

Review Article

Interactions between oestrogen and the renin angiotensin system - potential mechanisms for gender differences in Alzheimer's disease

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Abstract: Interactions between oestrogen and the renin angiotensin system (RAS) are reviewed and explored from the perspective where these interactions may modulate risk of developing Alzheimer's disease (AD). AD is more prevalent in women than men, partly attributed to women's increased life expectancy; however underlying vascular differences may also contribute to AD risk. The RAS is a key regulator of blood pressure (BP). Pharmacological inhibition of angiotensin converting enzyme (ACE) and blockade of angiotensin II type 1 receptors (AT1R) are widely used to treat hypertension. Variation in components of the RAS such as ACE, neprilysin (NEP) and AT1R have been reported in AD, some of which may also directly alter AD neuropathology with changes in amyloid beta (A β) levels, cognitive decline and neuroinflammation. Recently, RAS inhibiting drugs have been shown to attenuate the incidence, progression and pathology of AD. Oestrogen is also thought to prevent hypertension by reducing the vasoconstrictive actions of the RAS. Reduced oestrogen levels in women during the menopausal transition may therefore increase their risk of hypertension and/or RAS-mediated changes to cerebrovascular or AD pathology. Specifically, oestrogen prevents the production and action of angiotensin II (Ang II), thought to exert harmful effects of the RAS in both hypertension and AD, while also potentially facilitating RAS-mediated A β degradation. These oestrogen-RAS interactions may partly explain current conflicting findings regarding oestrogen depletion and hormone therapy with respect to AD risk. Clinical trials targeting either the RAS or oestrogen systems for AD prevention and treatment should perhaps give closer attention to key biochemical components of these pathways as potential confounders to primary and secondary outcome measures.

Keywords: Oestrogen, renin angiotensin system (RAS), gender difference, Alzheimer's disease

Introduction

Alzheimer's disease (AD) is the most common form of dementia [1]. An estimated 26.6 million people worldwide have AD, with numbers expected to quadruple by 2050 [2]. Midlife vascular risk factors including hypercholesterolemia and hypertension increase the risk of AD in later life. Anti-hypertensive drugs show promise in helping prevent or treat AD [1].

This paper reviews how oestrogen levels fluctuate and decline throughout a woman's life, focussing on how these changes relate to the renin angiotensin system (RAS) and the impact of reversing oestrogen depletion via hormone

therapy (HT). The RAS is implicated in AD, and hence post-menopausal oestrogen depletion may contribute to RAS-mediated gender differences in AD development. Inhibition of RAS and oestrogen pathways will be discussed and the resultant implications for future treatment of AD.

The amyloid component of AD

The peptide amyloid beta (A β) is formed from sequential cleavage of the amyloid precursor protein (APP) by β - and γ - secretases [3]. The most common isoforms of A β are A β ₁₋₄₀ and A β ₁₋₄₂ (the numbers refer to the number of constitutive amino acids) [3]. The accumulation of A β in

