G. A. (2014). MicroRNA-181a mimic inhibits the renin-angiotensin system and attenuates hypertension in a neurogenic model of hypertension. *Hypertension, 64*(suppl_1), A038-A038.

Jacob, H. J., Lindpaintner, K., Lincoln, S. E., Kusumi, K., Bunker, R. K., Mao, Y.-P., ... Lander, E. S. (1991). Genetic mapping of a gene causing hypertension in the stroke-prone spontaneously hypertensive rat. *Cell, 67*(1), 213–224.

Jeppesen, P. L., Christensen, G. L., Schneider, M., Nossent, A. Y., Jensen, H. B., Andersen, D. C., ... Sheikh, S. P. (2011). Angiotensin II type 1 receptor signalling regulates microRNA differentially in cardiac fibroblasts and myocytes. *British Journal of Pharmacology, 164*(2), 394–404.

Jiang, L., Zhou, X., Yang, H., Guan, R., Xin, Y., Wang, J., ... Wang, J. (2013). ACE2-Ang-(1-7)-Mas axis in brain: A potential target for

prevention and treatment of ischemic stroke. *Current Neuropharmacology, 11*(2), 209–217.

Jiang, L., Zhou, X., Yang, H., Guan, R., Xin, Y., Wang, J.,… Wang, J. (2018). Upregulation of AT1 Receptor Mediates a Pressor Effect through ROS-SAPK/JNK Signaling in Glutamatergic Neurons of Rostral Ventrolateral Medulla in Rats with Stress-Induced Hypertension. *Frontiers in physiology, 9*.

Jin, W., Reddy, M. A., Chen, Z., Putta, S., Lanting, L., Kato, M., ... Tangirala, R. K. (2012). Small RNA sequencing reveals microRNAs that modulate angiotensin II effects in vascular smooth muscle cells. *Journal of Biological Chemistry, 287*(19), 15672–15683.

Kalita, J., Somarajan, B. I., Kumar, B., Mittal, B., & Misra, U. K. (2011). A study of ACE and ADD1 polymorphism in ischemic and hemorrhagic stroke. *Clinica Chimica Acta, 412*(7–8), 642–646.

Kandalam, U., & Clark, M. A. (2010). Angiotensin II activates JAK2/STAT3 pathway and induces interleukin-6 production in cultured rat brainstem astrocytes. *Regulatory Peptides, 159*(1–3), 110–116.

Kang, Y.-M., Ma, Y., Zheng, J.-P., Elks, C., Sriramula, S., Yang, Z.-M., et al. (2009). Brain nuclear factor-kappa B activation contributes to neurohumoral excitation in angiotensin II-induced hypertension. *Cardiovascular Research, 82*(3), 503–512.

Kaul, S., & Munshi, A. (2012). Genetics of ischemic stroke: Indian perspective. *Neurology India, 60*(5), 498.

Kemp, J. R., Unal, H., Desnoyer, R., Yue, H., Bhatnagar, A., & Karnik, S. S. (2014). Angiotensin II-regulated microRNA 483-3p directly targets multiple components of the renin–angiotensin system. *Journal of Molecular and Cellular Cardiology, 75,* 25–39.

Keramatipour, M., McConnell, R. S., Kirkpatrick, P., Tebbs, S., Furlong, R. A., & Rubinsztein, D. C. (2000). The ACE I allele is associated with increased risk for ruptured intracranial aneurysms. *Journal of Medical Genetics, 37*(7), 498–500.

Khakh, B. S., Beaumont, V., Cachope, R., Munoz-Sanjuan, I., Goldman, S. A., & Grantyn, R. (2017). Unravelling and exploiting astrocyte dysfunction in Huntington's disease. *Trends in Neurosciences, 40*(7), 422–437.

Kim, V. N. (2005). MicroRNA biogenesis: Coordinated cropping and dicing. *Nature Reviews Molecular Cell Biology, 6*(5), 376.

Kim, C. W., Kumar, S., Son, D. J., Jang, I.-H., Griendling, K. K., & Jo, H. (2014). Prevention of abdominal aortic aneurysm by Anti–MicroRNA-712 or Anti–MicroRNA-205 in angiotensin II–infused mice. *Arteriosclerosis, Thrombosis, and Vascular Biology, 34*(7), 1412–1421.

