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Quitterer, Ursula; AbdAlla, Said

Abstract: With ageing of the global society, the frequency of ageing-related neurodegenerative diseases such as Alzheimer's disease (AD) is on the rise worldwide. Currently, there is no cure for AD, and the four drugs approved for AD only have very small effects on AD symptoms. Consequently, there are enormous efforts worldwide to identify new targets for treatment of AD. Approaches that interfere with classical neuropathologic features of AD, such as extracellular senile plaques formed of aggregated amyloid-beta (Abeta), and intracellular neurofibrillary tangles of hyperphosphorylated tau have not been successful so far. In search for a treatment approach of AD, we found that inhibition of the angiotensin-converting enzyme (ACE) by a centrally acting ACE inhibitor retards symptoms of neurodegeneration, Abeta plaque formation and tau hyperphosphorylation in experimental models of AD. Our approach is currently being investigated in a clinical setting. Initial evidence with AD patients shows that a brain-penetrating ACE inhibitor counteracts the process of neurodegeneration and dementia. Moreover, centrally acting ACE inhibitors given in addition to the standard therapy, cholinesterase inhibition, can improve cognitive function of AD patients for several months. This is one of the most promising results for AD treatment since more than a decade.

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Review

Improvements of symptoms of Alzheimer`s disease by inhibition of the angiotensin system

Ursula Quitterer[a,b,*], Said AbdAlla[a]

[a] Molecular Pharmacology, Department of Chemistry and Applied Biosciences, ETH Zurich, Winterthurerstrasse 190, CH-8057, Zurich, Switzerland
[b] Institute of Pharmacology and Toxicology, Department of Medicine, University of Zurich, Winterthurerstrasse 190, CH-8057, Zürich, Switzerland

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ABSTRACT

With ageing of the global society, the frequency of ageing-related neurodegenerative diseases such as Alzheimer`s disease (AD) is on the rise worldwide. Currently, there is no cure for AD, and the four drugs approved for AD only have very small effects on AD symptoms. Consequently, there are enormous efforts worldwide to identify new targets for treatment of AD. Approaches that interfere with classical neuropathologic features of AD, such as extracellular senile plaques formed of aggregated amyloid-beta (Abeta), and intracellular neurofibrillary tangles of hyperphosphorylated tau have not been successful so far. In search for a treatment approach of AD, we found that inhibition of the angiotensin-converting enzyme (ACE) by a centrally acting ACE inhibitor retards symptoms of neurodegeneration, Abeta plaque formation and tau hyperphosphorylation in experimental models of AD. Our approach is currently being investigated in a clinical setting. Initial evidence with AD patients shows that a brain-penetrating ACE inhibitor counteracts the process of neurodegeneration and dementia. Moreover, centrally acting ACE inhibitors given in addition to the standard therapy, cholinesterase inhibition, can improve cognitive function of AD patients for several months. This is one of the most promising results for AD treatment since more than a decade.

1. Introduction

Alzheimer`s disease (AD) is the most frequent form of dementia, and with increasing age of the global society on the rise worldwide [1]. Currently, there are only four drugs approved for the treatment of AD: three cholinesterase inhibitors, and the NMDA (N-methyl-D-aspartate) glutamate receptor antagonist, memantine [2]. All these drugs alleviate symptoms of dementia for only a few months but cannot halt disease progression [2]. Thus, there is an urgent need for new drugs to improve therapy of AD.

Research on pathomechanisms identified major neuropathologic features in brains of AD patients, which are characterized by extracellular plaques of aggregated amyloid-beta (Abeta), and intracellular neurofibrillary tangles formed of hyperphosphorylated PHF (paired helical filament) tau [3]. Impaired clearance and/or enhanced generation of aggregation-prone amyloid-beta, Abeta oligomers and formation of Abeta plaques are considered to be hallmarks of the aging-induced process of neurodegeneration while neurofibrillary tangles of hyperphosphorylated tau could form as a consequence of aberrant Abeta accumulation [4–6]. According to this amyloid hypothesis of AD, Abeta is the major pathologic driver, which triggers the disease [6]. This conclusion is supported by several lines of evidence, which established the disease relevance of Abeta. Mutations in the amyloid-beta region of the amyloid precursor protein (APP) are associated with familial Alzheimer`s disease, FAD [7]. Transgenic animal models with neuron-specific expression of FAD-associated APP mutants reproduce major AD symptoms such as cognitive impairment, neurodegeneration and accumulation of Abeta plaques with increasing age [8,9]. In recent years, the amyloid hypothesis of AD was complemented by evidence, which also supports a major role of PHF tau in AD pathogenesis. In

Abbreviation: AD, Alzheimer`s disease; ACE, angiotensin-converting enzyme; ACE2, angiotensin-converting enzyme 2; Abeta, amyloid-beta; PHF, paired helical filament; APP, amyloid precursor protein; FAD, familial Alzheimer`s disease; NMDA, N-methyl-D-aspartate; AT1 receptor, type-1 angiotensin II receptor; *AGTR1*, the gene symbol for the human type-1 angiotensin II receptor; RAAS, renin angiotensin aldosterone system; ROS, reactive oxygen species; Tg2576 mice, transgenic mice with neuron-specific expression of APPSwe; APPSwe, the Swedish mutation of the human amyloid precursor protein APP695 containing the double mutation K670N M671L which was identified in a Swedish family with FAD; LOAD, late-onset Alzheimer`s disease; GWAS, genome-wide association study; SNP, single nucleotide polymorphism; HPA axis, hypothalamic pituitary adrenocortical axis; CUMS, chronic unpredictable mild stress

* Corresponding author at: Professor of Molecular Pharmacology ETH Zurich, room Y17M70 Winterthurerstrasse 190, CH-8057, Zurich, Switzerland.
E-mail address: ursula.quitterer@pharma.ethz.ch (U. Quitterer).