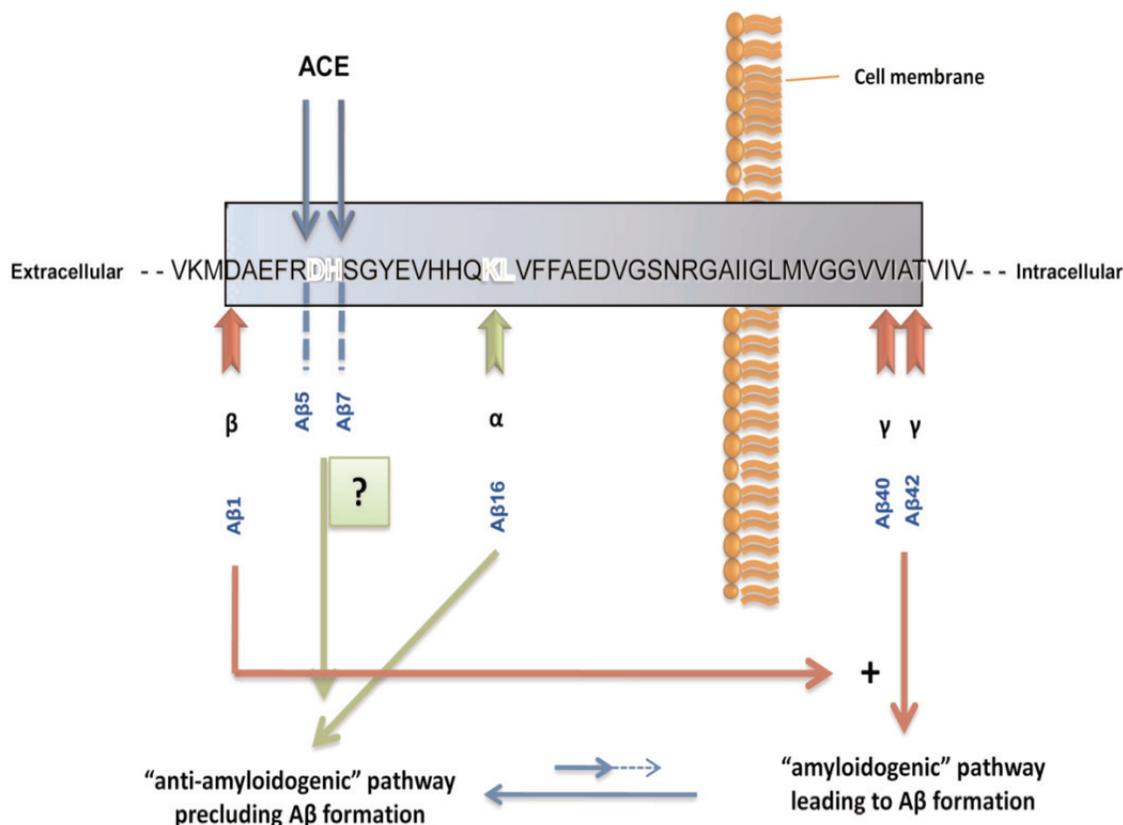


Figure 1. Formation of A β from APP. A β formation is determined by α -, β - or γ - secretase cleavage of APP. Equilibrium throughout life is disrupted in AD, with increased β - secretase processing. A β is initially produced as a soluble monomer, but can combine with other monomers to form multimeric complexes of varying solubility before forming insoluble fibrils. Sites of secretase and ACE cleavage of A β are shown. Taken from [3].

late onset AD is likely due to A β clearance dysfunction rather than A β overproduction.

Throughout life, soluble A β levels decrease and insoluble A β levels increase. In AD, both soluble, oligomeric and insoluble A β levels increase, particularly the A β_{1-42} variant, which leads to the formation of AD senile plaques [4]. A β (mainly A β_{1-42}) is also toxic to neuronal cells, partly due to induction of reactive oxygen species and inflammation as well as apoptosis of neurones via tumour necrosis factor (TNF) type I receptor signalling and intracellular calcium level disruption [5, 6].

Enhanced β -secretase activity on APP gives rise to increased insoluble and decreased soluble A β formation which has been shown in AD [4]. Yet numerous enzymes including neprilysin (NEP) and ACE degrade A β (Figure 1). Changes to the activities of these A β degrading enzymes

(ADEs) are likely to alter the pathology of AD [7].
The Renin Angiotensin System (RAS)

The RAS (see Figure 2) is best known for maintaining blood pressure (BP) through water and electrolyte balance, and preservation of vascular tone [8]. Vasoconstrictive properties of RAS are mediated by Ang II acting on the angiotensin type 1 receptor (AT1R) and angiotensin type 2 receptor (AT2R). Ang II binding to AT1R promotes vasoconstrictive (i.e. pro-hypertensive) responses, which AT2R (vasodilatory) binding counters [9]. The AT1R is also important in cell proliferation, hypertrophy, generation of oxidative radicals and inflammation [9, 10]. The long-standing view of a single circulatory RAS (cRAS) has more recently been replaced by acceptance of numerous organ based systems, including the brain RAS [9].

