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The Implications of Angiotensin-Converting Enzymes and Their Modulators in Neurodegenerative Disorders: Current and Future Perspectives

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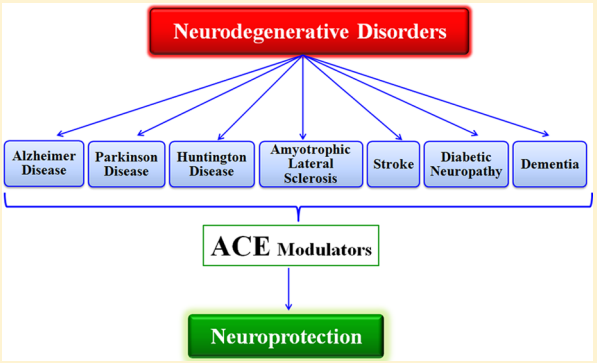
ABSTRACT: Angiotensin converting enzyme (ACE) is a dipeptidyl peptidase transmembrane bound enzyme. Generally, ACE inhibitors are used for the cardiovascular disorders. ACE inhibitors are primary agents for the management of hypertension, so these cannot be avoided for further use. The present Review focuses on the implications of angiotensin converting enzyme inhibitors in neurodegenerative disorders such as dementia, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, stroke, and diabetic neuropathy. ACE inhibitors such as ramipril, captopril, perindopril, quinapril, lisinopril, enalapril, and trandolapril have been documented to ameliorate the above neurodegenerative disorders. Neurodegeneration occurs not only by angiotensin II, but also by other endogenous factors, such as the formation of free radicals, amyloid beta, immune reactions, and activation of calcium dependent enzymes. ACE inhibitors interact with the above cellular mechanisms. Thus, these may act as a promising factor for future medicine for neurological disorders beyond the cardiovascular actions. Central acting ACE inhibitors can be useful in the future for the management of neuropathic pain due to following actions: (i) ACE-2 converts angiotensinogen to angiotensin$_{(1-7)}$ (hepatapeptide) which produces neuroprotective action; (ii) ACE inhibitors downregulate kinin B_1 receptors in the peripheral nervous system which is responsible for neuropathic pain. However, more extensive research is required in the field of neuropathic pain for the utilization of ACE inhibitors in human.



KEYWORDS: *Angiotensin converting enzyme, Alzheimer's disease, hypertension, neurodegeneration, neuropathic pain, ramipril*

Angiotensin converting enzyme (ACE, EC 3.4.15.1) is a dipeptidyl peptidase transmembrane bound enzyme. It is also known as dipeptidyl hydrolase, dipeptidylcarboxypeptidase I, peptides P, kininase II, angiotensin-I converting enzyme, and peptidyldipeptidase.[1,2] ACE has two different isoforms, that is, somatic ACE, and testicular/germinal ACE. The somatic ACE is a large protein, that is, 150−180 kDa. It bears two identical catalytic domains and a cytoplasmic tail. It is found in various epithelial and neural cells. The germinal ACE is a small protein as compared to somatic ACE, that is, 100−110 kDa. It has a single catalytic domain corresponding to the COOH-terminal domain of somatic ACE. It is found in developing spermatids and mature sperm cells only.[3,4] In addition, soluble ACE has also been identified in many biological fluids. It is formed by the proteolytic cleavage of plasma membrane bound ACE at the COOH terminal domain.[5,6] ACE is distributed throughout the body tissues, for example, epithelial cells, smooth muscle cells, monocytes, T-lymphocytes, adipocytes, kidney, heart, testis, brain, nerve, and various biological fluids, that is, broncho-alveolar, cerebrospinal fluid (CSF), plasma, urine, and serum.[6−8] ACE is abundantly expressed in dendrite cells.[9] ACE expressed by the brain tissue contributes to the local renin-angiotensin-aldosterone system (RAAS) which converts amyloid beta 42 (Aβ42, that aggregates into plaques) to amyloid beta 40 (Aβ40, that is thought to be less toxic).[7] Even other cells also express ACE, that is, hypothalamic paraventricular nucleus,[10] nigros-triatal dopamine neurons,[11] retinal neurons, Muller glial cells,[12] and central neurons.[13]

The structure of ACE has N (amino terminal) and C (carboxy terminal) domains. The N domain has a major role in the local RAAS in the brain. It is a family of M_2 metallopeptidase (also known as metalloprotease, the metal ions are responsible for the catalytic action of this enzyme). Metallopeptidase has four main protease types with more than 50 families. Both the somatic ACE and germinal ACE consist of a 28-residue hydrophilic C-terminal cytoplasmic domain, a 22 residue hydrophobic transmembrane domain that anchors the protein in the membrane. The N-terminal ectodomain is heavily glycosylated with mannose, galactose, fructose, *N*-acetylneuraminic acid, and *N*-acetylglucosamine,[14] whereas the ectodomain of somatic ACE has two similar domains, that is, N domain and C domain.[15] Soluble ACE lacks the