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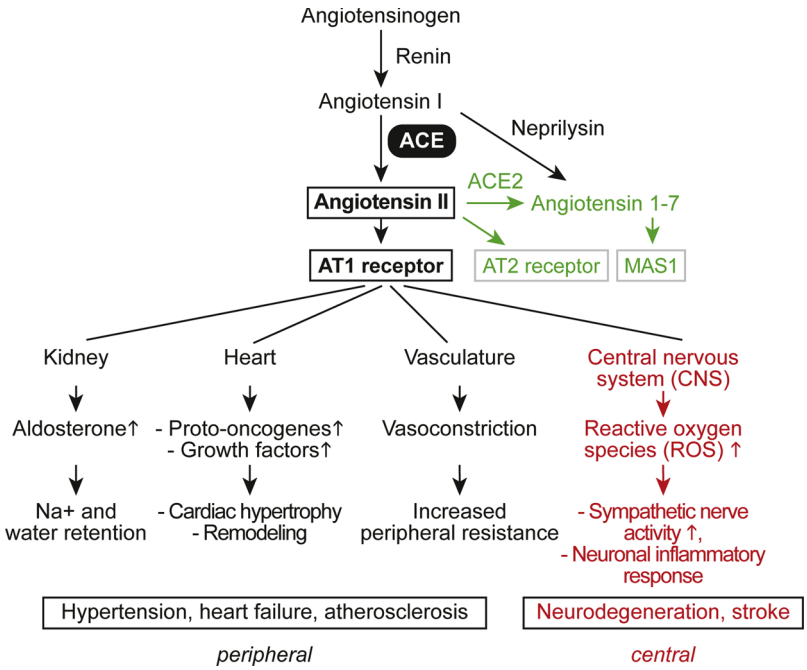

Fig. 1. Overview of major physiologic and pathophysiologic functions of peripheral and central ACE, and the AT1 receptor, which can be targeted by approved drugs. Components of the angiotensin system, which counteract functions of ACE and the AT1 receptor are coloured in green (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

transgenic mice, a dementia-associated tau mutant strongly accelerated disease progression induced by brain-specific expression of an FAD-related mutant of APP [10,11]. In patients, the content of hyperphosphorylated PHF tau correlates with neuronal loss in AD brains [5]. Based on these data, it was concluded that aggregated Abeta and hyperphosphorylated PHF tau synergistically enhance the irreversible neurodegenerative process and dementia in AD [12–14].

Because of the causal involvement in disease symptoms of experimental AD models, treatment approaches were developed, which interfere with Abeta production and/or enhance Abeta clearance and degradation [15–21]. One of the most promising approaches targets the formation of Abeta plaques by Abeta-specific antibodies. But this concept is currently under discussion because all major clinical trials with Abeta-targeting antibodies did not show any improvement of disease symptoms, notably dementia [15–18]. Moreover, active immunization against Abeta could induce severe neurological side effects and meningoencephalitis [19]. In addition, inhibition of Abeta generation by a small molecule inhibitor of the rate-limiting Abeta-generating enzyme, beta-secretase (BACE), also was ineffective in AD patients in a phase III clinical trial and had severe side effects [20,21]. In view of these disappointing results, it is questioned whether Abeta is the right target [22]. Instead, inhibition of PHF tau accumulation is the focus of several experimental and clinical trials with tau-specific antibodies [23,24]. Outcome data of these clinical trials currently are not available. Taken together, development of a successful treatment strategy for AD currently is not feasible because the right target is lacking.

In search for a possible target for AD treatment, we focussed on the neuronal angiotensin system because several components of this system are altered in AD brains. Notably, neuronal levels of the angiotensin II-generating angiotensin-converting enzyme, ACE, are increased in brains of AD patients [25–27]. By stimulation of the type-1 angiotensin II receptor (AT1 receptor) encoded by the type-1 angiotensin II receptor gene (*AGTR1*), ACE-generated angiotensin II is known to promote neurodegeneration and brain ageing [28,29]. On the other hand, it was found that ACE could be an Abeta-degrading enzyme [30]. From these in vitro data, it was discussed that inhibition of ACE could aggravate AD symptoms by increasing the accumulation of Abeta [30]. However, in vivo studies did not show an enhanced Abeta generation upon genetic inactivation of ACE or ACE inhibition [31]. In addition, so far, all Abeta-targeting approaches failed to improve AD symptoms in larger cohorts of patients [15–22].

Therefore, we focussed on ACE inhibition as a potential neuroprotective approach and analysed the impact of ACE inhibition on symptoms of AD in different experimental AD models. We found that ACE inhibition with a brain-penetrating ACE inhibitor, captopril, retarded major AD symptoms, and triggered a neuro-regenerative gene expression signature in AD mice [32,33]. Notably, ACE inhibition prevented the AD-related decreases in transcript levels of 38 hippocampal genes with established functions in neuronal regeneration and cognition [32]. Captopril not only retarded AD-related hippocampal neurodegeneration, but also actively promoted hippocampal neuro-regeneration. Active neuro-regeneration by captopril was documented by up-regulation of transcript levels of 12 hippocampal genes encoding neuronal structure-forming proteins above the levels of the young control group [32]. ACE-inhibition-induced hippocampal neuro-regeneration was further confirmed by immuno-fluorescence detection of hippocampal Epha4, the Ephrin type-A receptor 4, which is reduced in hippocampal biopsy specimens from AD mice and AD patients before the onset of memory decline [32,34]. Immuno-fluorescence microscopy documented that six months of captopril treatment had promoted the regeneration of Epha4-positive CA1 neuronal processes of aged 18-month-old Tg-2576 AD mice, which were substantially degenerated not only in 18-month-old AD mice but also in 12-month-old AD mice [32]. Other experimental data complement these findings and show that central ACE inhibition-mediated neuroprotection could be attributed to suppression of pro-inflammatory microglia and astrocyte activation, and attenuation of oxidative stress [35]. This neuroprotective activity of central ACE inhibition, which is deduced from our and other experimental studies, is supported by recent clinical data, which document beneficial neuroprotective activity of brain-penetrating ACE inhibitors [36].