Angiotensins, like A β , may affect memory forma-

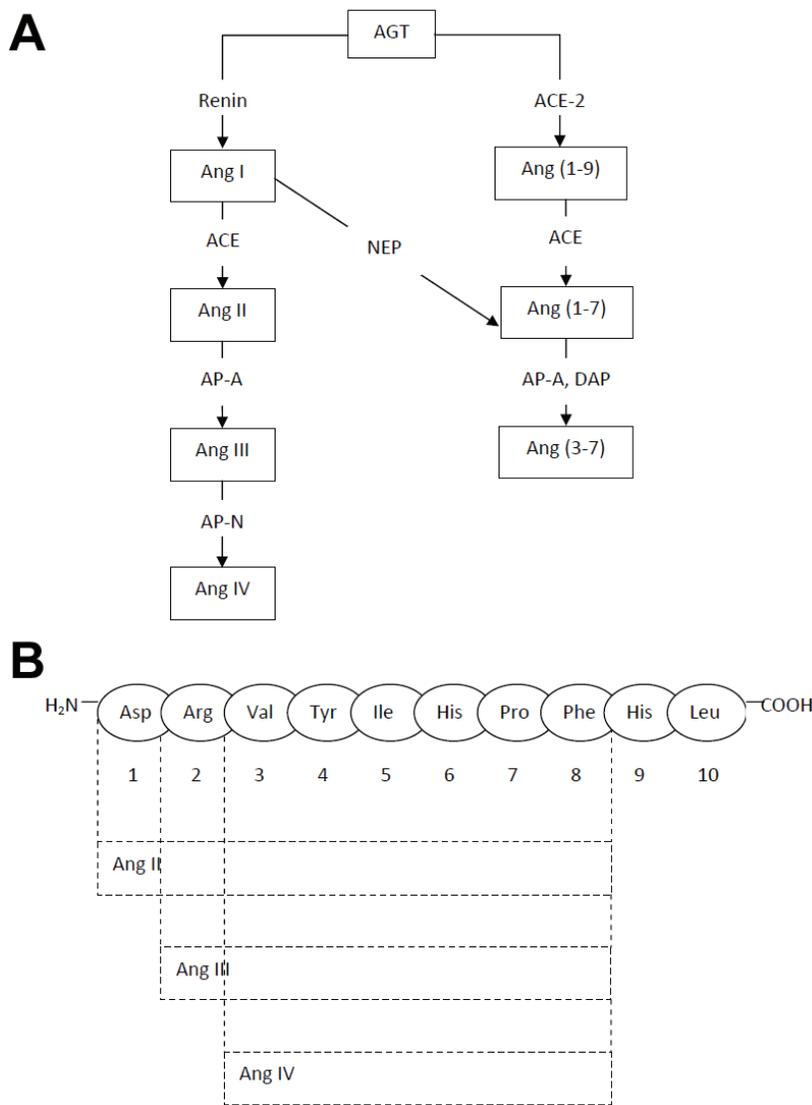


Figure 2. Angiotensins in the RAS. (A) Schematic of the RAS pathway. In the vasoconstrictive arm, Ang I is cleaved from angiotensinogen (AGT) by renin. Ang II is produced from Ang I by ACE. Ang II acts as a vasoconstrictor while ACE-2 cleavage of AGT and in turn the eventual production of Ang (1-7) works to vasodilate and oppose the actions of Ang II. Ang=angiotensin; AP-A=aminopeptidase-A; AP-N=aminopeptidase-N; DAP=dipeptidyl aminopeptidase. Not all intermediary metabolites and enzymes are shown. (B) Schematic of angiotensins (including their amino acid composition) derived from the cleavage of the decapeptide Ang I at various amino acid positions. Adapted from [80, 86].

tion. Both Ang II and angiotensin III (Ang III) inhibit long term potentiation (LTP), however angiotensin IV (Ang IV) enhances LTP [11]. A role of Ang IV in memory formation and recall is also supported by high densities of the Ang IV receptor (also known as insulin-regulated aminopeptidase (IRAP)) in the hippocampus, amygdala and

prefrontal cortex [12]. IRAP agonists improve spatial learning, whereas antagonists cause noticeable cognitive deficits [13].

Oestrogen levels fluctuate throughout life

Multiple factors contribute to the increased incidence of AD in women, including longevity and oestrogen decline during the peri- and post-menopausal transition [14, 15]. With increasing life expectancy, a third of women’s lives are now spent in a post-menopausal, low oestrogen state [16].

Prior to menopause oestradiol (E2) is the predominant circulating oestrogen (Figure 3). At menopause, E2 levels fall precipitously to approximately 10% of premenopausal levels, while levels of oestrone (E1) decline to a lesser extent [17]. E1 and E2 continue to be synthesized by peripheral conversion of adrenal androstenedione and aromatization of testosterone, causing a shift in the E1/E2 ratio with E1 becoming the predominant oestrogen post-menopause [18].

Oestrogen and the RAS

Hypertension is more prevalent in men than in women pre-menopause, but this pattern changes during the menopausal transition [19, 20]. This is partly due to the ability of oestrogens to reduce hypertensive effects of the RAS [21, 22].