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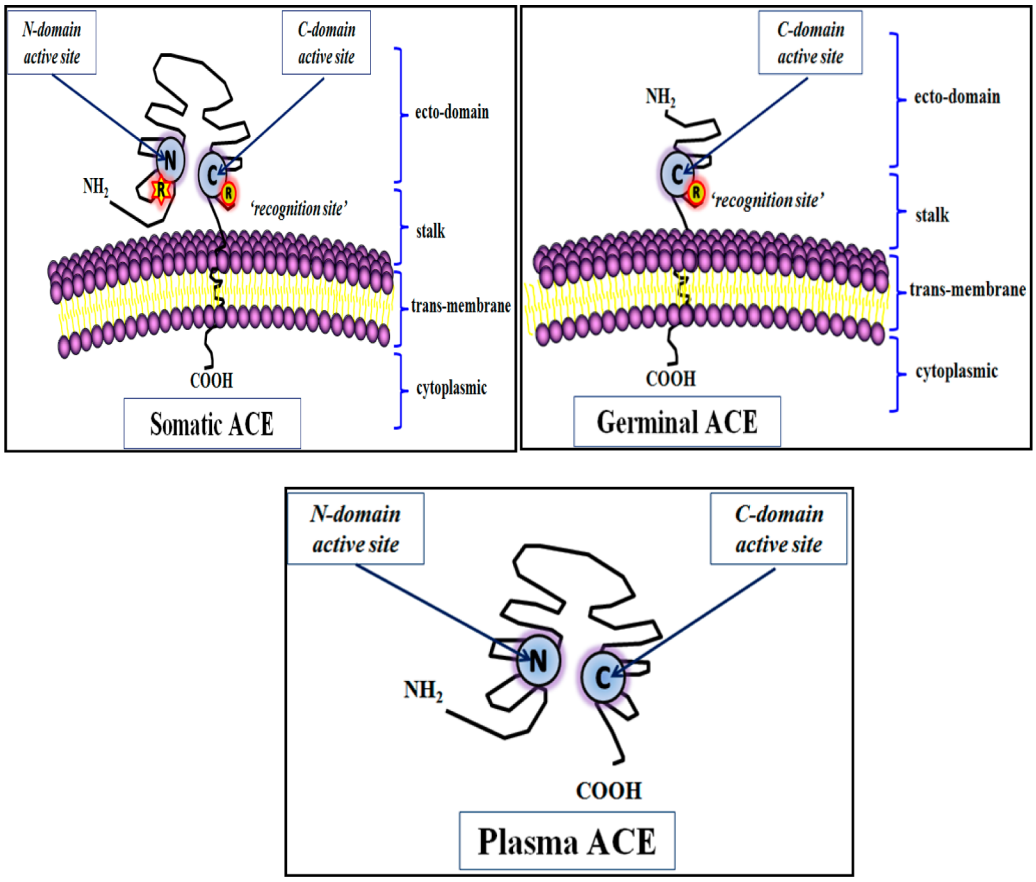

Figure 1. Structure of different ACE, that is, somatic, germinal (testis), and plasma (soluble) ACE. Somatic and germinal ACE have structural similarities and a major discrepancy is loss of the N-domain active site in germinal ACE, whereas soluble ACE has no recognition site for cell membrane binding property.

transmembrane portion and a cytosolic domain through the cleavage of the membrane bound residues.[16] The structure of the N-terminal domain of somatic ACE is still unknown, but the C-terminal domain is identical to that of germinal ACE. Both domains have different functions, but angiotensin I peptide (AT-I) conversion takes place within the C domain. The selective inhibition of C domain is enough to prevent vasoconstriction induced by the AT-I peptide[17] (see Figure 1).

1. PHYSIOLOGICAL ACTION OF ACE

In the RAAS pathway, ACE plays a role in the conversion of AT-I to AT-II peptides.[2,18] The AT-II peptide binds to angiotensin 1 receptor (AT_1R) and angiotensin 2 receptor (AT_2R). AT_1R is responsible for multiple physiological actions, that is, vasoconstriction, superoxide production, sympathetic activation, release of aldosterone, sodium water retention, and increase in cell growth functions. Whereas AT_2R produces vasodilation, decrease in cell growth, and apoptosis.[18] Moreover, ACE has also been known to degrade the vasoactive peptidelike bradykinin (in the lungs), that is a potent vasodilator.[19] ACE degrades bradykinin that mainly acts in the vascular tissue of respiratory system.[20] In addition to this, it also produces physiological effects via direct binding of bradykinin-2 receptor (BK_2R) and indirect activation of bradykinin-1 receptor (BK_1R) via des-Arg9-bradykinin intermediate metabolite.[21,22] These receptors are a family of seven transmembrane G-protein-coupled receptors (GPCRs) and also known as kinin 1 and kinin 2 receptors.[23] In addition, the activation of BK_1R is widely expressed in the vascular tissue as well as in the nerve endings that are responsible for vasodilation, inflammation, and pain signaling processes.[24] The BK_2R is expressed in coronary artery, adrenal medulla, hippocampal region of the brain, and ciliary muscles of the eye, and widely distributed in blood vessels in which activation provokes vasodilation.[25−28] It also causes contraction of nonvascular smooth muscles, that is, bronchus and gut;[29,30] natriuresis and neuronal excitation by the release of glutamate and accumulation of intracellular calcium in the brain astrocytes.