2. ACE is a key component of the peripheral and neuronal renin-angiotensin-aldosterone system, RAAS

The physiologic and pathophysiologic functions of the angiotensin-converting enzyme, ACE, are well-established [28]. By generation of angiotensin II, ACE is the key component of the renin-angiotensin-aldosterone system, RAAS (Fig. 1).

ACE generates angiotensin II from its precursor angiotensin I, which is derived from renin-mediated cleavage of angiotensinogen.

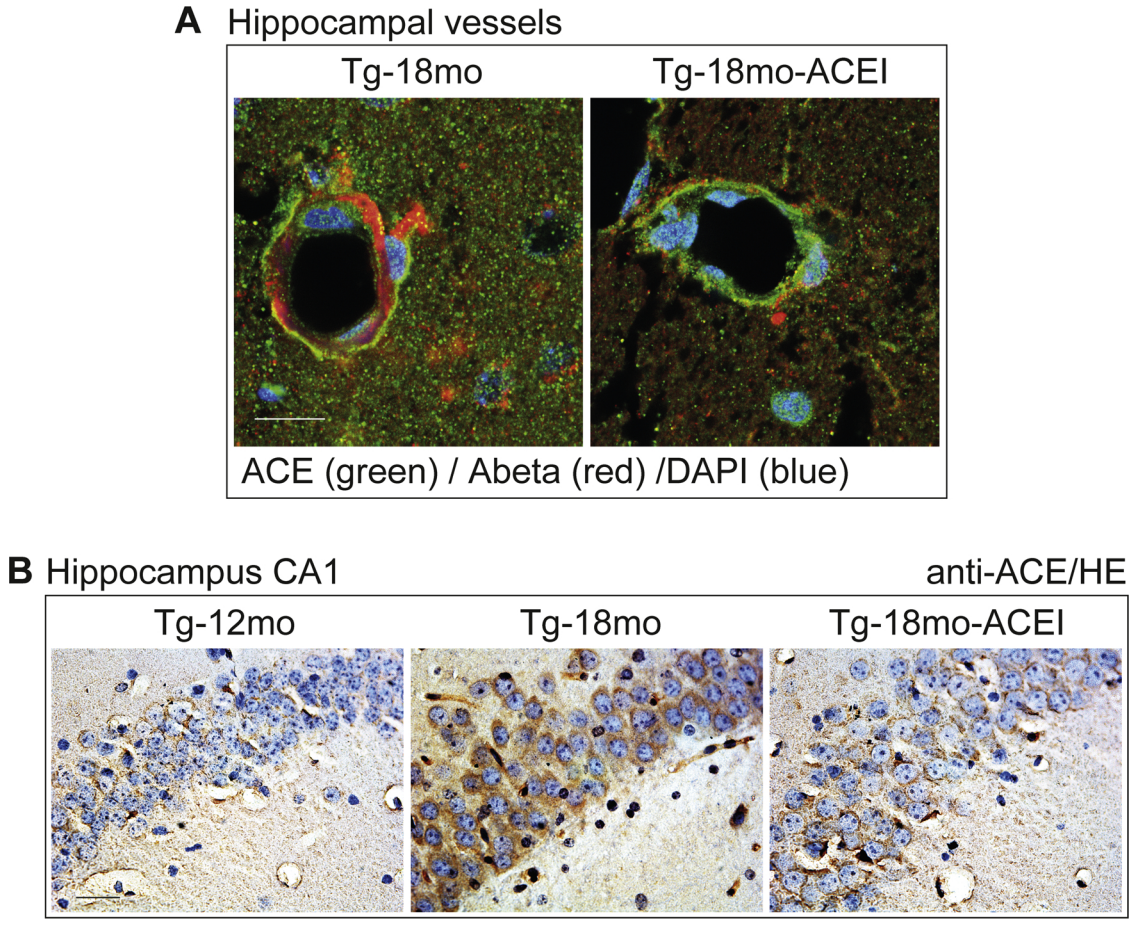

Fig. 2. Immunohistological localization of ACE in aged AD mice. **A**, Immunofluorescence analysis localized ACE (green) and Abeta (red) in hippocampal vessels and neurons of aged 18-month-old Tg2576 AD mice without (left) and with ACE inhibition (ACEI) with captopril (right); bar: 25 µm. **B**, Detection of neuronal ACE on hippocampal CA1 neurons by immunohistology with anti-ACE antibodies; bar: 25 µm. Cell nuclei were stained with DAPI (**A**) and hematoxylin (HE; **B**). Images were adapted from [32] (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Angiotensin II exerts major physiologic and pathophysiologic functions by activating the angiotensin II AT1 receptor protein, which is encoded in humans by *AGTR1* (Fig. 1). Target organs of angiotensin II are the kidney, the heart and the vasculature. In the kidney, the AT1 receptor controls salt and water homeostasis, in part by stimulating the formation of aldosterone. In the heart, enhanced AT1 receptor activation promotes cardiac remodelling and aggravates the progression of heart failure. In the vasculature, AT1 stimulates vascular contraction and the synthetic vascular smooth muscle phenotype, and thereby contributes to the pathophysiology of hypertension, and atherosclerosis [28,37]. Based on these important pathophysiologic processes, inhibition of angiotensin II generation by an ACE inhibitor is currently one of the most important treatment approaches for hypertension, ischemic heart disease and heart failure (Fig. 1).