Effects on RAS-mediated vasoconstriction

Oestrogen affects AGT gene expression and synthesis through modulation of regulatory elements in the gene promoter [23, 24]. This in-

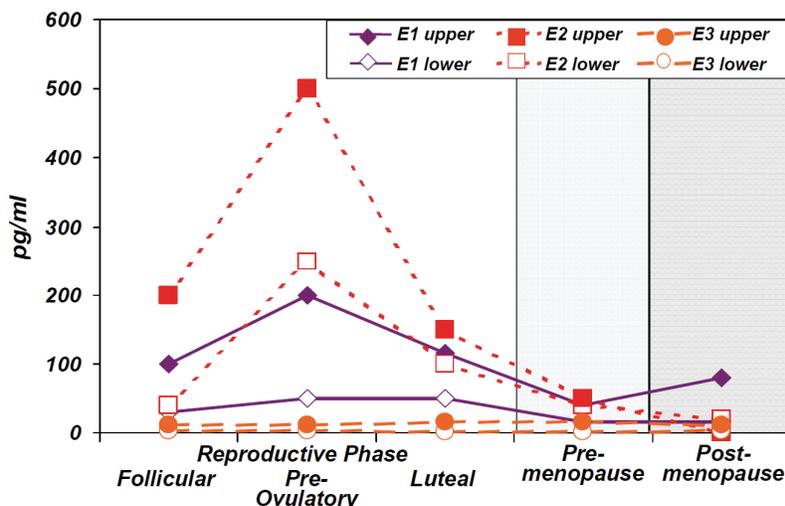


Figure 3. Monthly fluctuations of endogenous oestrogen levels. Oestrogenic fluctuations across the menstrual cycle and the post-menopausal state are shown such that E1 becomes the predominant oestrogen post-menopause. Taken from [108].

increases the concentrations of AGT found in women [25]. Promotion of AGT is countered by a number of downstream mechanisms to prevent hypertensive effects.

Conflicting evidence surrounds oestrogen and renin. Pre-menopausal women exhibit lower renin levels than both their post-menopausal counterparts and men [21]. While oestrogen can interfere with regulatory elements in the renin gene promoter in a similar fashion to AGT, the gene expression of renin may be controlled to a larger extent by β -adrenergic stimulated rises in cyclic adenosine monophosphate (cAMP) [21, 26]. Oestrogen decreases circulating adrenaline and noradrenaline, which may therefore indirectly decrease plasma renin concentrations [21].

E2 attenuated ACE activity *in vivo* [22]. In humans, age-related decreases in ACE activity in girls between 8 and 18 years have been reported, possibly caused by inhibition of ACE mRNA [27].

The net effect of E2 on Ang II is unclear [28, 29]. While AGT levels may increase, renin and ACE activities are reduced by oestrogen. The rate of Ang II synthesis may be dependent on the extent of renin and ACE inhibition over the rise in AGT.

Oestrogen also downregulates AT1R gene expression in rats [30-32]. Additionally, oestrogen sensitive binding proteins are thought to post-transcriptionally regulate AT1R mRNA [33].

These two mechanisms allow oestrogen to attenuate AT1R responses to Ang II. Indeed, the vasoconstrictor response in the aortic rings and mesenteric vessels to Ang II is weaker in women [32].

Effects on RAS-mediated vasodilation

AT2R and ACE-2 have been mapped to the X chromosome, providing scope for gender differences [34, 35]. AT2R mRNA expression is raised during oestrous of spontaneously hypertensive rats (SHRs) and increased ACE-2 expression in response to oestrogen is suggested [32]. Oestrogen increases circulating Ang (1-7), with female SHRs particularly sensitive to its vasodilatory effects [19, 36]. Oestrogen may augment the effect of Ang (1-7) further by facilitating nitric oxide (NO) and prostaglandin release [19, 36]. NEP protein level and activity is also substantially elevated in female hypertensive and control models, suggesting preferential NEP derived Ang (1-7) effects may occur in women [28]. Although beyond the scope of this paper, it is noteworthy this picture is complicated with the crossover of the RAS and the kallikrein-kinin system, with NEP able to degrade the vasodilator bradykinin [37]. However, additional evidence suggests that oestrogen may serve to restore any bradykinin-related changes to vascular tone resulting from upregulation of NEP by enhancing the vasodilatory effect of bradykinin [38].

Thus, while oestrogen increases AGT synthesis,

the attenuation of renin and ACE results in an overall downregulation of the RAS. Although there remains ambiguous data on Ang II levels, its vasoconstrictive actions are reduced due to oestrogen-associated decreases in AT1R and increases in AT2R production. Further vasodilatory effects of oestrogen on the RAS may derive from NEP increases with downstream Ang (1-7) action but it is noteworthy there are possible additional bradykinin-related changes to the vasculature.

