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Endothelin receptor antagonists: Potential in Alzheimer's disease

Jennifer Palmer*, Seth Love

Dementia Research Group, Institute of Clinical Neurosciences, School of Clinical Sciences, University of Bristol, Frenchay Hospital, Bristol BS16 1LE, United Kingdom

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ABSTRACT

Alzheimer's disease (AD) is believed to be initiated by the accumulation of neurotoxic forms of Aβ peptide within the brain. AD patients show reduction of cerebral blood flow (CBF), the extent of the reduction correlating with the impairment of cognition. There is evidence that cerebral hypoperfusion precedes and may even trigger the onset of dementia in AD. Cerebral hypoperfusion impairs neuronal function, reduces the clearance of Aβ peptide and other toxic metabolites from the brain, and upregulates Aβ production. Studies in animal models of AD have shown the reduction in CBF to be more than would be expected for the reduction in neuronal metabolic activity. Aβ may contribute to the reduction in CBF in AD, as both $A\beta_{1-40}$ and $A\beta_{1-42}$ induce cerebrovascular dysfunction. $A\beta_{1-40}$ acts directly on cerebral arteries to cause cerebral smooth muscle cell contraction. $A\beta_{1-42}$ causes increased neuronal production and release of endothelin-1 (ET-1), a potent vasoconstrictor, and upregulation of endothelin-converting enzyme-2 (ECE-2), the enzyme which cleaves ET-1 from its inactive precursor. ET-1 and ECE-2 are also elevated in AD, making it likely that upregulation of the ECE-2–ET-1 axis by $A\beta_{1-42}$ contributes to the chronic reduction of CBF in AD. At present, only a few symptomatic treatment options exist for AD. The involvement of ET-1 in the pathogenesis of endothelial dysfunction associated with elevated Aβ indicates the potential for endothelin receptor antagonists in the treatment of AD. It has already been demonstrated that the endothelin receptor antagonist bosentan, preserves aortic and carotid endothelial function in Tg2576 mice, and our findings suggest that endothelin receptor antagonists may be beneficial in maintaining CBF in AD.

Contents

1. Introduction

Alzheimer's disease (AD) is a progressive, degenerative disease of the brain that leads to deficits in cognitive function. Manifestations can include amnesia, aphasia, apraxia, agnosia and psychiatric symptoms such as depression, personality change, delusions and hallucinations. Sufferers experience difficulties in activities of daily living; as the disease progresses these include such basic tasks as dressing, feeding and toileting [1]. AD is the most common of the diseases that cause dementia, of which the estimated global prevalence in 2005 was 24.3 million people [2]. In the absence of effective prevention or curative treatments, this number is predicted to double every 20 years as populations age, to 81.1 million by 2040. About 43% of patients are estimated to need a high level of care equivalent to that in a nursing home [3]. There is clearly a pressing need to find interventions to delay disease onset and progression.

* Corresponding author at: University of Bristol, Dementia Research Group, John James Laboratories, The Day Hospital Frenchay Hospital, Bristol, United Kingdom.
E-mail address: jen.palmer@bristol.ac.uk (J. Palmer).

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2. Pathological findings in AD

The brain undergoes atrophy, reflecting a decrease in the volume of the cerebrocortical ribbon and cerebral white matter, resulting from shrinkage or death of neurons, loss of the dendrites and degeneration of nerve fibres [4–6]. In advanced disease there is neuronal loss from the hippocampus, entorhinal regions and neocortex [7]; the cornu ammonis (CA) can be as much as 66% smaller than normal in end-stage AD with over 80% loss of neurons [8]. Loss of neocortical synapses is a relatively early abnormality that progresses with AD severity [7,9–12].

The two 'hallmark' pathological lesions in the AD brain are the extracellular parenchymal deposits of Aβ peptide that form plaques and the intracellular aggregates of hyperphosphorylated tau protein that form neurofibrillary tangles (NFTs) [13]. Hyperphosphorylated tau also aggregates within nerve cell processes, as neuropil threads, and in most AD patients Aβ also accumulates in the walls of cerebral blood vessels, causing amyloid angiopathy (CAA) – present to some extent in over 90% of patients with AD and about one-third of elderly people who do not have AD [14]. After cleavage from its precursor, Aβ initially takes the form of a coiled single peptide but this tends to aggregate, resulting in a dynamic equilibrium of monomeric, dimeric, oligomeric, protofibrillar (soluble) and fibrillar (insoluble) states [15]. Although a diagnosis of AD requires, amongst other pathological abnormalities, the presence of Aβ plaques, which are predominantly made up of the insoluble fibrillar form, there is poor correlation between Aβ plaque load and cognitive impairment or neuronal loss [16,17]. The correlation between soluble Aβ and cognitive impairment is much stronger, suggesting that soluble species of Aβ are more toxic than fibrillar forms [17]. There is recent evidence from *in vitro* and *in vivo* studies that the major toxic species of Aβ are the soluble oligomeric forms [18–21]. Oligomeric Aβ is increased in brain tissue from AD patients [22–26], and correlates with cognitive impairment [23,25,27]. The size or conformation of oligomer may be critical in determining toxicity, in that soluble Aβ aggregates from AD cases were reported to be more toxic than soluble Aβ aggregates from age-matched controls [28]. Both Aβ and tau are normal constituents of the brain but have an abnormal insoluble fibrillary structure in AD. Physiological levels of Aβ probably have important physiological roles [29] but AD is believed to be initiated by the abnormal accumulation of Aβ peptide within the brain [30]. The amount of Aβ in the brain is determined by the balance between its production and clearance. Familial autosomal dominant forms of AD, which either increase overall production of Aβ or increase the ratio of $A\beta_{1-42}$:$A\beta_{1-40}$, account for fewer than 5% of cases. The mechanisms by which Aβ accumulates in late-onset sporadic AD (LOAD), the major form of the disease, are unknown. There is evidence of increased activity of the rate-limiting enzyme in Aβ synthesis, β-secretase (BACE-1) in LOAD [31–33] but animal studies suggest that this may, at least in part, simply be a reaction to the accumulation of Aβ [34]. Another possible explanation for the accumulation of Aβ in LOAD is an impairment of Aβ clearance. Several potential pathways of Aβ clearance have been identified. These include perivascular drainage [35,36], receptor-mediated transport across the blood–brain barrier [37,38] and proteolytic degradation of Aβ within the brain [39–41].