In addition to the peripheral angiotensin system, all components of the RAAS are also found in brain [38,39]. Activation of the sympathetic nervous system is considered as one of the major functions of brain RAAS [40]. Furthermore, central nervous system ACE could be a contributing factor to hypertension and stroke [41,42]. By angiotensin II AT1 receptor-stimulated generation of reactive oxygen species (ROS), central nervous system ACE exerts neurodegenerative activity [35,43]. Apart from these functions, neuronal ACE and angiotensin II are increasingly recognized for their involvement in neuropsychiatric and neurodegenerative disorders such as depression, anxiety, mood disorders, dementia, Parkinson`s disease and Alzheimer`s disease [36,44–48].

Our review is focused on components of the angiotensin system, which are targets of approved classes of antihypertensive drugs, i.e. ACE and the angiotensin II AT1 receptor (Fig. 1). Functions of ACE and the AT1 receptor are interconnected with other components of the angiotensin-system, which currently cannot be targeted by approved drugs directly. For instance, detrimental functions of ACE as the major angiotensin II-generating enzyme, are counteracted by the angiotensin II-degrading enzyme, ACE2, not only in the periphery but also in brain [49]. In agreement with this notion, deficiency of ACE2, in ACE2 knockout mice, causes cognitive impairment [49]. The underlying mechanism involves increased reactive oxygen species (ROS) generation, most likely by unrestrained activation of the AT1 receptor as a consequence of exaggerated angiotensin II levels [49]. ACE2 inactivates angiotensin II to generate angiotensin 1–7, which can exert independent vasodilatory effects, mainly by activation of MAS1 [50,51]. Upon inhibition of ACE, beneficial ACE2-dependent angiotensin 1–7 generation is enhanced, and this activity distinguishes ACE inhibitors from AT1 antagonists [52]. Another component of the angiotensin system is the angiotensin II AT2 receptor (AGTR2). The AT2 receptor antagonizes functions of the AT1 receptor [53], and activation of the AT2 receptor by angiotensin II is enhanced under conditions when the AT1 receptor is blocked by an AT1-specific antagonist [54]. In addition to beneficial actions of the AT2 receptor in peripheral organs, the AT2 receptor exerts neuroprotection and promotes neuronal regeneration [55,56].

Taken together, detrimental neurodegenerative functions of ACE and the AT1 receptor are counteracted by other components of the angiotensin system, i.e. ACE2, MAS1 and the AT2 receptor.

Consequently, strengthening of this “good” side of the angiotensin system needs to be considered when beneficial therapeutic effects of ACE inhibitors and AT1 receptor antagonists are evaluated, regarding the treatment of cardiovascular disease and central nervous system disorders.

3. ACE protein and activity are increased in brains from AD patients and experimental AD models

A potential role of ACE in the pathogenesis of AD is discussed for several decades. Major evidence came from histopathologic studies, which found that the ACE protein is increased in brains from AD patients [25–27]. We also found an increased hippocampal ACE protein and activity in the experimental AD model of Tg2576 mice [32], which recapitulates features of FAD by neuron-specific expression of APPSwe, i.e. the human amyloid precursor protein, APP695, containing the double mutation K670 N, M671 L, which was identified in a Swedish family with FAD [8]. Immunohistology localized the ACE protein in brain vessels of aged Tg2576 AD mouse brains (Fig. 2A; and [32]). In agreement with AD patients [27], vascular ACE was localized in brains of Tg2576 AD mice in close proximity to vascular Abeta plaque deposits (Fig. 2A; and [32]). ACE was found on the perivascular side in close proximity to basal lamina whereas vascular Abeta deposits were facing the vessel lumen indicative of cerebral amyloid angiopathy (Fig. 2A; and [32]). Again, this finding is complementary to the localization of ACE in brains of AD patients [27]. In addition, ACE and Abeta were localized on hippocampal neurons and neuronal processes (Fig. 2A,B; and cf. Fig. 3). This phenotype of Tg2576 AD mice recapitulates major features of brains from AD patients [26,27]. In the Tg2576 AD model, treatment with the ACE inhibitor, captopril, led to a decrease in vascular Abeta accumulation (Fig. 2A; and [32]). In addition, treatment with the ACE inhibitor, captopril, for six months counteracted the AD-related increase in hippocampal ACE (Fig. 2B; and [32]).

In view of the increased ACE protein and activity in AD brains, a pathophysiologic role of ACE in AD and neurodegeneration is under investigation for more than 20 years. Initially, the increased ACE activity in AD brains was discussed to promote degradation of Abeta in vivo because ACE has measurable Abeta-degrading activity in vitro [30]. In contrast to the in vitro situation with abundant amounts of enzyme and substrate, in vivo data did not show a significant degradation of Abeta peptides by ACE [31,57]. Moreover, ACE inhibition with an ACE inhibitor did not lead to an increased Abeta accumulation in vivo [57,58]. Instead, central ACE inhibition retarded AD pathology in brains of AD animal models [32,58–60]. Notably, treatment with different brain-penetrating ACE inhibitors, e.g. perindopril and captopril, decreased Abeta plaque load and/or Abeta levels [32,58–60]. In similar experiments, the Abeta-degrading activity of other vasopeptidases such as neprilysin (neutral endopeptidase, NEP), and endothelin-converting enzyme was documented in vitro and in vivo, and also in AD animal models [31,61–64].

In summary, the dominant function of ACE in vivo is the generation of angiotensin II. By inhibition of angiotensin II peptide generation, ACE inhibitors prevent the activation of the AT1 receptor, and ensuing AT1 receptor inhibition is a sufficient cause for a decreased AD pathology in various AD models and patients [65–69]. In vivo, the beneficial AT1-inhibitory effect of ACE inhibitors apparently dominates over other enzymatic activities of ACE, which can be measured in vitro because in vivo, the endogenously expressed ACE does not significantly degrade Abeta peptides [31,57]. Inefficient ACE-mediated cleavage of Abeta peptides in vivo could - at least partially - be a consequence of Abeta peptide phosphorylation at serine-8 [70]. Furthermore, AT1 receptor inhibition-independent modulation of other neuroprotective targets of the angiotensin system, e.g. as a consequence of an increased angiotensin 1–7 generation, could further contribute to the unique neuroprotective profile of ACE inhibitors in vivo [52].