Oestrogen throughout life

Menstrual cycle

The menstrual cycle is characterized by cyclic changes in oestrogen which peak during the luteal phase and decline in the follicular phase [39]. In rats, brain AGT secretion correlates with oestrogen fluctuations in the ovarian and peripheral plasma [40]. Despite the activation of some RAS components in the luteal phase, increases in plasma Ang II and increase in BP are not apparent [41, 42]. Instead there is decreased peripheral vascular resistance, suggesting a reduced response to Ang II, which may reflect oestrogen-mediated effects on ACE activity, AT1R and AT2R expression, as well as augmenting NEP and its associated vasodilatory responses. Thus oestrogen can contribute to regulation and fine tuning of BP via specific actions on mediators of the RAS and their receptors. This well evolved system maintains homeostasis throughout the reproductive life of a woman.

Menopause

The loss of oestrogens during menopause is associated with increasing BP such that elderly women are more likely to be hypertensive than age matched men [20, 43]. Animal models suggest that post-menopause, the behaviour of the RAS is opposite to that seen pre-menopause.

Effects on RAS-mediated vasoconstriction

Ovariectomised rats have lower AGT in hypothalamic and thalamic regions [40]. This should contribute to an overall lowering of BP, but increased BP is seen which may be partly due to increased sympathetic drive and renin release from postmenopausal weight gain [44]. Downstream feedback mechanisms in the RAS, such as increased ACE activity and binding densities

could also be involved [45].

Despite increased BP in menopause, plasma Ang II levels appear to be paradoxically reduced [44]. This may be explained by an alteration in the AT1R:AT2R ratio, promoting AT1R binding. Indeed, AT1R binding density post ovariectomy is increased with subsequent enhanced vasoconstriction [32, 45].

Data from human studies support *in vivo* findings. In post-menopausal women, AGT levels are significantly lower due to reduced oestrogen-mediated modulation of the AGT promoter [25]. Renin levels are also significantly lower in HT users and men, suggesting oestrogen loss raises renin levels and promotes vasoconstriction [21].

Effects on RAS-mediated vasodilation

Post-menopausal oestrogen loss causes reduced AT2R with an associated raised risk of hypertension [32, 46]. There is also RAS-mediated downregulation of vasodilators including atrial natriuretic peptide (ANP) and NO [44].

The vasodilatory arm of the RAS is generally suppressed with loss of oestrogens decreasing ACE-2 activity and protein expression in hypertensive rats [47]. The decrease in ACE-2 protein is likely due to a loss of oestrogen-mediated transcription of ACE-2 [47].

Overall, the menopausal decline in oestrogen counters vasodilatory effects seen in the RAS pre-menopause. Although there is decreased AGT synthesis, this is countered by increases in: renin levels; ACE activity; vasoconstrictive effects of Ang II via increased AT1R and decreased AT2R expression; as well as reduced vasodilatory responses through decreased ACE-2 activity and protein expression.

Hormone therapy

Hormone therapy (HT) is used to reduce symptoms associated with decreases in E2 such as osteoporosis, coronary heart disease, hot flushes and mood disturbances [16, 48]. Some evidence suggests that HT in women reduces AD risk [49]. After menopause, the predominant form of oestrogen is E1; thus, for HT to mimic premenopausal physiology, it is necessary to administer E2. However, many clinical studies evaluating the therapeutic efficacy of HT in

healthy older women, (i.e. the Women's Health Initiative), used conjugated equine oestrogen (CEE), a preparation rich in E1. In general, studies utilising E2 formulations of HT, particularly when administered during the menopausal transition, have shown a beneficial cognitive effect in comparison to studies utilising E1 preparations [50].

Effects on RAS-mediated vasoconstriction

Oral HT induces a hepatic first pass effect-mediated increase in plasma AGT [51].

Transdermal oestrogen increases total blood renin, probably at the level of gene expression [26, 52]. However this increase in total blood renin is not accompanied by increases in active renin or plasma renin activity [52]. Suppression of β -adrenergic activity is a potential explanation for this discrepancy [21, 52]. Increases in Ang II may further attenuate renin secretion, acting as negative feedback on the RAS [53]. Thus, oral HT stimulates the renin substrate AGT, while transdermal and oral HT downregulate the conversion of AGT to Ang I by inhibiting the rate-limiting step of the system.

