

Review

Two Opposing Functions of Angiotensin-Converting Enzyme (ACE) That Links Hypertension, Dementia, and Aging

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Abstract

A recent report from the American Heart Association in 2018 shows that over 103 million American adults have hypertension. The angiotensin-converting enzyme (ACE) (EC 3.4.15.1) is a dipeptidyl carboxylase that, when inhibited, can reduce blood pressure through the renin-angiotensin system. ACE inhibitors are used as a first-line medication to be prescribed to treat hypertension, chronic kidney disease, heart failure among others. It has been suggested that ACE inhibitors can reduce the symptoms in mouse models. Despite the benefits of ACE inhibitors, previous studies also have suggested that alterations in the ACE gene are risk factors for Alzheimer's disease (AD) and other neurological diseases. In mice, overexpression of ACE in the brain reduces symptoms of the AD-model systems. Thus, we find opposing effects of ACE on health. To clarify the effects, we dissect the functions of ACE as follows: (1) angiotensin-converting enzyme that hydrolyzes angiotensin I to make angiotensin II in the renin-angiotensin system; (2) amyloid-degrading enzyme that can hydrolyze beta-amyloid and reduce amyloid toxicity. The efficacy of the ACE inhibitors is well established in humans, while the knowledge specific to AD remains to be open for further research. We provide an overview of ACE and inhibitors that link a wide variety of age-related comorbidities from hypertension to Alzheimer's disease to aging. ACE also serves as an example of the middle-life crisis theory that assumes deleterious events during the midlife, leading to age-related later events.

1. Introduction

The human angiotensin-converting enzyme (ACE) (EC 3.4.15.1) plays a major role in the angiotensin-renin system that regulates blood pressure and salt balance. ACE was first reported as a hypertensin-converting enzyme [1]. In 1958, Braun-Menendez and Page suggested a revision of nomenclature from hypertensin to angiotensin [2]. ACE inhibitors has been initially reported as a medication to treat hypertension [3,4]. The history of angiotensin and ACE have been described elsewhere [5]. The ACE gene encodes a protein with 732 amino-acid residues and a molecular weight of 80,073 [6]. Clinically, it is an important target for the treatment of hypertension, Current first-line medications for hypertension include angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, and calcium channel blockers [7].

Primary hypertension, or essential hypertension, is the condition of having high blood pressure. Although no clear cause for primary hypertension is known, a combination of genetics, poor diet, and lack of exercise is thought to play a role. In contrast, secondary hypertension is high blood pressure caused by another medical condition. diabetes, Cushing's syndrome, pheochromocytoma, hyperparathyroidism, hypokalemia, or primary hyperaldosteronism are several examples of conditions that may cause secondary hypertension [8]. Secondary hypertension can be diagnosed following a series of screening and lab tests to identify underlying factors and impacted organs [9].

Our recent studies suggested that the ACE gene is associated with a broad range of neurological diseases, including AD, Parkinson's disease, Amyotrophic lateral sclerosis, Multiple sclerosis, Parkinson's disease, and Schizophrenia [10,11], which is consistent with the findings from other

groups [12,13]. ACE inhibitors are well-established medications for hypertension, which is also a major risk of cognitive impairment and dementia [14] and of death by COVID-19 [15]. Here we overview the underlying mechanisms of ACE relevant to AD and age-related comorbidities. We hope to provide the links between ACE and hypertension, AD, neurological diseases and aging.

2. Mechanism of ACE

ACE has a dipeptidyl carboxypeptidase activity that can hydrolyze and cleave the c-terminal dipeptide of angiotensin I (10 amino-acid residues) to make angiotensin II (8 amino-acid residues). ACE has another activity as an amyloid-degrading enzyme (ADE) that can hydrolyze beta-amyloid (Discussed in Section of 3.2 below). The N and C domains of ACE are active sites, which possess a zinc ion-binding site. Previous studies have shown that inhibition of the C domain led to control of blood pressure, while inhibition of the N domain led to little or no impact [16,17]. By binding to the C domain of ACE, the conversion of angiotensin I to angiotensin II is prevented, leading to disruption of the renin-angiotensin-aldosterone system (RAAS). Angiotensin II acts as a vasoconstrictor by stimulating Gq proteins on the vascular smooth muscle, activating an IP3-dependent pathway that increases intracellular calcium levels and causes constriction.