Kim-Mitsuyama, S., Izumi, Y., Izumiya, Y., Namba, M., Yoshida, K., Wake, R., ... Iwao, H. (2006). Dominant-negative c-Jun inhibits rat cardiac hypertrophy induced by angiotensin II and hypertension. *Gene Therapy, 13*(4), 348.

Kohlstedt, K., Trouvain, C., Boettger, T., Shi, L., Fisslthaler, B., & Fleming, I. (2013). AMP-activated protein kinase regulates endothelial cell angiotensin-converting enzyme expression via p53 and the post-transcriptional regulation of microRNA-143/145. *Circulation Research, 112*(8), 1150–1158.

Kretzschmar, M., & Massagué, J. (1998). SMADs: Mediators and regulators of TGF-β signaling. *Current Opinion in Genetics & Development, 8*(1), 103–111.

Krupinski, J., Kumar, P., Kumar, S., & Kaluza, J. (1996). Increased expression of TGF-β1 in brain tissue after ischemic stroke in humans. *Stroke, 27*(5), 852–857.

Kumar, A., Vivekanandhan, S., Srivastava, A., Tripathi, M., Padma Srivastava, M., Saini, N., ... Prasad, K. (2014). Association between angiotensin converting enzyme gene insertion/deletion polymorphism and ischemic stroke in North Indian population: A case–control study and meta-analysis. *Neurological Research, 36*(9), 786–794.

Lambert, D. W., Lambert, L. A., Clarke, N. E., Hooper, N. M., Porter, K. E., & Turner, A. J. (2014). Angiotensin-converting enzyme 2 is subject to post-transcriptional regulation by miR-421. *Clinical Science, 127*(4), 243–249.

Lanz, T. V., Ding, Z., Ho, P. P., Luo, J., Agrawal, A. N., Srinagesh, H., ... Wyss-Coray, T. (2010). Angiotensin II sustains brain inflammation in mice via TGF-β. *The Journal of Clinical Investigation, 120*(8), 2782–2794.

Lassègue, B., & Griendling, K. K. (2010). NADPH oxidases: Functions and pathologies in the vasculature. *Arteriosclerosis, Thrombosis, and Vascular Biology, 30*(4), 653–661.

Lee, Y., Kim, M., Han, J., Yeom, K. H., Lee, S., Baek, S. H., et al. (2004). MicroRNA genes are transcribed by RNA polymerase II. *The EMBO journal, 23*(20), 4051–4060.

Li, Z., Bains, J. S., & Ferguson, A. V. (1993). Functional evidence that the angiotensin antagonist losartan crosses the blood-brain barrier in the rat. *Brain Research Bulletin, 30*(1–2), 33–39.

Lin, H., Pan, S., Meng, L., Zhou, C., Jiang, C., Ji, Z., ... Guo, H. (2017). MicroRNA-384-mediated Herpud1 upregulation promotes angiotensin II-induced endothelial cell apoptosis. *Biochemical and Biophysical Research Communications, 488*(3), 453–460.

Lonn, E. M., Bosch, J., López-Jaramillo, P., Zhu, J., Liu, L., Pais, P., ... Dans, A. (2016). Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. *New England Journal of Medicine, 374*(21), 2009–2020.

Lyle, A. N., & Griendling, K. K. (2006). Modulation of vascular smooth muscle signaling by reactive oxygen species. *Physiology, 21*(4), 269–280.

Malueka, R. G., Dwianingsih, E. K., Sutarni, S., Bawono, R. G., Bayuangga, H. F., Gofir, A., et al. (2018). The D allele of the angiotensin-converting enzyme (ACE) insertion/deletion (I/D) polymorphism is associated with worse functional outcome of ischaemic stroke. *International Journal of Neuroscience, 128*(8), 697–704.

Malueka, R. G., Dwianingsih, E. K., Sutarni, S., Gofir, A., & Setyopranoto, I. (2017). Association between ace gene polymorphism and functional outcome of ischemic stroke. *Journal of the Neurological Sciences, 381,* 618.

Markoula, S., Giannopoulos, S., Kostoulas, C., Tatsioni, A., Bouba, I., Maranis, S.,… Kyritsis, A. P. (2011). Gender association of the angiotensin-converting enzyme gene with ischaemic stroke. *Journal of the Renin-Angiotensin-Aldosterone System, 12*(4), 510-515.