Animal studies show that high E2 concentrations reverse and prevent the effects of ovariectomy on ACE activity in the periphery and heart [19, 45, 54]. Oestrogen therapy also reduced ACE gene expression, and therefore decreased ACE activity [22]. Indeed, in monkeys, oral oestrogen increases Ang I, but not Ang II [54].

Oestrogen alters the balance of AT1R:AT2R, lowering AT1R expression in vascular smooth muscle cells, the hypothalamus, adrenal cortex, and kidney [31, 53, 55]. Oestrogen also lowers AT1R binding [45, 56]. Oestrogen may directly interfere with AT1R gene transcription via modulation of oestrogen response elements and activator protein-1 (AP-1) [31, 32]. Oestrogen-mediated increases in NO is another proposed mechanism to downregulate AT1R expression [57, 58].

Effects on RAS-mediated vasodilation

In female mice undergoing HT, AT2R gene expression and binding is upregulated [32, 46, 59]. The mechanisms of action of oestrogen on the AT2R are equivocal – there is no oestrogen response element on the AT2R promoter so altered expression may be via influences on AP-

1, or by inhibition of Na⁺, K⁺-ATPase [46].

Oestrogen administration increases Ang (1-7) in transgenic animals [19]. Promoting Ang (1-7) lowers BP by preventing the retention of sodium ions, thus countering the effects of Ang II. Oestrogen increases Ang (1-7) relative to Ang II, possibly by inhibiting ACE activity [19]. It is also possible Ang (1-7) levels increase due to oestrogen effects on ACE-2.

In animal models of oestrogen replacement there were increases in ACE-2 and NEP activity [47]. However, in the renal cortex of mRen(2). Lewis rat models of hypertension, as well as in normotensive Lewis controls, ACE-2 activity was higher in males [28]. Conversely, Ang (1-7) is significantly higher in females, with amplified depressor effects in the presence of oestrogen [19, 28]. Changes to Ang (1-7) levels likely reflect subtle shifts between ACE, NEP and ACE-2.

Oral and transdermal HT decrease systolic and diastolic BP, which is likely explained by the effects of oestrogen outlined above [43]. The effects of HT largely mimic those of endogenous oestrogen. Discrepant findings are likely due to methodological differences, such differential HT formulation and administration [51]. HT increases plasma AGT synthesis with oral administration, however there is reduced plasma renin activity due to indirect inhibition of β -adrenergic activity and ACE activity. There is limited evidence of an effect of HT on Ang II, however reported decreases in AT1R and increases in AT2R expression and binding have a net effect of reducing vasoconstriction. Conversely, vasodilation is upregulated via increases in Ang (1-7), possibly due to raised ACE-2 or NEP activity or inhibition of ACE. The Kronos Early Estrogen Prevention Study (KEEPS) however, did not show a significant relationship between blood pressure and either CEE or transdermal E2, in recently menopausal women over the 4 year clinical trial [60]. Additional follow up data is required to elicit longer term effects which may support animal models.

Relevance to AD

The brain RAS and communication with the cRAS

The brain RAS contains molecules present in the cRAS including AGT, renin, ACE and Ang II. The brain RAS regulates hormone release, cen-

tral and peripheral BP, water and sodium levels and sympathetic nerve activity [61].

The cRAS and brain RAS communicate possibly by AT1R activation or via the circumventricular organs [61, 62]. AGT is synthesised by astrocytes and its production may be enhanced by increased systemic Ang II binding to the AT1R on brain vessels [63]. This is supported by observed reductions in AGT, ACE mRNA expression and Ang II in response to Angiotensin Receptor Blocker (ARB) treatment. The cRAS may also influence the gene expression of the brain RAS [64].

Hypertension and A β

Hypertension is a major risk factor for cognitive dysfunction and subsequent AD [65]. Reduced cerebral blood flow is one explanation where hypoxia can directly affect β -secretase regulation, raising A β ₁₋₄₀ and A β ₁₋₄₂ levels and possibly promoting tangle formation [66, 67].

Ang II, the blood brain barrier (BBB) and inflammation

Sustained hypertension can disrupt the normal separation of molecules from the vasculature and brain. Ang II may directly cause BBB leakage via AT1R and promote the entry of immune cells to the brain, activating resident microglia and astrocytes, features common to AD [68-70]. BBB dysregulation also releases cytokines such as TNF- α and interleukin-6 (IL-6), enhancing inflammatory processes resembling AD [71].

A secondary role of Ang II is as a pro-inflammatory mediator of increased vascular permeability, ROS formation, recruitment of inflammatory molecules and tissue repair remodelling [69, 72]. Ang II causes upregulation of NF- κ B, a transcription factor that maintains an immune response via pro-inflammatory cytokine release and adhesion molecules such as VCAM-1 and ICAM-1 [73, 74].