In this context, the role of the ACE I/D (insertion/deletion) polymorphism also was investigated. Individuals with the DD genotype (homozygous for the deletion) have a two-fold increased serum ACE activity [71]. Nevertheless, large meta-analyses did not find convincing evidence of a major disease relevance of the ACE I/D polymorphism, neither for cardiovascular disease nor AD symptoms and cognition [72,73]. Other ACE variants, e.g. ACE variant rs4291, rs4343 and rs1800764 also did not show a significant association with late-onset AD in a large multi-centre study with ten Caucasian case-control populations [74]. In agreement with these data, a meta-analysis of all publicly available datasets for genome-wide association studies (GWAS), did not find a significant disease association between single nucleotide polymorphisms (SNPs) of the ACE gene or any other component of the renin-angiotensin-system and AD risk [75].

The largest genetic study on AD from the International Genomics of Alzheimer`s Project, IGAP, with data from 35,274 AD cases with clinical and autopsy-diagnosed AD and 59,163 controls confirmed that all

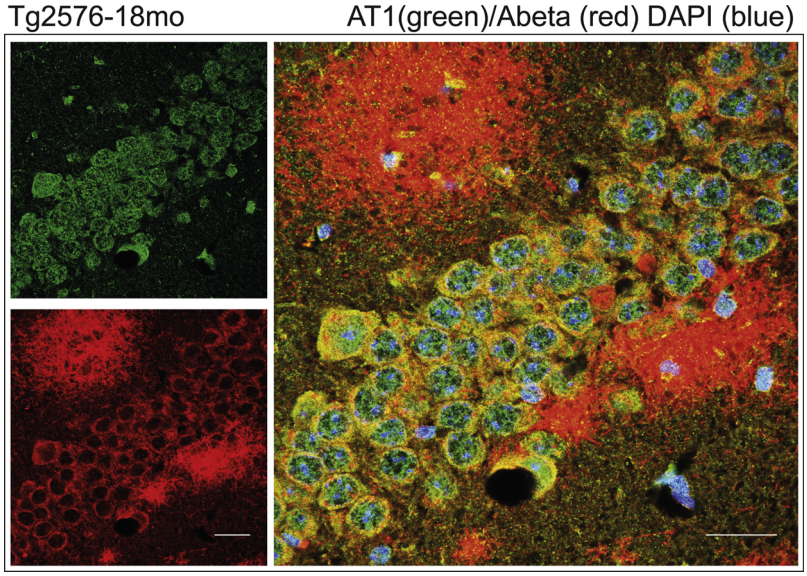

Fig. 3. Immunofluorescence localization of the AT1 receptor (green) and Abeta plaques (red) on hippocampal neurons of an aged Tg2576 AD mouse (bar: 25 μm). Images were adapted from [32] (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

previously investigated ACE variants did not show significant association with LOAD risk, i.e. late-onset Alzheimer`s disease [76]. Instead, the study suggested for non-Hispanic Whites a weak association between LOAD risk and a previously unrecognized rare SNP (MAF, minor allele frequency: 0.02, i.e. 2%) in the ACE locus (rs138190086; ref [76].). Because the study did not find any eQTLs (expression quantitative trait loci) in close proximity to the newly identified AD-related SNP [76], the impact of this SNP on ACE expression level is unknown. GWAS loci are intergenic. Therefore, the actual risk gene is often distinct from the nearest annotated gene to the associated SNP. Thus, the gene that is influenced by rs138190086 within the ACE locus could be different from ACE and still awaits to be identified.

Taken together, this lacking (or weak) disease associations of ACE polymorphisms with AD risk are most likely attributable to the fact that genetic polymorphisms have minor impacts on risks of genetically complex disorders such as cardiovascular disease and AD. Limitations of the “pure” genetic approach eventually could be overcome by the direct measurement of blood ACE and angiotensin II levels. In agreement with this notion, data from a recent study showed a significant association between elevated blood ACE, high angiotensin II levels, and a worse cognitive function [77].

4. ACE inhibition counteracts major risk factors of AD by inhibition of the AT1 receptor

By the increased generation of angiotensin II, the up-regulated ACE protein in aged Tg-2576 AD mice could enhance major symptoms of Alzheimer`s disease by activation of the AT1 receptor [65–68]. Notably, genetic deficiency of the angiotensin II AT1a receptor in a transgenic AD model, led to a significantly decreased Abeta plaque formation [66]. Likewise, a reduction in Abeta plaque load of AD mice was achieved by treatment with different AT1 receptor antagonists [65,67,68]. In frame of our immunohistological studies, we localized the AT1 receptor in brains of aged Tg2576 AD mice. Immunohistology detected the angiotensin II AT1 receptor on hippocampal neurons of aged 18-month-old Tg2576 mice (Fig. 3; and ref. [32]).

The AT1 receptor was localized in close proximity to insoluble Abeta plaque deposits (Fig. 3; and [32]). Because an increased ACE protein and activity were also found on hippocampal neurons (cf. Fig. 2B; and [32]), the increased ACE-dependent angiotensin II generation in AD brain could directly enhance Abeta generation and symptoms of neurodegeneration by AT1 receptor stimulation [65–69]. In agreement with this concept, inhibition of ACE with the brain-penetrating, captopril, led to a significantly decreased Abeta plaque load of aged Tg2576 AD mice [32].