In pathological conditions, a rise in the level of bradykinin in the respiratory system causes acute respiratory distress syndrome (ARDS, a form of acute lung injury), dry cough, inflammation, and apoptosis via release of proinflammatory mediators such as cytokines (TNF-α and interferon-γ) and chemokines, that is, $CXCL_5$.[31−33] Bradykinin has pleiotropic actions, that is, decreased blood pressure, increased vascular permeability, and promotion of classical symptoms of inflammation such as vasodilation, hyperthermia, edema, and pain (warning signal). In addition, it has beneficial effects, that is, potent antithrombogenic, antiproliferative, and antifibrogenic effects.[34] Bradykinin is an endogenous nonapeptide that is catabolised by ACE. ACE inhibitors increase the level of bradykinin by the reduction of catabolic action of bradykinin(1−9) [$BK_{(1-9)}$]. $BK_{(1-9)}$ produces pain sensation by direct stimulation of nociceptors in the peripheral nervous system, but this action is of short duration and its half-life is short (15 s).[35] In addition, $BK_{(1-9)}$ is not only degraded by ACE, but also by other enzymatic pathways, that is,

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aminopeptidase P, carboxypeptidase, dipeptidyl peptidase IV, endothelin converting enzyme, neprilysin, propyl oligopeptidase, and neutral endopeptidase are also involved.[35,36] Furthermore, bradykinin has reported to produce pro- and antinociceptive actions in a dose dependent manner.[37] Bradykinin has also been documented to produce the antiapoptotic action via decreasing caspase-3 activation.[38,39] ACE plays role in lung injury by rising the level of AT-II peptide but not through bradykinin.[38]

AT-II peptide also causes nociceptive pain that is ameliorated by angiotensin$_{(1-7)}$ (AT_{1-7}) peptide via inhibition of Mas receptors associated protein-38 mitogen-activated protein kinase (p^{38} MAPK) phosphorylation in mice.[40] In contrast, AT-II peptide also exerts an antinociceptive action at variable time points, but generally it has high pain sensitivity, because, the pain attenuating action is in diurnal pattern (24 h light and dark cycles). This diurnal pattern of pain variation is identified due to the chronic activation of AT_2R.[41] At phasic pain (dark cycle), it exerts an antinociceptive effect. Though, in tonic pain (light cycle), it exerts weak circadian fluctuation of several pain responses in mice.[42] Furthermore, angiotensin III peptide (AT-III) as well as angiotensin IV peptide (AT-IV) are biologically active, that are formed from AT-II peptide via ACE activity. But the action of these has not been yet reported for cardiovascular, renal, and neuropathic pain.[43,44] Rises in the level of AT-II peptide and their receptors, that is, AT_1R and AT_2R, are responsible in the pathogenesis of neurodegenerative disorders in animals and in human.[45−47] AT-IV peptide is a metabolite of AT-II peptide that acts on specific AT_4R which is mainly responsible for improving cognitive dysfunction.[48] ACE inhibitors have potential antihypertensive and neuroprotective actions.[11,49] Recent reports suggested that ACE has cardioprotective and neuroprotective actions through the formation of $AT_{(1-7)}$ (heptapeptide of angiotensin) by angiotensin converting enzyme 2 (ACE 2). Whereas, angiotensin converting enzyme 1 (ACE 1) mediated $AT_{(1-9)}$ (nonapeptide of angiotensin) peptide causes the potential damage of different organ systems.[50−53] This hypothesis is reported in animal as well as in human studies.[11,52]

2. PATHOLOGICAL ACTION OF ACE

ACE plays a major role in various pathological conditions such as inflammation, Alzheimer's disease,[54] hypertension,[55] cardiac hypertrophy,[56] and ischemic heart disease.[57] The elevation of ACE is involved in sarcoidosis, leprosy, hyperthyroidism, liver cirrhosis, biliary cirrhosis, diabetes mellitus, multiple myeloma, amyloidosis, Gaucher disease, pneumoconiosis, histoplasmosis, and tuberculosis.[58−60] Whereas, low levels of ACE in serum are observed in renal disease, obstructive pulmonary disease, and hypothyroidism.[61,62] These changes in ACE level alter the pathological process via AT-II peptide. The abundant rise in the AT-II peptide leads to various cardiovascular disorders such as hypertension, congestive heart failure, arrhythmia, and endothelial dysfunction;[63−65] renovascular disorder, that is, diabetic renal failure, nephropathy;[66,67] neurological disorders, that is, stroke, multiple sclerosis, Alzheimer's disease, and neuropathy.[68−70]

Generally, ACE plays a role in the elevation of blood pressure. The essential role of ACE in the blood pressure homeostasis is supported by knockout mice.[71] Additionally, ACE 1 inactivates bradykinin, that is responsible for vasodilatory and cardioprotective properties by promoting the formation of nitric oxide by the endothelium.[72] ACE 1 knockout mice exhibited an approximate 35% reduction in blood pressure, resulting in hypotension and subsequent organ damage. Thus, despite the many factors, ACE 1 contributes to blood pressure in mammals by nitric oxide, endothelin and adrenergic stimulation. These redundant systems are not enough to overcome disruption of the RAAS.[73,74] It has also been noticed that AT-II peptide binds to AT_2R, resulting in many processes that counter balance the binding of AT-I peptide.

3. THE PHARMACOLOGY OF ACE INHIBITORS IN VARIOUS NEURODEGENERATIVE DISORDERS

ACE plays a critical role in the development of various disorders because it modulates the essential endopeptides (angiotensinogen, bradykinin, substance P, and β-amyloid) in the circulation as well as at tissue levels.[75−77] The structural and functional polymorphism of this ACE is responsible for conversion of the above endopeptides, which produces various neurological disorders such as dementia, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, stroke, and diabetic neuropathy.[75,78,79] This Review is focused on the role of ACE inhibitors in neurodegenerative disorders.