Since oestrogen downregulates AT1R expression, thereby attenuating the response to Ang II, menopausal oestrogen loss may exacerbate BBB permeability and thus be a potential risk factor for AD [30-33, 45].

Anti-hypertensive drugs, ACE and AD

Many large-scale studies have shown that anti-

hypertensive drugs reduce dementia incidence and progression [75-77]. Beyond cardiovascular benefits, there is now a theoretical BP-independent mechanism of cognitive improvement involving blocking the formation of Ang II, thereby reducing inflammatory responses and maintaining BBB integrity [78, 79].

Ang II-targeting anti-hypertensives, ACE-inhibitors (ACE-Is) as well as ARBs, may also counter the extent to which Ang II inhibits acetylcholine (ACh) release [80, 81].

For ACE-Is, cognitive benefits are dependent on whether they cross the BBB, for example captopril and perindopril (centrally acting drugs). Non-centrally acting drugs such as enalapril and imidapril have shown no effect and in some instances, may increase the risk of dementia compared to participants not taking anti-hypertensives [78, 82]. However for ACE-Is, there may be a caveat. Increased ACE levels have been correlated with decreased A β aggregation, fibril formation, deposition and cell survival [83]. Thus ACE-I mediated benefits on cognition via inhibition of Ang II may coincide with adverse elevations of A β . As yet, definitive evidence of ACE mediated degradation of A β is lacking, although recent findings show how long term exposure of people to ARBs has a very positive effect on AD-related pathology [84]. Incidentally, women who have lower (gene-variant associated) circulating ACE levels are at increased risk of developing AD [85].

There are possible explanations for these unresolved discrepancies. Firstly, centrally acting drugs may reduce brain Ang II and hence increase ACh release [86]. Secondly, central inhibition of Ang II increases cerebral perfusion [87]. Thirdly, inhibition of Ang II formation by ACE-Is raises Ang I, potentially favouring increased production of the vasodilators Ang (1-9), Ang (1-7) and Angiotensin (3-7) (Ang (3-7)) [88]. Ang (3-7) activates the AT4 receptor, which potentiates potassium-mediated ACh release and hence improves cognition [88]. Fourthly, there are increased concentrations of ACE, and Ang II and AT1R in the parietal cortex of AD brain [89]. ACE upregulation may thus act as a compensatory response to control A β levels which ACE-Is (but not ARBs) could interfere with [90, 91]. Hence, the menopausal loss of oestrogen and subsequent increase of ACE activity may predispose women to cognitive decline in later life [45].

ARBs therefore may have a lot to offer in AD. Not only do they reduce BBB permeability, they also prevent the potentially harmful effects of angiotensin II by selectively targeting AT1R and do not interfere with ACE [92].

The effect of ARBs on cognition have been proposed, as with ACE-Is, to be partly independent of their anti-hypertensive action [93]. ARBs are marginally less effective than ACE-Is at combating cardiovascular disease, but may be more effective in prevention of AD [94, 95]. This differential effect may be due to the interaction of ACE with A β . Furthermore, blockage of Ang II binding may aid greater Ang IV formation which can lead to further cognitive enhancement, particularly in executive function [88, 96].

Although ACE-Is and ARBs co-administered have been shown to offer the greatest protection from dementia due to their additive effect, such co-prescribing is now thought to be deleterious because of renal complications [94]. Ang IV analogues may also be useful, given their ability to enhance cognition, however, as yet these molecules are too large and hydrophobic to cross the BBB and are rapidly degraded by aminopeptidases [88]. Efforts to correct this are currently underway [12].

NEP and AD

NEP is important in the RAS as it modulates vasodilation via changes to Ang I and bradykinin. However, NEP also degrades monomeric and oligomeric forms of A β ₁₋₄₀ and A β ₁₋₄₂ [97]. *In vivo* NEP deficiency coincides with raised A β , particularly in the hippocampus [98, 99]. Examination of post-mortem normal and AD patients supports this, with an age related decline in NEP protein levels that inversely correlates with increasing A β [100].

Females have increased NEP protein and activity [28]. In human and animal models, oestrogen levels are proportional to NEP activity. Oestrogen deficiency decreases NEP activity, which is reversed by HT [101, 102]. The regulation of NEP by oestrogen appears to be dependent on its receptors ER- α and ER- β . Once these receptors are activated it is proposed NEP mRNA transcription is induced [102]. This therefore provides a mechanism for oestrogen-mediated A β degradation in pre-menopausal women which is lost later in life.