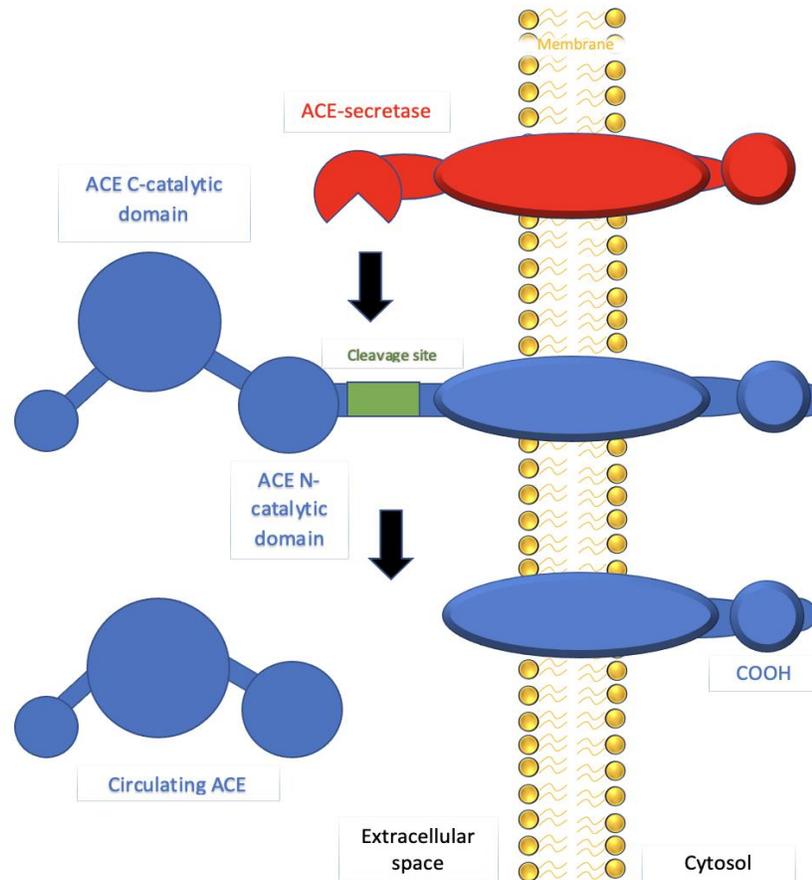


Figure 1: A Diagram of the two major domains of ACE, in addition to the process in which circulating ACE is released.