Beneficial effects of angiotensin II AT1 receptor inhibition are well documented regarding neuroprotection and slowing the progression of AD [65–69]. ACE/AT1 receptor inhibition-mediated neuroprotection was previously attributed to the attenuation of oxidative stress, and the modulation of aberrant astroglial activation [35]. But do ACE inhibitors and AT1 receptor antagonists interfere with the pathogenesis of Alzheimer`s disease directly? Pathomechanisms of AD initially were deduced from disease-causing mutations identified in cases of familial Alzheimer`s disease, FAD, with autosomal-dominant inheritance of the disease. Mutations were identified in the amyloid precursor protein, APP, of early-onset FAD patients (i.e. patients with the autosomal dominant-form of early-onset AD) and led to the amyloid hypothesis of AD [6,7,78,79]. However, specific genetic changes, which ultimately cause AD, are rare (less than 1%) and usually do not occur in patients with late-onset sporadic AD, which encompass more than 95% of all AD cases [79]. Therefore, the pathogenesis of late-onset sporadic AD could have additional causes and risk factors. Search for pathomechanisms led to the concept that late-onset sporadic AD is caused by a synergistic interplay between genetic, environmental and lifestyle risk factors [1,80]. Among different risk factors, the greatest risk factor of late-onset sporadic AD is advanced age [1]. In addition to advanced age, there are only a few other risk factors with well-established impact on the pathogenesis of AD and vascular dementia, i.e. diabetes, smoking, midlife hypertension, obesity, physical inactivity, depression, and low educational level [80].

Considering advanced age and the other seven major risk factors of AD, it is noteworthy to mention that ACE inhibitors and AT1 antagonists, target almost all of these major dementia-accelerating risk factors.

(I) Aging: Genetic and pharmacologic inhibition of ACE and/or the AT1 receptor has direct anti-aging effects and leads to an extended life span of experimental models [81–83].

(II) Diabetes type 2 and insulin resistance: Numerous studies show that ACE and AT1 receptor inhibition ameliorate symptoms of diabetes type 2 and improve insulin resistance [84–86]. Brains of AD patients are characterized by insulin resistance, and the metabolic syndrome is associated with an enhanced Abeta plaque accumulation [87,88]. Consequently, improvement of insulin resistance is considered as an emerging new therapeutic target in AD [87], and modulation of serum adipocytokines and glucose homeostasis is considered to contribute to retardation of cognitive decline achieved by ACE inhibitors and angiotensin II AT1 receptor antagonists [89]. The antidiabetic activity of ACE inhibitors seems even stronger compared to AT1 antagonists and involves AT1 receptor inhibition-dependent and independent effects [90,91].

(III) Obesity: Genetic deficiency and inhibition of ACE and other components of the angiotensin system document that ACE inhibition has direct anti-obesity effects [92–95]. The anti-obesity effect of ACE inhibition could involve an increased abundance of angiotensin 1–7, and this effect distinguishes ACE inhibitors from AT1 antagonists [95].

(IV) High blood pressure: Midlife hypertension is a well-established risk factor for dementia later in life, in part by deterioration of the structure and function of cerebral blood vessels [96]. In addition, experimental data in mice and pigs provide evidence for a causal association of hypertension with enhanced AD pathology [97]. In agreement with these data, a higher systolic blood pressure is not only associated with an increased incidence of brain infarcts but also with an increased AD pathology, specifically tau tangles [98]. Moreover, in patients with diagnosed AD, hypertension is associated with worse cognitive function, behavioural symptoms and hippocampal glucose hypometabolism [99]. Therefore, adequate blood pressure control by ACE inhibitors and AT1 receptor antagonists seems to act in synergy with other beneficial activities of these drugs. Adequate blood pressure control is more important in midlife and early old age (< 75 years) as the dementia risk associated with increased systolic blood pressure declines in old age [98,100].

(V) Depression: ACE inhibitors and AT1 receptor antagonists have positive effects on symptoms of depression [46,101]. This antidepressant activity of ACE inhibitors and AT1 receptor antagonists could account for the observed decreased risk of mood disorders in patients treated with ACE inhibitors and AT1 antagonists compared to other antihypertensive medications [45].

(VI) Cognition: Numerous lines of evidence provide strong evidence that continuous angiotensin II stimulation impairs cognitive function by stimulation of the AT1 receptor [102]. Impaired cognitive function stimulated by angiotensin II involves a decrease in cerebral blood flow, an increased oxidative stress, neuroinflammation and neuronal senescence [102]. A direct angiotensin II AT1 receptor-stimulated effect on cognition involves inhibition of the potassium-stimulated release of acetylcholine in rat and human brain cortex [103,104]. Consequently, an ACE inhibitor-mediated decrease in angiotensin II peptide levels could improve cognition by increasing the cognition-enhancing acetylcholine [105]. Numerous subsequent studies with experimental models and patients support these early findings and show that inhibition

of the ACE-AT1 receptor axis by ACE inhibitors and/or AT1 antagonists leads to a better outcome regarding cognition and dementia symptoms, partly independent of direct actions on brain Abeta levels e.g. [34,106–116].

Despite this multifaceted activity, the beneficial profile of ACE inhibitors and AT1 receptor antagonists could eventually be overcome by the strong influence of potent genetic risk factors of AD such as the APOE epsilon4 allele and/or modulated by the ACE genotype [117,118]. Nevertheless, centrally acting AT1 antagonists and ACE inhibitors target basically all of the major risk factors, which are known to contribute to vascular dementia and AD.

5. Stress is a causative factor of ACE induction in Alzheimer`s disease

We elucidated the cause of ACE up-regulation in Alzheimer`s disease. Our focus was the activation of the hypothalamic pituitary adrenocortical (HPA) axis with subsequently increased corticosteroid generation, which is a well-established trigger of ACE up-regulation [119–121]. In agreement with the involvement of the HPA axis in ACE induction, we found that chronic unpredictable mild stress (CUMS), which mimics environmental stress as an important risk factor of AD, promoted a strong induction of the hippocampal ACE protein and activity [33]. This finding is relevant to the pathophysiology of AD in patients, because the CUMS model recapitulates major features of sporadic AD with an increased hippocampal content of hyperphosphorylated PHF tau and an enhanced amyloid-beta (Abeta) generation [33,122,123]. The Alzheimer-like and/or AD-aggravating phenotype induced by CUMS is linked to advanced age because this phenotype only develops in aged 15-month-old rats and aged Tg2576 AD mice whereas young rats are not sensitive to the CUMS protocol [33,124–126]. Moreover, we found that ACE is causally involved in these AD-like neuropathologic features, which can be prevented by ACE inhibition [33]. Consequently, the CUMS model can be considered as a non-transgenic model of early sporadic AD [122]. Findings with the CUMS model could thus be relevant to the pathogenesis of AD in patients because the CUMS model mimics stress as a major risk factor for AD [127,128].