It should also be noted Miners et al. (2010) reported NEP increases throughout life, and, after adjusting for neuronal loss, NEP activity was increased in AD [4]. This may however, like with ACE, be a compensatory upregulation to try to limit the extent of A β pathology. More recently, the same group report NEP may protect against the occurrence of cerebral amyloid angiopathy (the deposition of A β in blood vessel walls) [103].

Therapeutic potential of Oestrogen in AD?

Oestrogen could have potential as a therapy to treat or reduce the incidence of AD. Oestrogen levels fluctuate through reproductive life (**Figure 4**) but drop off markedly around mid-life which coincides with the timeframe in which the earliest stages of AD are thought to take root [104] and which may increase women's vulnerability to developing the disease and how oestrogen supplementation may be of therapeutic benefit [105]. An important consideration remains the risk of endometrial carcinoma and breast cancer which must be considered when contemplating oral formulations [102]. The cancer risk is thought to be mediated through ER- α , and therefore ER- β specific drug targets have more potential [106]. Although ER- β is able to independently regulate NEP expression, many benefits of oestrogen on the RAS may be through ER- α [102, 107]. Gene therapy also offers possibilities. Using lentivirus vectors to deliver NEP into mice cells already expressing human APP and secreting A β had a marked decrease in extracellular A β ₁₋₄₂, while cells expressing NEP were less susceptible to A β mediated cell death. These effects of NEP were also observed *in vivo* [98].

Concluding remarks

The RAS is a complex interaction of vasomodulatory molecules which regularly interact and are partly regulated by oestrogen. The effect of oestrogen may protect against AD by inhibiting Ang II levels (via ACE) and stimulating NEP which could minimise the development of A β pathology. The ability of oestrogen to interfere with Ang II signalling may protect the vasculature from pro-inflammatory and hypoxic damage, although the role of bradykinin is as yet unclear. We propose that changes in the modulation of RAS molecules between pre- and post-menopause could alter the risk of hypertension and AD in women compared to men. These

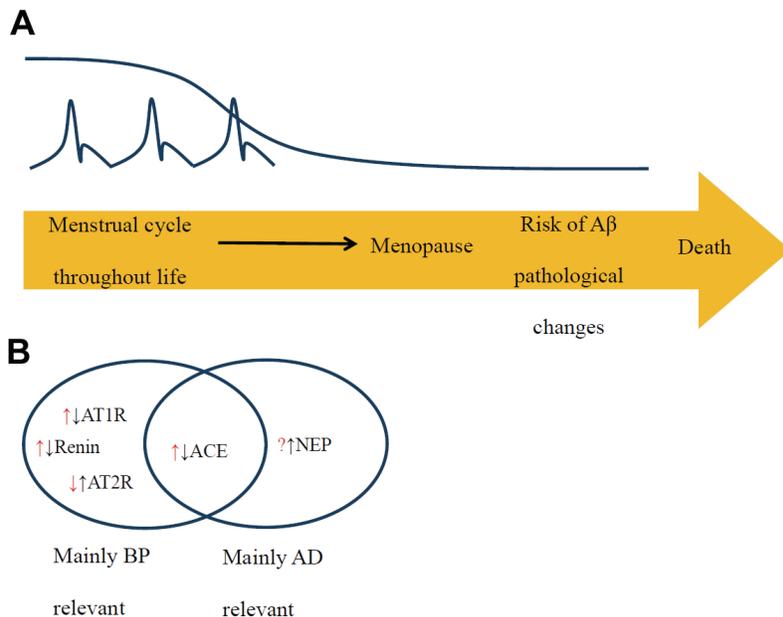


Figure 4. Fluctuations of endogenous oestrogen levels throughout life and proposed interactions between oestrogen and both blood pressure and Alzheimer's disease. (A) Shows the changes of oestrogen throughout life and illustrates how oestrogen oscillates throughout a woman's reproductive life, as well as the overall gradual decline in the hormone as women age. (B) The Venn diagram shows the key changes oestrogen has on the RAS and the overlap between effects on BP and AD. The red arrow indicates the change post-menopause, and the black arrow the effect of oestrogen.

mechanisms may go some way towards explaining the higher incidence and prevalence of AD seen in women. Additionally, the complex interaction of the RAS with both BP and Aβ degrading enzymes may explain why there has been variance in the outcomes of clinical trials conducted to date of HT for the prevention of AD.

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