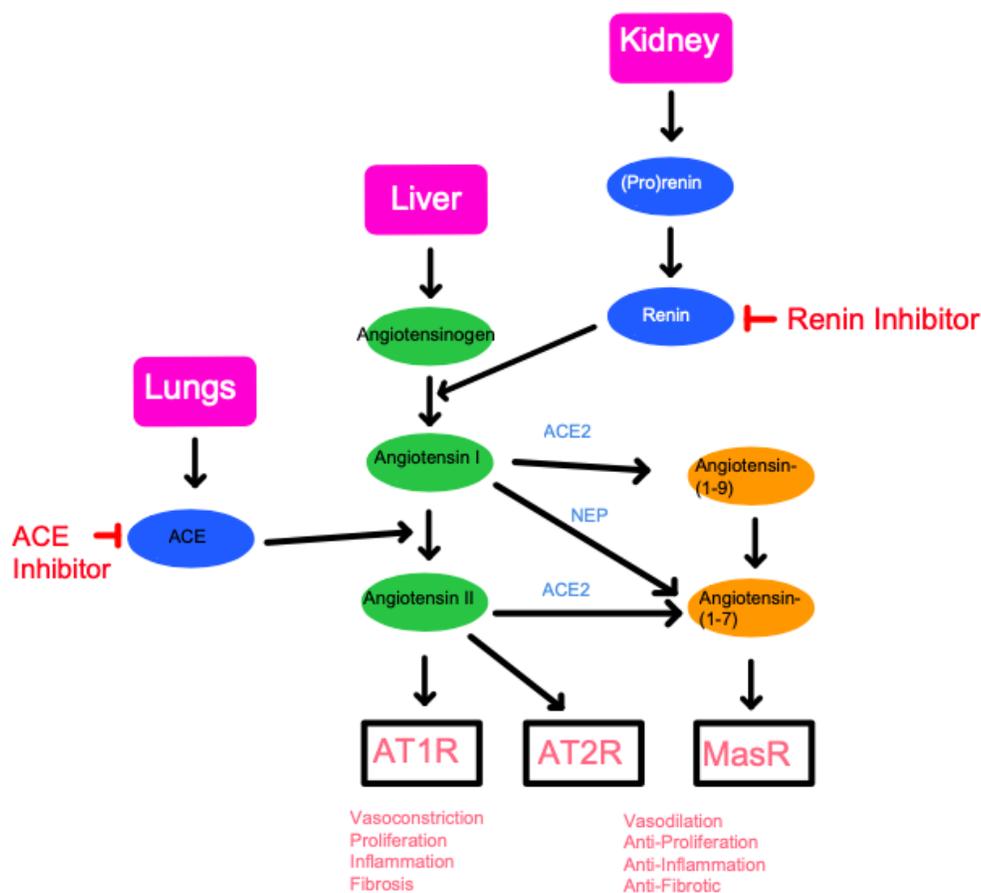


Figure 2: A schematic diagram of the RAS pathway and the points in which inhibition may occur. A summary of the final physiological effects followed by binding of each target is listed at the bottom of the diagram.

ACE hydrolyzes angiotensin I to make angiotensin II. Angiotensin II is a vasoconstrictor, which has two major receptors it can interact with to produce homeostatic actions. Angiotensin II Type-1 receptor (AGT1R) has well-documented functions in vasoconstriction, cellular proliferation, inflammation, and fibrosis. Due to its significant role in increasing blood pressure, AGT1R is a major target for anti-hypertensive drugs, specifically ARBs. Conversely, Angiotensin II Type-2

receptor (AGT2R) does not have as clearly defined of a role as AGT1R and is an ongoing subject of research [18]. Past studies have suggested that AGT2R primarily functions as an antagonist for AGT1R, inducing contradicting effects such as vasodilation and inhibition of cell proliferation, inflammation, and fibrosis. In addition, studies have shown that the Mas receptor, which responds to Angiotensin (1-7), induces similar effects to AGT2R. Due to this observed function of regulating the proinflammatory effects of Angiotensin II, studies have tested and demonstrated the impact of the receptor Mas axis on macrophage function and inflammation diseases [19]. Thus, a defect in the Mas receptors, or a deficiency in ACE2, has been shown to cause an increase in inflammatory responses within the CNS and the vascular systems.

3. ACE as a gene that links hypertension, Alzheimer's disease (AD) and aging

3.1. ACE as a link to hypertension

Hypertension develops over time. Despite varying definitions, a threshold of early-onset hypertension is at the age of fewer than 55 years old [20] when recommending first-line medications, such as ACE inhibitors [21]. ACE converts angiotensin I to angiotensin II, latter of which has an effect on vasoconstriction and increases blood pressure. Thus, ACE inhibitors can reduce angiotensin II, a vasoconstrictor, to the physiological effect of vasodilation and a subsequent decrease in blood pressure (i.e., vaso-protection against hypertension). ACE inhibitors may also downregulate sympathetic activity, leading to less cardiovascular burden. Other cardiovascular effects of ACE inhibitors include the promoted renal excretion of sodium and water, leading to a further decrease in blood volume. ACE inhibitors and angiotensin II

receptor blockers (ARBs) are also known to reduce the risk of hospitalization for heart failure in ethnics dependent manner [22]. Thus, ACE inhibitors and ARBs are first-line medications for treating hypertension, chronic kidney disease and heart failure.

ACE has been a point of interest with previous studies have shown that hypertension is a strong independent risk factor for the development of cognitive impairment and dementia [14].

Abnormalities such as chronically elevated blood pressure or a series of mini-strokes have been associated with impaired cognitive function and the onset of various forms of dementia, including AD. A wide variety of cardiovascular diseases are also sensitive to hypertension [23,24].

3.1. ACE that link to Alzheimer's disease (AD) and diverse neurological diseases

In humans, ACE polymorphisms are associated with AD. Two groups conducted population studies that suggested an association with late-onset AD (LOAD) by investigating an insertion/deletion (I/D) polymorphism of the ACE gene [25,26]. However, more than 70 case-control studies and family-based studies have investigated the genetic association between ACE and AD, mixed with positive and negative results, according to the AlzGene database (Accessed Oct 1, 2021) [27]. A series of meta-analysis studies further confirmed the significance of the genetic association between ACE and AD [28-32]. More details of polymorphisms are discussed elsewhere [33].

Importantly, the ACE gene is associated with a broad range of neurological diseases, including AD, Amyotrophic lateral sclerosis (ALS), Multiple sclerosis (MS), Parkinson's disease (PD), and Schizophrenia [10-13]. AD and the other neurological diseases were seen to have a strong association with ACE, TNF, and MTHFR [10]. The studies have significant clinical implications that patients with a risk factor gene of AD may show diverse neurological symptoms such as ALS, MS, PD and Schizophrenia. Thus, patients with AD may show diverse symptoms in addition to those directly relevant to AD.