Martínez-Rodríguez, N., Posadas-Romero, C., Villarreal-Molina, T., Vallejo, M., Del-Valle-Mondragón, L., Ramírez-Bello, J., ... Vargas-Alarcón, G. (2013). Single nucleotide polymorphisms of the angiotensin-converting enzyme (ACE) gene are associated with essential hypertension and increased ACE enzyme levels in Mexican individuals. *PLoS ONE, 8*(5), e65700.

Matarin, M., Brown, W. M., Dena, H., Britton, A., De Vrieze, F. W., Brott, T. G., ... Chanock, S. J. (2009). Candidate gene polymorphisms for ischemic stroke. *Stroke, 40*(11), 3436–3442.

Mengesha, H. G., Petrucka, P., Spence, C., & Tafesse, T. B. (2019). Effects of angiotensin converting enzyme gene polymorphism on hypertension in Africa: A meta-analysis and systematic review. *PLoS ONE, 14*(2), e0211054.

Miller, A. J., & Arnold, A. C. (2019). The renin–angiotensin system in cardiovascular autonomic control: Recent developments and clinical implications. *Clinical Autonomic Research, 29*(2), 231–243.

Moore, J. P., Vinh, A., Tuck, K. L., Sakkal, S., Krishnan, S. M., Chan, C. T., ... Kemp-Harper, B. K. (2015). M2 macrophage accumulation in the aortic wall during angiotensin II infusion in mice is associated with fibrosis, elastin loss, and elevated blood pressure. *American Journal of Physiology-Heart and Circulatory Physiology, 309*(5), H906–H917.

Munshi, A., Das, S., & Kaul, S. (2015). Genetic determinants in ischaemic stroke subtypes: Seven year findings and a review. *Gene, 555*(2), 250–259.

Munshi, A., & Kaul, S. (2010). Genetic basis of stroke: An overview. *Neurology India, 58*(2), 185.

Munshi, A., Sultana, S., Kaul, S., Reddy, B. P., Alladi, S., & Jyothy, A. (2008). Angiotensin-converting enzyme insertion/deletion polymorphism and the risk of ischemic stroke in a South Indian population. *Journal of the Neurological Sciences, 272*(1–2), 132–135.

Nemecz, M., Alexandru, N., Tanko, G., & Georgescu, A. (2016). Role of microRNA in endothelial dysfunction and hypertension. *Current Hypertension Reports, 18*(12), 87.

Ning, Q., & Jiang, X. (2013). Angiotensin II upregulated the expression of microRNA-224 but not microRNA-21 in adult rat cardiac fibroblasts. *Biomedical reports, 1*(5), 776–780.

Ohkuma, T., Jun, M., Rodgers, A., Cooper, M. E., Glasziou, P., Hamet, P., ... Neal, B. (2019). Acute increases in serum creatinine after starting angiotensin-converting enzyme inhibitor-based therapy and effects of its continuation on major clinical outcomes in Type 2 diabetes mellitus: The ADVANCE Trial. *Hypertension, 73*(1), 84–91.

Pannu, H., Kim, D. H., Seaman, C. R., Van Ginhoven, G., Shete, S., & Milewicz, D. M. (2005). Lack of an association between the angiotensin-converting enzyme insertion/deletion polymorphism and intracranial aneurysms in a Caucasian population in the United States. *Journal of Neurosurgery, 103*(1), 92–96.

Peck, G., Smeeth, L., Whittaker, J., Casas, J. P., Hingorani, A., & Sharma, P. (2008). The genetics of primary haemorrhagic stroke, subarachnoid haemorrhage and ruptured intracranial aneurysms in adults. *PLoS ONE, 3*(11), e3691.

Peña-Silva, R. A., & Heistad, D. D. (2015). Stages in discovery: ACE2 and stroke. *Hypertension, 66*(1), 15.

Pera, J., Slowik, A., Dziedzic, T., Wloch, D., & Szczudlik, A. (2006). ACE I/D polymorphism in different etiologies of ischemic stroke. *Acta Neurologica Scandinavica, 114*(5), 320–322.