In addition to stress, advanced age is another factor, which could contribute to a higher activity of the ACE-AT1 receptor axis in a typical aging disease such as Alzheimer`s disease [129–131]. Aging-induced sensitization of the detrimental ACE-AT1 receptor axis could in part be mediated by down-regulation of the beneficial ACE2 and AT2 receptor [130]. Taken together, stress in synergy with advanced age could be a common inducer of ACE in brains of experimental AD models and AD patients (Fig. 4).

6. ACE inhibition retards symptoms of neurodegeneration in Tg2576 mice as a model of FAD

We established the causal involvement of ACE in neurodegeneration and AD symptoms in the experimental Tg2576 AD model by treatment with the brain-penetrating ACE inhibitor, captopril. Tg2576 AD mice develop hippocampal Abeta plaques beginning at an age of 12 months as a consequence of neuronal-specific expression of the APPSwe mutant, which was identified in a Swedish family with early-onset familial Alzheimer`s disease, FAD [8]. Tg2576 AD mice were treated for 6 months with captopril, starting at an age of 12 months. Hippocampal whole genome microarray gene expression profiling demonstrated that ACE inhibition induced a neuro-regenerative gene expression signature and prevented the AD-related decreases in transcript levels of 38 hippocampal genes with established functions in neuronal regeneration and cognition [32]. Captopril not only retarded the AD-related neurodegeneration, but also actively promoted hippocampal neuro-regeneration. Active neuro-regeneration by captopril was documented by

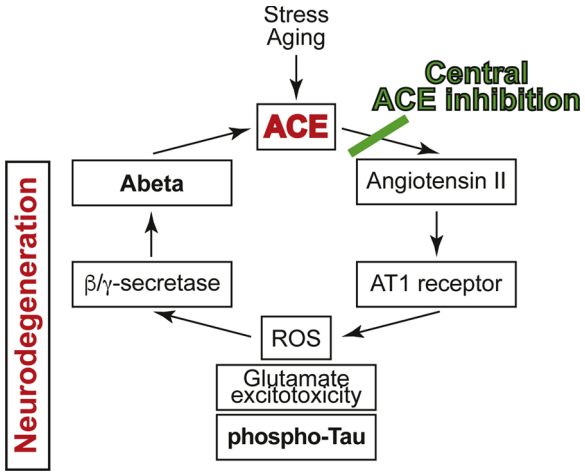

Fig. 4. Schematic representation of a vicious neurodegenerative circle triggered by ACE-dependent angiotensin II AT1 receptor activation (modified from [32]).

up-regulation of transcript levels of 12 hippocampal genes encoding neuronal structure-forming proteins above the levels of the young control group [32]. Notably, ACE inhibition "actively" triggered the expression of hippocampal neuronal genes, which are known to be defective in AD models and AD patients [32], such as the ephrin type-A receptor 4, *Epha4* [34], the sodium channel protein type 1 subunit alpha, *Scn1a* [132], and the potassium voltage-gated channel subfamily C member 1, *Kcnc1* [133]. Concomitantly, ACE inhibition with captopril led to the regeneration of neuronal processes of hippocampal CA1 neurons, which are degenerated in AD mice [32]. In addition, hippocampal Abeta plaque load was significantly reduced in 18-month-old Tg2576 AD mice after 6 months of ACE inhibition compared to untreated age-matched Tg2576 controls [32].

These findings are complemented by other studies, which also showed that central ACE inhibition retards symptoms of neurodegeneration, reduces Abeta accumulation and improves cognition in experimental models of AD [32,58–60]. The underlying neuroprotective mechanism could involve the reduced generation of reactive oxygen species, which is triggered by AT1 receptor activation [32]. Other experimental data confirm that central ACE inhibition-mediated neuroprotection can be attributed to attenuation of oxidative stress and downregulation of extracellular superoxide dismutase [35]. In addition, ACE inhibition could retard brain aging by suppression of pathologic pro-inflammatory astroglial activation mediated by angiotensin II AT1 receptor activation [35,134,135]. The CUMS model with early symptoms of early sporadic AD delineated that ACE inhibition dampens glutamate excitotoxicity and mediates a decrease in hippocampal PHF tau hyperphosphorylation (Fig. 4; [33]). Additional neuroprotective activities of ACE inhibition are conceivable, e.g. those mediated by an increased availability of bradykinin, which could exert neuroprotection by stimulation of the bradykinin B2 receptor [136]. Although, further studies are needed to address this possibility. Apart from bradykinin, ACE inhibition also promotes the accumulation of angiotensin 1–7 (Fig. 1; and [52]), which could improve cerebral blood flow upon activation of the AT1-inhibitory MAS1 and promote neuro-regeneration by stimulation of the AT2 receptor [50,51,137].

Taken together, treatment with a centrally acting ACE inhibitor retarded the development of major AD-related neuropathologic features in the hippocampus of experimental models of FAD and sporadic AD, i.e. tau hyperphosphorylation, glutamate excitotoxicity and Abeta accumulation [32,33]. These neuroprotective effects of centrally active ACE inhibitors could be attributed to inhibition of angiotensin II AT1 receptor activation, because angiotensin II-induced AT1 receptor activation is known to promote PHF tau hyperphosphorylation and enhance glutamate excitotoxicity in vivo [138–140]. AT1-inhibitory

effects of ACE inhibitors could finally account for a decrease in Abeta accumulation because the synergistic interplay between AT1 receptor-mediated ROS generation [32,35], AT1 receptor-triggered PHF tau phosphorylation and glutamate excitotoxicity enhances Abeta-generation by increased activation of Abeta-generating beta- and gamma-secretases (Fig. 4; and [141–143]).