The foundation for the link between AD and age-related comorbidities is not known. However, hypertension and strokes are independent risk factors of cognitive impairment and dementia [34,35]. The onset of cognitive impairment is common after long-term hypertension and stroke [35]. Chronic inflammation is commonly seen in patients with comorbidities including hypertension and diabetes prior to the development of AD [36]. Chronic inflammation in the brain may be an intermediary component in the progression of AD and becomes more common with the aging process. The understanding of age-related comorbidities should open a new avenue for research to understand the mechanisms that link a wide variety of pathophysiology in aging.

3.2. Two opposing health effects of ACE on Alzheimer's disease (AD)

As discussed above, ACE inhibitors as treatment options for hypertension and other health conditions, while alterations of the ACE gene are associated with AD. Why do the seemingly opposing health effects of ACE occur?

We dissect the effects into a few functions:

(1) ACE as an angiotensin-converting enzyme that hydrolyzes angiotensin I to make angiotensin II in the renin-angiotensin system. ACE is a dipeptidyl carboxylase (EC 3.4.15.1) that hydrolyzes two c-terminal amino-acid residues. As an angiotensin-converting enzyme, ACE cleaves two amino acids from angiotensin I to make angiotensin II. ACE inhibitors will reduce the production of angiotensin II, leading to vasodilation and reduced blood pressure. In this case, inhibiting the activities as an angiotensin-converting enzyme would relieve hypertension and hypertension sensitive health conditions, including heart failure, diabetes mellitus, or chronic kidney disease [37]. In mice, it also reduces AD symptoms in the mouse AD model [38]. Thus, ACE inhibitors are beneficial to health.

(2) ACE as an amyloid-degrading enzyme (ADE) that can hydrolyze beta-amyloid and reduce amyloid toxicity. ADE represents a group of broadly defined enzymes, currently, including 14 enzymes: ACE, Acyl peptide hydrolase, Aminopeptidase A, Cathepsin B, Endothelin-converting enzyme, Glutamate carboxypeptidase II, Insulin-degrading enzyme, MBP, MMP-2, MMP-9, NEP2, Neprilysin, Plasmin, and PreP [39,40]. ACE has an activity of beta-amyloid amyloid-degrading enzymes (ADEs) that can hydrolyze and convert A β 1-42 to A β 1-40 in homogenates of the mouse Tg2576 AD model and human AD autopsy [41] which is consistent with its dipeptidyl carboxypeptidase activity that cleaves the c-terminal two amino-acid residues. ACE can also cleave A β 1-40 into two smaller peptides (A β 1-7 and A β 8-40) [42-44]. In mice, inhibitions of ACE can worsen the accumulation of A β 1-42 in the mouse model [41]. Consistently,

overexpression of ACE in the brain resident microglia, peripheral myelomonocytes and macrophages can alleviate the symptoms of the double-transgenic APPSWE/PS1 Δ E9 (AD+) mice [45,46]. The studies have been performed in the AD model systems in mice and, thus, the ADE activity may be important when accumulation of beta-amyloid causes pathologic problems. The efficacy of the ADE activity remains to be investigated in humans.

ACE is also known to have broad specificity to substrates, including enkephalins, C-terminal extended proenkephalins, luteinizing hormone-releasing hormone, substance P and a protected chemotactic tripeptide [47], cholecystokinin-8, gastrin analogues [48] and kinins [49]. However, it is not clear how the ACE substrates are relevant to AD and thus we do not discuss them further.

3.3 ACE as a link to aging (life extension- model systems)

To elucidate any mechanisms in which existing drugs may potentially increase lifespan, previous studies have been conducted on model species with ACE inhibitors and homologs of ACE. In the nematode, *Caenorhabditis elegans*, the *acn-1* gene, a homolog of nematode ACE, was used to explore the relation between the use of ACE inhibitors and longevity [50]. The application of the ACE inhibitor, Captopril, leads to a reduction of *acn-1* activity, resulting in lifespan extension, increased stress resistance and in a delay in age-related degenerative changes (i.e., reduction in pharyngeal pumping). Further analysis indicated that the lifespan effects of Captopril are additive to other known life-extending interventions (and genes), including the insulin/IGF-1 pathway (*age-1* and *daf-2*), caloric restriction (*eat-2*), a nicotinamide adenine dinucleotide

(NAD) dependent deacetylase (sir-2.1), heat shock (hsf-1) and mitochondria insufficiency (isp-1).