3.1. Dementia. Dementia is a neurodegenerative disorder and it is the common form of cognitive disorder.[80] The other forms of dementia are vascular dementia, frontotemporal dementia, Lewy body dementia, progressive supranuclear palsy, corticobasal degeneration, normal pressure hydrocephalus, and Creutzfeldt−Jakob disease.[81,82] The symptoms of dementia are depression, anxiety, agitation, motor imbalance, tremor, speech and language difficulty, trouble in eating and swallowing, delusions and hallucinations, memory distortions, and restlessness.[83] The major risk factors of dementia progression are hypertension, neuronal excitation, diabetes, stress, smoking, ischemia, normal-pressure hydrocephalus, subdural hematoma hypoxia, trauma, hypo- and hyperthyroidism, vitamin B_{12} deficiency, Lyme disease, and neurosyphillis infection.[84−86] At the cellular level, alterations of the balance of inhibitory and excitatory neurotransmitters in the brain, proapoptotic protein expression, ionic imbalance, free radical formation, and calcium dependent and independent activation of various cytosolic kinases, phosphatises, and phospholipases are responsible for the damage of neurons and neurodegenerative disorders such as dementia.[87] The central ACE activity in different brain parts is responsible for the development of cognitive disorders, that is, dementia.[88] The rise in ACE activity is observed in dementia patients.[89] Ramipril treatment produces an attenuating effect on chronic cerebral ischemia induced vascular dementia in rats via free radical scavenging action and protection of white matter lesions along with cerebrovascular insufficiency.[90] The centrally acting ACE inhibitors, that is, perindopril, ameliorate β-amyloid and chronic cerebral hypoperfusion induced vascular dementia associated cognitive impairment in rodents.[91,92] Administration of lisinopril has been documented to produce the amelioration of hypertension associated vascular dementia in rats.[93] In addition, the Systolic Hypertension in Europe (Syst-Eur) and Perindopril Protection Against Recurrent Stroke Study (PROGRESS) trials have documented that enalapril and perindopril, respectively, attenuated cognitive impairment and the risk of dementia.[94] Furthermore, the treatment with ACE inhibitors, that is, captopril and perindopril, ameliorates Alzheimer's type of dementia.[89]

3.2. Alzheimer's Disease. Alzheimer's disease (AD) is also a neurodegenerative disorder that causes loss of learning and memory functions at an old age. The factors affecting the development of AD are modifiable (i.e., smoking, alcohol,

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hypertension, atherosclerosis, diabetes, and hypercholesterolemia) and nonmodifiable factors (i.e., age, head trauma, apolipoprotein E_4 gene expression, and mutation of chromosomes). The pathogenesis of AD is through the alteration of neuronal proteins, that is, amyloid precursor protein (APP), Aβ peptide that leads to the formation of neurofibrillary tangles, tau hyperphosphorylation, and amyloid plaques in the brain cortex and hippocampus regions.[95] These changes are due to the actions of intracellular enzyme cascades, that is, secretase (α, β, and γ isotypes), beta-site APP-cleaving enzyme ($BACE_1$ and $BACE_2$), presenilins (P_1 and P_2), apolipoprotein E-epsilon 4 variant (ApoE-ε4), alpha$_2$-macroglobulin, and abnormal activation of calcium dependent kinases (PKC, ERK_2, Src, and RTK).[96−98] ACE metabolizes Aβ proteins that are responsible for the development of memory dysfunctions.[99] However, overexpression of ACE in myelomonocytic cells alters the immune response, that causes amelioration of AD.[54]

The physiological level of AT-II peptide has an anticholinergic effect,[91] pro-oxidant,[100] improves the regional cerebral perfusion of hemodialysis patients,[101] increase the risk of white matter hyper-intensities,[102] and increase Aβ induced neurotoxicity.[103] In pathological conditions, the excess release of AT-II peptide (potent neurotoxic molecule) causes the potential unwanted actions in the nervous system. Administration of ACE inhibitor, i.e., perindopril attenuates the intracerebroventricular (i.c.v.) injection of A$\beta_{(1-40)}$ induced Alzheimer disease in mice.[104] Administration of lisinopril has been documented to attenuate Alzheimer disease by antioxidant and anti-inflammatory actions.[82] In addition, captopril and perindopril also produce neuroprotection in transgenic mice (aged Tg2576 mice) model of AD by reduction of amyloidogenic process (by beta- and gamma-secretases), and decreased hippocampal reactive oxygen species (ROS).[49,89] Another study shows that ramipril induces rise in Aβ levels in transgenic APP (SWE)/PS1 ($\Delta E9$) mice brain.[99] Treatment of lisinopril ameliorates pathogenesis of vascular dementia associated AD via inhibition of substrate V degradation. Substrate V is a fluorogenic substrate of insulin degrading enzyme and other metalloproteases enzymes that are responsible for the degradation of Aβ proteases in AD patients.[105] In contrast, ACE inhibitor, that is, ramipril, causes neuronal damage in AD patients by reduction of AT-II peptide level in CSF along with the increase in cerebral blood flow.[106] Whereas, administration of enalapril and lisinopril has been documented to attenuated cognitive impairment.[107] Furthermore, perindopril improves AD via learning and memory function in rats as well as in humans.[108,109]