From our data, a vicious circle was deduced, which consists of ACE-mediated angiotensin II generation and ensuing activation of the neurodegenerative and Abeta-enhancing AT1 receptor (Fig. 4).

7. ACE inhibition retards symptoms of neurodegeneration in the chronic unpredictable mild stress (CUMS) model, which recapitulates features of sporadic AD

The Tg2576 AD model and other genetic AD models with transgenic expression of mutated APP variants isolated from FAD patients recapitulate major features of early-onset, familial Alzheimer`s Disease, FAD [8,9]. In contrast to FAD with inherited gene mutations, which ultimately cause the disease, AD-causing genetic changes usually do not occur in patients with late-onset sporadic AD, which affects more than 95% of all AD patients [144–146]. Therefore, we searched for a non-genetic model of AD and applied the chronic unpredictable mild stress (CUMS) model to reproduce features of sporadic AD [33]. Four weeks of chronic unpredictable mild stress induced major features of sporadic AD such as an increased hippocampal content of hyperphosphorylated PHF tau and the enhanced generation of Abeta [33]. This neurodegenerative phenotype is only observed in aged rats at an age of 15 months, whereas young rats are insensitive to stress and do not develop these features of neurodegeneration [33,124]. Thus, the CUMS model develops an ageing-dependent phenotype of neurodegeneration, which closely resembles the late-onset sporadic form of AD, for which age is the best-established risk factor [1,147].

When we applied the CUMS model with features of sporadic AD, we found that CUMS up-regulated the hippocampal ACE protein and ACE activity in aged rats [33]. Concomitantly, chronic unpredictable mild stress induced a neurodegenerative hippocampal gene expression signature, which was documented by the down-regulation of microtubule-associated protein, MAP2, and synuclein gamma [33]. In addition, glutamate excitotoxicity was enhanced by stress as evidenced by a decrease in glutamate decarboxylase activity, and down-regulation of the inhibitory NMDA receptor subtype, *Grin3a* [33], which is neuroprotective and could counteract glutamate excitotoxicity [148,149]. The up-regulated ACE level contributed to this neurodegenerative process because captopril prevented these symptoms of neurodegeneration [33].

Despite Abeta plaque load, most genetic AD models do not develop overt neuronal loss, which is the major hallmark of AD in patients. To enhance the process of neurodegeneration, we subjected aged Tg2576 AD mice to the CUMS protocol [125,126]. Chronic mild stress increased the hippocampal content of hyperphosphorylated PHF tau in aged Tg2576 AD mice [125]. Concomitantly, aged Tg2576 AD mice subjected to CUMS, showed a significant neuronal loss in the hippocampal CA1 region [125]. This finding is relevant to the human disease, because neuronal loss in the hippocampal CA1 region occurs early in AD progression and accounts for major symptoms of dementia [150,151].

Taken together, we found a causal relationship between increased ACE-dependent generation of angiotensin II, and the development of major AD symptoms (Fig. 4). A hypersensitive HPA axis with increased vulnerability to stress was identified as trigger for neuronal ACE in experimental AD models (Fig. 4). Because an increased sensitivity towards psychosocial stress is also an established risk factor of AD in patients [127,128], our data from experimental models of FAD and sporadic AD could be of major relevance for the human disease.

8. Translation of our findings from experimental models into clinical practice

The relevance of our findings for AD patients is currently under investigation. Several clinical data already have shown that inhibition of ACE retards the process of neurodegeneration leading to dementia and the incidence of AD [111–116,152]. Data from clinical practice confirm that the neuroprotective activity is linked to centrally acting ACE inhibitors [111–116,152]. The effect of central ACE inhibition leads to reduced activation of the AT1 receptor; in fact, the neuroprotective effects of centrally acting AT1 receptor antagonists appear to be even stronger [112]. A recent study determined the treatment effect of centrally acting ACE inhibitors as add-on therapy to an acetylcholinesterase inhibitor in AD patients. Outcome data of this study show that a centrally acting ACE inhibitor could improve AD dementia symptoms for about 9 months after diagnosis of AD, compared to the treatment with a non-centrally acting ACE inhibitor, which led to a deterioration of cognitive function [116]. This is a remarkable success considering that the last drug approval for AD, i.e. memantine, was about 15 years ago. Although, ACE inhibitors do not cure AD, the significant improvement of symptoms of dementia with these within 9 months is a much better outcome compared to the one with Abeta-targeting approaches in phase III clinical trials, which did not find any measurable effect on AD symptoms [15–22]. A recent overview of all clinical trials of amyloid-beta-targeting therapies for Alzheimer disease supports this conclusion [153]. Even if there are still Abeta-targeting drug candidates with apparently promising results in early stages of clinical development, the failure of all amyloid-beta-targeting compounds in large clinical trials during the past 20 years does not leave much room for expectations to achieve substantial clinical benefit with the amyloid-beta-targeting approach in the future [153]. Instead, efforts could be redirected to interfere with modifiable risk factors, as it is achieved, e.g. by ACE inhibitors and AT1 receptors antagonists, which target virtually all major risk factors of AD. Consequently, centrally acting ACE inhibitors (captopril, fosinopril, lisinopril, perindopril, ramipril, trandolapril) and/or AT1 receptor antagonists could be considered for prevention of neurodegeneration and dementia in patients at risk [36,116]. Finally, the neuroprotective targets discovered by our studies with ACE inhibition, could be exploited to develop urgently needed AD therapeutics in the near future.

Declarations of interest

None.

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