Peterson, M. C. (2005). Circulating transforming growth factor ß-1: A partial molecular explanation for associations between hypertension, diabetes, obesity, smoking and human disease involving fibrosis. *Medical Science Monitor, 11*(7), RA229–RA232.

Peterson, J. R., Burmeister, M. A., Tian, X., Zhou, Y., Guruju, M. R., Stupinski, J. A., ... Davisson, R. L. (2009). Genetic silencing of Nox2 and Nox4 reveals differential roles of these NADPH oxidase homologues in the vasopressor and dipsogenic effects of brain angiotensin II. *Hypertension, 54*(5), 1106–1114.

Prabhakar, P., De, T., Nagaraja, D., & Christopher, R. (2014). Angiotensin-converting enzyme gene insertion/deletion polymorphism and small vessel cerebral stroke in Indian population. *International Journal of Vascular Medicine*, 1–4.

Ruilope, L. M., Redón, J., & Schmieder, R. (2007). Cardiovascular risk reduction by reversing endothelial dysfunction: ARBs, ACE inhibitors, or both? Expectations from the ONTARGET Trial Programme. *Vascular Health and Risk Management, 3*(1), 1.

Saavedra, J. M. (2005). Brain angiotensin II: New developments, unanswered questions and therapeutic opportunities. *Cellular and Molecular Neurobiology, 25*(3–4), 485–512.

Sacco, R. L., Kasner, S. E., Broderick, J. P., Caplan, L. R., Connors, J., Culebras, A., … Higashida, R. T. (2013). An updated definition of stroke for the 21st century: A statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke, 44*(7), 2064–2089.

Saito, Y., & Berk, B. C. (2001). Transactivation: A novel signaling pathway from angiotensin II to tyrosine kinase receptors. *Journal of Molecular and Cellular Cardiology, 33*(1), 3–7.

Santos, R. A., de Silva, A. C. S., Maric, C., Silva, D. M., Machado, R. P., de Buhr, I., … Bader, M. (2003). Angiotensin-(1–7) is an endogenous ligand for the G protein-coupled receptor Mas. *Proceedings of the National Academy of Sciences USA, 100*(14), 8258–8263.

Sayed-Tabatabaei, F., Oostra, B., Isaacs, A., Van Duijn, C., & Witteman, J. (2006). ACE polymorphisms. *Circulation Research, 98*(9), 1123–1133.

Schrader, J., Lüders, S., Kulschewski, A., Hammersen, F., Plate, K., Berger, J. r., … Group, M. S. (2005). Morbidity and mortality after stroke, eprosartan compared with nitrendipine for secondary prevention: Principal results of a prospective randomized controlled study (MOSES). *Stroke, 36*(6), 1218–1224.

Sharma, N. M., & Patel, K. P. (2017). Post-translational regulation of neuronal nitric oxide synthase: Implications for sympathoexcitatory states. *Expert opinion on therapeutic targets, 21*(1), 11–22.

Sica, D. A. (2010). The evolution of renin-angiotensin blockade: Angiotensin-converting enzyme inhibitors as the starting point. *Current Hypertension Reports, 12*(2), 67–73.

Sica, D. A. (2016). *A Review of antihypertensive drugs and choosing the right antihypertensive for recurrent stroke prevention hypertension and stroke* (pp. 245–257). New York: Springer.

Slowik, A., Borratynska, A., Pera, J., Betlej, M., Dziedzic, T., Krzyszkowski, T., … Szczudlik, A. (2004). II genotype of the angiotensin-converting enzyme gene increases the risk for subarachnoid hemorrhage from ruptured aneurysm. *Stroke, 35*(7), 1594–1597.

Smeda, J. S., VanVliet, B. N., & King, S. R. (1999). Stroke-prone spontaneously hypertensive rats lose their ability to auto-regulate cerebral blood flow prior to stroke. *Journal of Hypertension, 17*(12), 1697–1705.

Sriramula, S., Cardinale, J. P., Lazartigues, E., & Francis, J. (2011). ACE2 overexpression in the paraventricular nucleus attenuates angiotensin II-induced hypertension. *Cardiovascular Research, 92*(3), 401–408.

Sriramula, S., Xia, H., Xu, P., & Lazartigues, E. (2015). Brain-targeted ACE2 overexpression attenuates neurogenic hypertension by inhibiting COX mediated inflammation. *Hypertension, 65*(3), 577.