3.3. Parkinson's Disease. Parkinson's disease (PD) was first coined by James Parkinson in 1867.[110] Parkinson's disease is also known as "Paralysis Agitans" because of the alteration of neuromuscular changes and it is characterized by abnormal involuntary movements of the body.[111] At the molecular level, the imbalance in major neurotransmitters, that is, dopamine (DA) and acetylcholine (Ach), in brain regions (nigrostratial pathway) play a major role in the pathogenesis of PD.[112] The symptoms of PD are bradykinesia, tremors-at-rest, and rigidity.[113] The major risk factors of PD are toxins, free radicals, smoking, alcoholism, and trauma.[114−116] In the brain site, dopaminergic neuron damage plays a potent role in PD by decreasing DA and increasing Ach that cause ionic imbalance, alteration of mitochondrial permeability transition pore (MPTP), calcium dependent caspase and kinase, leading to neuronal apoptosis.[117,118] In addition, the central activity of angiotensin is involved in the damage of dopaminergic degeneration in the substantianigra, caudate nucleus, and putamen by a rise in the levels of nicotinamide adenine dinucleotide phosphate (NADPH), oxidases-derived superoxide, and microglial activation.[119] In this region, ACE regulates the conversion of AT-I to AT-II peptide. AT-II peptide activates AT_1R and enhances NADPH dependent free radical formation and acts as a proinflammatory compound.[120,121] A rise in the central ACE activity is observed in PD patients.[122] ACE inhibitor, that is, perindopril, treatment in PD has been reported to increase dopamine levels in the striatal region of rat brain.[123] The preclinical studies reported that treatment of captopril ameliorates 1-methyl-4-phenyl-1,2,3,6-tetrahydropyrine (MPTP) and 6-hydroxy dopamine (6-OHDA) induced dopaminergic degeneration in rodents.[11,124] In addition, perindopril also resulted in significant improvement of motor impairment in PD patients along with a rise in dopamine precursor (i.e., 3,4-dihydroxy- L-phenylalanine) in the brain.[125] ACE inhibition produces a rise in bradykinin levels that causes neuroinflammation.[126] BK_2R has been documented to produce neuroprotective action.[127] In addition, administration of captopril is known to attenuate the development of PD via a rise in 6-OHDA levels in rat brain.[124]

3.4. Huntington's Disease. Huntington's disease (HD) is one of the neurodegenerative disorders similar to PD. The similarities are changes of behavior, thinking, and movement symptoms.[128,129] The discrepancy of HD is that it is a genetic disease that causes progressive neuropsychological symptoms.[130] The major cardinal symptoms of HD are uncontrollable movements of the limbs, trunk, and face (also called Huntington's chorea); progressive loss of mental abilities; and the development of psychiatric problems.[131] The risk component of HD is a genetic defect of the fourth chromosome. The biochemical changes in the brain remains to be explored. The brain microglia has neuroprotective action in physiological conditions,[132] whereas, under pathological conditions, it releases abundant free radicals that ultimately causes neuronal death in HD patients.[133] The level of ACE is reduced in corpus striatum and substantianigra in the brain of HD patients.[134,135] Recent reports suggested that AT-II peptide activates microglia that produces neurodegeneration via release of inflammatory cytokines, that is, TNF-α.[136] Activation of bone marrow-derived microglia mitigates neurodegeneration via release of neurotrophic factors.[137] The administration of captopril in women with Huntington's disease along with hypertension deteriorates the nervous system, whereas ameliorative action has been observed after 5 days of drug withdrawal.[138]

3.5. Amyotrophic Lateral Sclerosis. Amyotrophic lateral sclerosis (ALS) is a motor neuron degenerative disorder, that is, Charcot disease, Lou Gehrig's disease.[139] ALS is characterized by muscle spasticity, rapid muscle weakness because of muscle atrophy, dysarthria (difficulty in speaking), dysphagia (swallowing), and dyspnea (breathing). The types of ALS are frontotemporal dementia and monomelic amyotrophy.[140] The major risk factors of ALS are heredity, age, sex, environmental components (smoking), lead, certain metals, chemicals, traumatic injuries, and viral infections.[141,142] AT-II peptide has a protective action of motor neuron by stimulation of AT_2R.[143] In addition, cerebrospinal fluid AT-II peptide levels are reduced in ALS patients.[144] The treatment of temocapril has an ameliorative potential in damaged motor neuron disease, such as in motor neuropathy and amyotrophic lateral sclerosis through its neurotrophic activity via a rise in neurite outgrowth and choline acetyltransferase (ChAT) activity.[145]