In the fruit fly, *Drosophila melanogaster*, another ACE inhibitor, Lisinopril, was to study the impacts of Ance, an ortholog of ACE, in the three genotypes from the reference panel lines [51]. Mean lifespan was increased following the application of Lisinopril in a genotype-specific manner with the degree of change to lifespan, age-specific speed, endurance, and strength depending on the genotype. Among the three genotypes studied, the ones that had an improvement of physical performance while on Lisinopril had a reduction in the age-related aggregation of protein in skeletal muscle, suggesting a role of stress resistance in lifespan extension. The results showed a significant involvement of skeletal muscle Ance in the lifespan of *Drosophila* species and that there is genetic variation in the phenotypic responses to ACE inhibitors.

Mouse models have also been of interest in the study of the ACE inhibitor mechanism and lifespan longevity. A study that uses the combined application of statin, simvastatin, and ACE inhibitor, Ramipril, results in an increased mean lifespan for a group of isocalorically fed mice subjects [52]. Another study using the mouse model was able to show how ACE inhibitors can rescue neuronal loss in the knock-in mice with the ACE1 variant, R1279Q [53]. Mice with ACE R1279Q experienced greater hippocampal neurodegeneration with aging, which was completely reversed by ACE inhibitors and AT1R blockers that can penetrate the brain to inhibit ACE1 and AT1R, respectively. Their results indicated that ACE1/angII signaling caused aging dependent, A β -accelerated selective hippocampal neuron vulnerability and female susceptibility.

3.3 ACE as a link to stress resistance and the middle-life crisis theory on aging

ACE inhibitors and mutations are associated with lifespan extension and stress resistance (discussed above). Increased resistance to multiple forms of stresses, or multiplex stress resistance, has been shown as a component of life extension in the model systems including yeasts, nematodes, fruit flies and mice [54-61]. ACE as an angiotensin-converting enzyme is used as a medication target to control hypertension and complications that may be triggered by hypertension. In contrast, ACE as an amyloid-degrading enzyme is to control more advanced phase, accumulation of beta-amyloid. The different activities of ACE support the notion of aging stages from transition state to more advanced pathological state [62-64]. Furthermore, those are consistent with the previous study that indicates the underlying mechanisms of the human Alzheimer's disease (AD) genes, including lipid metabolism, as well as in pathway-related amyloids and associated with neural and immune systems [10]. We view age-related comorbidities occurs during the middle of lifespan, where the onset of hypertension and associated health conditions occurs. At this stage, the function of ACE as an angiotensin-converting enzyme is more important to the health condition, while the function as an amyloid-degrading enzyme is more important when an abnormal accumulation of beta-amyloid starts. ACE provides an example for the middle-life crisis theory on aging describes middle life events which cause aging and age-related diseases in late life, which explain the transition to aging from normal to more advanced age-related changes [63,64].

4. Conclusions and Perspective

Hypertension is major comorbidity that develops over time. First-line medications include ACE inhibitors that have been well established in medicine. In contrast, growing evidence from genetic studies suggests that alterations in the ACE gene are risk factors of Alzheimer's disease (AD) and other neurological diseases. This seemingly controversial finding has been an intriguing topic but has never been discussed and clarified. To this end, we have dissected the functions of ACE and explained this seemingly controversial finding. ACE inhibitors are beneficial to reduce hypertension and associated health conditions. Later in life, ACE function as an amyloid-degrading enzyme starts to play a role in fighting against AD. This later-life ACE function remains to be explored in humans as a promising medication for AD and other related health conditions. The current understanding of hypertension medication is that hypertension should be treated to prevent vascular, stroke and mixed dementia [65], while the treatment for AD specific symptoms requires considerations. Although it can be argued that ACE inhibitors may reduce the amyloid-degrading activity of ACE, it has been argued that ACE inhibitors could inactivate abnormal ACE mutant enzymes [53], which has been shown to reduce the symptoms of the AD mouse model [38]. Importantly, inhibition of ACE confers life extension in the model systems, including the nematode, the fruit fly and the mouse, suggesting potential health benefits during lifespans (Discussed in Section 3.3). We reason that ACE inhibitors are beneficial until when the accumulation of amyloids causes health problems. The area of ACE inhibitors and ACE receptor inhibitors are a promising field to further explore. Taken together, the current status of understanding ACE in medications still has open questions specific to hypertension, other age-related comorbidities, and types of dementia.

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