Staalsø, J. M., Nielsen, M., Edsen, T., Koefoed, P., Springborg, J. B., Moltke, F. B., … Olsen, N. V. (2011). Common variants of the ACE gene and aneurysmal subarachnoid hemorrhage in a Danish population: A case-control study. *Journal of Neurosurgical Anesthesiology, 23*(4), 304–309.

Sun, Y., Liu, Y., Watts, L. T., Sun, Q., Zhong, Z., Yang, G.-Y., & Bian, L. (2014). Correction: Genetic Associations of Angiotensin-Converting Enzyme with Primary Intracerebral Hemorrhage: A Meta-analysis. *PloS one, 9*(1).

Taddei, S., & Bortolotto, L. (2016). Unraveling the pivotal role of bradykinin in ACE inhibitor activity. *American Journal of Cardiovascular Drugs, 16*(5), 309–321.

Tascilar, N., Dursun, A., Ankarali, H., Mungan, G., Ekem, S., & Baris, S. (2009). Angiotensin-converting enzyme insertion/deletion polymorphism has no effect on the risk of atherosclerotic stroke or hypertension. *Journal of the Neurological Sciences, 285*(1–2), 137–141.

ten Dijke, P., & Hill, C. S. (2004). New insights into TGF-β–Smad signalling. *Trends in Biochemical Sciences, 29*(5), 265–273.

Tsuda, K. (2012). Renin-angiotensin system and sympathetic neurotransmitter release in the central nervous system of hypertension. *International journal of hypertension, 2012*.

Tuncer, N., Tuglular, S., Kılıç, G., Sazcı, A., Us, Ö., & Kara, İ. (2006). Evaluation of the angiotensin-converting enzyme insertion/deletion polymorphism and the risk of ischaemic stroke. *Journal of Clinical Neuroscience, 13*(2), 224–227.

Villard, E., & Soubrier, F. (1996). Molecular biology and genetics of the angiotensin-I-converting enzyme: Potential implications in cardiovascular diseases. *Cardiovascular Research, 32*(6), 999–1007.

Villard, E., Tiret, L., Visvikis, S., Rakotovao, R., Cambien, F., & Soubrier, F. (1996). Identification of new polymorphisms of the angiotensin I-converting enzyme (ACE) gene, and study of their relationship to plasma ACE levels by two-QTL segregation-linkage analysis. *American Journal of Human Genetics, 58*(6), 1268.

Wang, X., & Abdel-Rahman, A. A. (2004). An association between ethanol-evoked enhancement of c-jun gene expression in the nucleus tractus solitarius and the attenuation of baroreflexes. *Alcoholism: Clinical and Experimental Research, 28*(8), 1264–1272.

Wei, L. K., Au, A., Menon, S., Griffiths, L. R., Kooi, C. W., Irene, L., … Hassan, M. R. A. (2017). Polymorphisms of MTHFR, eNOS, ACE, AGT, ApoE, PON1, PDE4D, and ischemic stroke: Meta-analysis. *Journal of Stroke and Cerebrovascular Diseases, 26*(11), 2482–2493.

Weigert, C., Brodbeck, K., Klopfer, K., Häring, H., & Schleicher, E. (2002). Angiotensin II induces human TGF-β1 promoter activation: Similarity to hyperglycaemia. *Diabetologia, 45*(6), 890–898.

Weir, M. R., & Dzau, V. J. (1999). The renin-angiotensin-aldosterone system: A specific target for hypertension management. *American Journal of Hypertension, 12*(S9), 205S–213S.

Wu, W.-H., Hu, C.-P., Chen, X.-P., Zhang, W.-F., Li, X.-W., Xiong, X.-M., et al. (2011). MicroRNA-130a mediates proliferation of vascular smooth muscle cells in hypertension. *American Journal of Hypertension, 24*(10), 1087–1093.

Yang, L.-x., Liu, G., Zhu, G.-f., Liu, H., Guo, R.-w., Qi, F., & Zou, J.-h. (2014). MicroRNA-155 inhibits angiotensin II-induced vascular smooth muscle cell proliferation. *Journal of the Renin-Angiotensin-Aldosterone System, 15*(2), 109-116.