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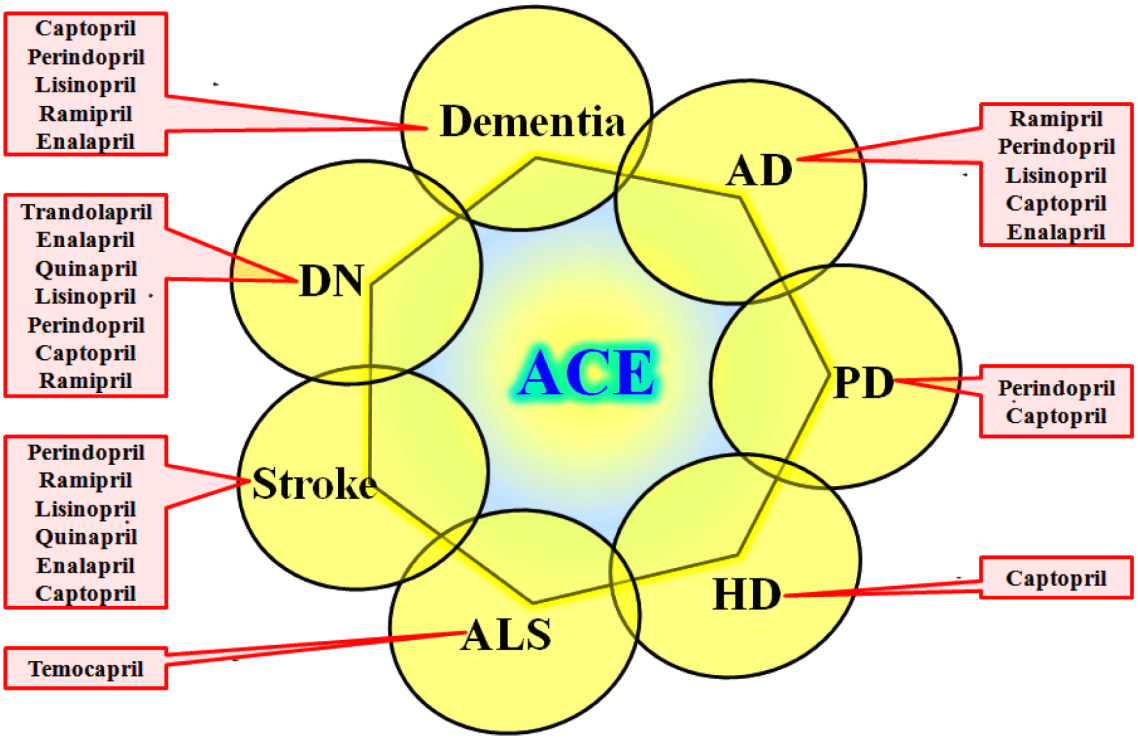

Figure 2. ACE involved in the pathogenesis of various neurological disorders. The overactivation of ACE elevates angiotensin levels in the nervous system that produce oxidative stress (by generation of free radicals), ionic imbalance (intracellular Ca^{2+} accumulation), neuroinflammation (rise in inflammatory cytokines, i.e., TNF-α, interleukines), activation of immune cells (glial, astrocytes, and Schwann cells), and upregulation of kinin receptors, which in turn leads to neuronal damage and neurodegeneration. Various ACE inhibitors modulate the pathogenesis of the above neurological diseases that are summarized in this figure. In addition, Table 1 summarizes the properties of central and noncentral acting ACE inhibitors inneurodegenerative disorders.

3.6. Stroke. Stroke also causes neurodegeneration by changes of cerebrovascular events, and it is the third leading cause of death in the world. The symptoms of stroke are severe headache, numbness, motor impairment, paralysis, and death because of vascular leakage, thrombosis, and cerebral infarction.[146,147] The risk factors for stroke are smoking, obesity, trauma, atherosclerosis, hypertension, diabetes, and renal failure.[148−150] The physiological processes, that is, platelet activation, thrombosis in cerebral arteries, hypoxia, ischemia, aneurysm, immune, and nonimmune cell activation in the brain cause stroke by changes of ATP (decrease) content, mitochondrial damage, ionic imbalance, glial cell activation, expression of cytokines, and chemokines.[151,152] In addition, central ACE-2 (type 2 of ACE) inactivates bradykinin (endogenous vasodilating substance) that is responsible for the pathogenesis of stroke.[153] Experimental animal studies reported that treatment of quinapril prevents stroke and mortality in stroke-prone spontaneously hypertensive rats.[154] Also, the treatment of ramipril, lisinopril, and perindopril ameliorate stroke progression in hypertensive rats.[155−157] Administration of enalapril attenuates middle cerebral artery occlusion (MCAO) induced changes of neurological activity, cerebral infarction, brain swelling, and edema in normotensive rats.[158] Furthermore, the treatment of captopril attenuates hemorrhagic stroke via alteration of cerebral blood flow in spontaneously hypertensive rats.[159] The intravenous administration of captopril also protects against MCAO induced cerebral infarction in rats.[160]

In clinical studies, ACE inhibitors, that is, perindopril and ramipril, reduce cognitive impairment.[161,162] Other studies, that is, Heart Outcomes Prevention Evaluation (HOPE) trial and Perindopril Protection Against Recurrent Stroke Study (PROGRESS) trial, have an ameliorative action in recurrent stroke along with improvement of blood pressure.[163] Another clinical trial, that is, Paramedic Initiated Lisinopril for Acute Stroke Treatment (PIL-FAST), produces amelioration of acute stroke.[164,165] A recent study, that is, Ongoing Telmisartan Alone and in Combination with Ramipril Global End point Trial (ONTARGET), also evidenced that the administration of ramipril possesses potential role in the attenuation of stroke risk in patients with diabetes and renal disease.[166]