Yang, Y., Ago, T., Zhai, P., Abdellatif, M., & Sadoshima, J. (2011). Thioredoxin 1 negatively regulates angiotensin II–induced cardiac hypertrophy through upregulation of miR-98/let-7. *Circulation Research, 108*(3), 305–313.

Yang, X., Long, L., Southwood, M., Rudarakanchana, N., Upton, P. D., Jeffery, T. K., … Morrell, N. W. (2005). Dysfunctional Smad signaling contributes to abnormal smooth muscle cell proliferation in familial pulmonary arterial hypertension. *Circulation Research, 96*(10), 1053–1063.

Yang, Y., Zhou, Y., Cao, Z., Tong, X. Z., Xie, H. Q., Luo, T., … Wang, H. Q. (2016). miR-155 functions downstream of angiotensin II receptor subtype 1 and calcineurin to regulate cardiac hypertrophy. *Experimental and Therapeutic Medicine, 12*(3), 1556–1562.

Yazawa, H., Miyachi, M., Furukawa, M., Takahashi, K., Takatsu, M., Tsuboi, K., … Kato, Y. (2011). Angiotensin-converting enzyme inhibition promotes coronary angiogenesis in the failing heart of Dahl salt-sensitive hypertensive rats. *Journal of Cardiac Failure, 17*(12), 1041–1050.

Yin, J.-X., Yang, R.-F., Li, S., Renshaw, A. O., Li, Y.-L., Schultz, H. D., et al. (2010). Mitochondria-produced superoxide mediates angiotensin II-induced inhibition of neuronal potassium current. *American Journal of Physiology-Cell Physiology, 298*(4), C857–C865.

Yusuf, S., Sleight, P., Pogue, J. F., Bosch, J., Davies, R., & Dagenais, G. (2000). Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *The New England Journal of Medicine, 342*(3), 145–153.

Zhang, Y., Huang, X.-R., Wei, L.-H., Chung, A. C., Yu, C.-M., & Lan, H.-Y. (2014). miR-29b as a therapeutic agent for angiotensin II-induced cardiac fibrosis by targeting TGF-β/Smad3 signaling. *Molecular Therapy, 22*(5), 974–985.

Zhang, Z., Xu, G., Liu, D., Fan, X., Zhu, W., & Liu, X. (2012). Angiotensin-converting enzyme insertion/deletion polymorphism contributes to ischemic stroke risk: A meta-analysis of 50 case-control studies. *PLoS ONE, 7*(10), e46495.

Zhao, J., Qin, X., Li, S., & Zeng, Z. (2014). Association between the ACE I/D polymorphism and risk of ischemic stroke: An updated meta-analysis of 47,026 subjects from 105 case–control studies. *Journal of the Neurological Sciences, 345*(1–2), 37–47.

Zhao, Y., Wu, J., Zhang, M., Zhou, M., Xu, F., Zhu, X. ,… Yun, S. (2017). Angiotensin II induces calcium/calcineurin signaling and podocyte injury by downregulating microRNA-30 family members. *Journal of Molecular Medicine, 95*(8), 887–898.

Zheng, L., Xu, C.-C., Chen, W.-D., Shen, W.-L., Ruan, C.-C., Zhu, L.-M., … Gao, P.-J. (2010). MicroRNA-155 regulates angiotensin II type 1 receptor expression and phenotypic differentiation in vascular adventitial fibroblasts. *Biochemical and Biophysical Research Communications, 400*(4), 483–488.

Zhu, N., Zhang, D., Chen, S., Liu, X., Lin, L., Huang, X., … Yuan, W. (2011). Endothelial enriched microRNAs regulate angiotensin II-induced endothelial inflammation and migration. *Atherosclerosis, 215*(2), 286–293.

Zimmerman, M. C., Lazartigues, E., Lang, J. A., Sinnayah, P., Ahmad, I. M., Spitz, D. R., et al. (2002). Superoxide mediates the actions of angiotensin II in the central nervous system. *Circulation Research, 91*(11), 1038–1045.

Zimmerman, M. C., Lazartigues, E., Sharma, R. V., & Davisson, R. L. (2004). Hypertension caused by angiotensin II infusion involves increased superoxide production in the central nervous system. *Circulation Research, 95*(2), 210–216.