3.7. Diabetic Neuropathy. Diabetic neuropathy (DN) is a microvascular complication of diabetes that comprises disorders of peripheral nerve damage. Diabetic peripheral neuropathy (DPN) is associated with considerable mortality, morbidity, and diminished quality of life.[167] The development of DN is because of hyperglycemia along with metabolic imbalances, that is, increasing blood glucose and their metabolites (sorbitol and aldose); ketone bodies;[168] advanced glycation end products (AGE), that enhance free radicals, ionic imbalance associated vascular, and neuronal damage.[169] In addition, hyperglycaemic conditions release tissue AT-II peptide by the activation of ACE. AT-II peptide is responsible for oxidative stress and endothelial damage that cause vasoconstriction, thrombosis, inflammation, and vascular remodeling in epineural vascular tissue.[170−172] Once DN is developed in the lower limbs, it may cause sensory loss in the upper limbs.[173] In fact, the development of DN is because of multiple factors, that is, formation of polyol, AGE, hexosamine, diacylglycerol, protein kinase C (PKC), oxidative stress, nitric oxide, and inflammation.[174,175] Recently, RAAS has also been identified in the

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Table 1. Summary of Central and Noncentral Acting ACE Inhibitors Inneurodegenerative Disorders[a]

Sl. no.	drug name	medical uses	pharmacokinetics	adverse effects	uses in neurodegenerative diseases	refs
			central acting ACE inhibitors			
1	ramipril (prodrug: Ramiprilat)	hypertension; congestive heart failure, stroke	A: 50−60% by GIT D: C_{max} of ramipril-1 and ramiprilat are 2−4 h; 73 and 56% of ramipril and ramiprilat PPB, respectively M: glucuronide conjugation E: 60% by kidney F: 50−60% $t_{1/2}$: 9−18 h	dry cough, reduce blood sugar in diabetic patients, sweating, signs of infection, yellowing of eyes, dark urine, abdominal pain, and neutropenia	dementia, AD, stroke, and DN	99, 106, 108
2	captopril	hypertension, heart and kidney failure	A: 72 ± 4% D: plasma protein bound (PPB) drug 30% M: cysteine disulfide cogugation E: 85% renal excretion F: 75−91 $t_{1/2}$: 1−2 h	dry cough, abdominal pain, constipation, diarrhea, fatigue, rash, fainting, numbness, liver failure, and angiodema	dementia, AD, PD, HD, stroke, and DN	49, 89
3	perindopril (prodrug: Perindoprilat)	high blood pressure, heart attacks, and renal problems	A: 65−75% D: 60% perindopril PPB M: glucuronide conjugation E: in urine F: 75% $t_{1/2}$: 0.8 to 1 h	cough, fatigue, headache, disturbances of mood and sleep, nausea, abdominal pain, and jaundice	dementia, AD, PD, stroke, and DN	49, 89
4	trandolapril (prodrug: Trandolaprilat)	heart failure	A: 30 min D: 80% and 94% protein binding M: diketopiperazine and glucuronide conjugation E: by kidney and liver F: 70% $t_{1/2}$: 15−24 h	nausea, vomiting, diarrhea, headache, dry cough, dizziness, and fatigue	DN and ALS	185, 186
5	lisinopril	hypertension, heart and kidney failure	A: 25% D: bound to serum proteins and crosses the BBB poorly M: do not undergo metabolism E: kidney F: 6−60% $t_{1/2}$: 12	hypotension, nausea, anxiety, drowsiness, nasal congestion, anaphylaxis, leukopenia, and thrombocytropenia	dementia, AD, stroke, and DN	82, 93
			noncentral acting ACE inhibitors			
6	quinapril (prodrug: Quinaprilat)	hypertension and heart failure	A: 60% D: peak plasma concn 1 h M: hepatic E: by kidney F: 60% $t_{1/2}$: 1.9−2.5 h	dizziness, cough, vomiting, stomach upset, angioedema, and fatigue	stroke and DN	189

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Table 1. continued

Sl. no.	drug name	medical uses	pharmacokinetics	adverse effects	uses in neurodegenerative diseases	refs
		noncentral acting ACE inhibitors				
7	enalapril (prodrug: Enalaprilat)	hypertension, diabetic nephropathy, CHF, and heart failure	A: 55−75% D: it crosses the blood-brain barrier (BBB) poorly, but Enalaprilat does not cross the BBB M: by liver esterases E: in urine F: 60% $t_{1/2}$: 11 h	dry cough, dizziness, rash, vomiting, increase serum creatinine, dizziness, syncope, and angioedema	dementia, AD, stroke, and DN	183, 184

[a]A, Absorption; D, distribution; M, metabolism; E, excretion; F, bioavalaibility; and $t_{1/2}$, half-life.

progression of DN.[170] ACE inhibitor has vasorelaxation, anti-adhesion, and anti-inflammatory properties by reduction of AT-II peptide.[176] AT-II peptide also produced antinociceptive action via enhancing the metabolism of bradykinin and substance P; and release of endogenous opioid peptides in the nervous system.[177−179] Administration of perindopril ameliorates STZ induced diabetic neuropathy in Sprague−Dawley rats.[180] Ramipril treatment attenuates diabetic neuropathy via inhibition of BK_2R in db/db mice.[181] The ACE inhibitor lisinopril is known to produce amelioration of streptozotocin (STZ) induced neuronal dysfunction along with modulation of nerve blood flow.[182] Moreover, the combined inhibition of ACE and neutral endopeptidase (NEP), that is, ilepatril, enalapril, and candoxatril, improve STZ induced change in the vascular response of the epineural artery of the sciatic nerve.[183,184] Furthermore, trandolapril has also been reported to produce similar ameliorative actions in DN by the reduction of NADPH oxidase activity that is the marker of oxidative stress.[185,186] Captopril administration has been documented to improve asymptomatic diabetic autonomic neuropathy in human.[187] In addition, quinapril treatment ameliorates diabetic autonomic neuropathy in long-term type-1 and type-2 diabetic patients.[188]

4. SUMMARY OF ACE INHIBITORS IN NEURODEGENERATIVE DISORDERS

Ramipril is an antihypertensive agent, and beyond this action it is reported to ameliorate various neurodegenerative disorders, that is, dementia, AD, stroke, and DN in rodents as well as in humans.[99,166] In addition, other central acting ACE inhibitors also attenuate neurodegenerative diseases, for example, captopril attenuates dementia, AD, PD, HD, stroke, and DN;[49,89] perindopril ameliorates dementia, AD, PD, stroke, and DN.[89,109] Lisinopril attenuates dementia, AD, stroke, and DN;[82,107] trandolapril and temocapril attenuate DN, and ALS respectively.[145,186] Furthermore, noncentral acting ACE inhibitors such as quinapril treat stroke and DN;[154,188] enalapril manages the symptoms of dementia, AD, stroke, and DN.[107,184] The relationship of ACE and their inhibitors in neurodegenerative disorders is summarized in Figure 2.

5. FUTURE DIRECTIONS

Various ACE inhibitors (i.e., ramipril, captopril, perindopril, quinapril, lisinopril, enalapril, and trandolapril) have been documented to ameliorate neurodegenerative disorders in animals and in humans. The clinical utilities of ACE inhibitors have also been documented by numerous clinical studies. In addition, ACE inhibitors contribute in the alteration of kinin systems that are involved in the pathogenesis of lungs and neurovascular systems. Bradykinin contributes to cardioprotective activity of ACE inhibition as documented by numerous studies. Furthermore, the utilization of ACE inhibitors cannot be avoided due their potential action in the cardiovascular disorders. ACE inhibitors may be useful for the management of neurodegenerative disorders, because of the following actions: (i) ACE-2 converts angiotensinogen to $AT_{(1-7)}$ (hepatapeptide) that produces neuroprotective action; (ii) downregulation of pronociceptive BK_1R in peripheral nervous system; (iii) activation of Mas receptors releases nitric oxide and prostaglandins that cause vasodilation, antiproliferation, and anti-remodeling that in turn causes regulation of neurovascular functions; (iv) biosynthesis of AT-IV peptide in brain causes

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improvement of learning and memory functions via activation of AT_4R; (v) enhancement of the metabolism of bradykinin and substance P; and (vi) release of endogenous opioid peptides. However, it has dual action on the central and peripheral nervous system. This Review may be helpful to carry out more extensive research in preclinical and clinical research laboratories at multicenter levels, so that more therapeutic outcomes based on ACE inhibitors may be expected for the management of neurodegenerative disorders.

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Author Contributions

P.K. and A.M. have made substantial contributions to collection, compilation, and conception of collected materials and also critically analyzed and interpreted in this form of materials. A.M. has been involved in drafting the manuscript or revising it critically for important intellectual content and final approval of the version to be published. M.K. has ensured the questions related to the accuracy or integrity of any part of this manuscript.

Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

6-OHDA, 6-hydroxy dopamine; A, absorption; ACE, angiotensin converting enzyme; ACE 1, angiotensin converting enzyme 1; ACE 2, angiotensin converting enzyme 2; Ach, acetylcholine; AD, Alzheimer's disease; AGE, advanced glycation end products; ALS, amyotrophic lateral sclerosis; APOE-ε_4, apolipoprotein E-epsilon-4 variant; APP, amyloid precursor protein; ARDS, acute respiratory distress syndrome; AT_{1-7}, angiotensin 1−7; AT_1R, angiotensin 1 receptor; AT_2R, angiotensin 2 receptor; AT_4R, angiotensin 4 receptor; AT-I, angiotensin I; AT-II, angiotensin II; AT-III, angiotensin III; AT-IV, angiotensin IV; Aβ, beta amyloid peptide; B_1, bradykinin-1; B_2, bradykinin-2; $BACE_1$, beta-site APP-cleaving enzyme 1; $BACE_2$, beta-site APP-cleaving enzyme 2; ChAT, choline acetyltransferase; CSF, cerebrospinal fluid; C-terminal, carboxy terminal; D, distribution; DA, dopamine; DN, diabetic neuropathy; DOCA, deoxycorticosterone acetate; DPN, diabetic peripheral neuropathy; E, elimination; $ERK_{1/2}$, extracellular signal regulated kinase; F, bioavalaibility; GPCR, G-protein coupled receptors; HD, Huntington's disease; HOPE, heart outcomes prevention evaluation; M, metabolism; MCAO, middle cerebral artery occlusion; MPP^+, 1-methyl-4-phenylpyridinium; MPTP, mitochondrial permeability transition pore; NADPH, nicotinamide adenine dinucleotide phosphate; N-terminal, amino terminal; ONTARGET, Ongoing Telmisartan Alone and in Combination with Ramipril; P_1, presenilins 1; P_2, presenilins 2; P^{38} MAPK, protein-38 mitogen-activated protein kinase; PD, Parkinson's disease; PILFAST, Paramedic Initiated Lisinopril for Acute Stroke Treatment; PKC, protein kinase C; PROGRESS, Perindopril Protection Against Recurrent Stroke Study; RAAS, renin angiotensin aldosterone system; STZ, streptozotocin; Syst-Eur, Systolic Hypertension in Europe; $t_{1/2}$, half-life; TNF-α, tissue necrosis factor-alpha

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