3. The cerebral vasculature in AD

The brain does not have the capacity to store significant energy reserves, thus its viability is dependent on a continuous supply of oxygen and glucose, delivered wholly by the blood. Blood flow is directed to the cerebral circulation at the expense of other regions when required [42]. Cerebrovascular autoregulation ensures that cerebral blood flow (CBF) remains independent of mean arterial pressure within a range of approximately 60–150 mm Hg [43]. This autoregulation is mediated by contraction of smooth muscle cells of cerebral vessels when intravascular pressure increases and relaxation when it decreases [44,45]. The distribution of CBF within the brain is regulated according to the activity of different brain regions. Neural activity increases the energy demands of the brain tissue, increasing the need for nutrient delivery and removal of toxic by-products of metabolism and heat by the circulating blood [46]. This is accomplished by increases in CBF which are highly restricted to the activated region and occur within seconds of the increase in neural activity [47–49], a phenomenon termed 'functional hyperaemia' [50] and requires neurons, astrocytes and vascular cells to work together as a neurovascular unit. Neurons that have axons or dendrites in contact with blood vessels, particularly interneurons, can rapidly communicate the need for increased blood flow by releasing vasoactive factors [51]. A direct link between functional hyperaemia and the activity of interneurons was shown by Iadecola et al. [52] in a study of blood flow in the cerebellar cortex. The increase in flow produced by stimulation of somatosensory fibres was markedly attenuated by inhibition or genetic deletion of neuronal nitric oxide synthase (NOS), present in high levels in interneurons [53,54]. The increase in CBF produced by activation of somatosensory fibres was also less in *cyclin D2*-null mice, which lack satellite interneurons [55].

There is evidence that vascular dysfunction and lowered CBF could be key factors in the development of AD, and may even trigger the onset of dementia [56]. AD patients have reduced CBF [57–62], the extent of the reduction correlating with the impairment of performance on mini-mental state examination [63–65]. Most cardiovascular risk factors (such as diabetes, hypertension, high cholesterol levels, atherosclerosis and obesity) are also risk factors for AD, suggesting an interrelationship between vascular and neurodegenerative pathology [66–75], and the onset of dementia [56,74,76]. In a large study of CBF velocity in people without clinical dementia (the Rotterdam Study, 1730 participants aged 55 years and older), those who had greater CBF velocity were less likely to go on to develop dementia [77], suggesting that cerebral hypoperfusion precedes and possibly contributes to the development of dementia. Higher CBF velocity was associated with significantly less cognitive decline, and larger hippocampus and amygdala volumes [77].

Patients with Down's syndrome have similar functional vascular abnormalities to those in AD, even before the formation of Aβ plaques and NFTs although soluble forms of Aβ may be elevated [78]. The earliest abnormality in transgenic mice that have AD-related *APP* mutations is a profound alteration in the regulation of CBF at 2–3 months of age [79–81]. Under normal circumstances there is a close relationship between CBF and cerebral glucose utilisation (CGU), which reflects neural metabolic activity [82,83]. AD patients show early reductions in CGU in temporal, parietal, and posterior cingulate cortices in a pattern that is distinct from that in normal ageing and other dementias [84–89]. Although reduction in CBF has long been known to be an early event in AD, it has been unclear whether this is simply a consequence of diminished metabolic demand because of neuronal dysfunction. The Rotterdam study suggested that cerebral hypoperfusion precedes and possibly contributes to the dementia but more convincing evidence came from studies of the relationship between CBF and CGU, which can be measured by positron emission tomography scanning using the glucose metabolic tracer [^{18}F]-fluorodeoxyglucose. The Tg2576 mouse model of AD, transgenic for human *APP* containing the Swedish double mutation, was found to show reduction in CBF and CGU before the formation of Aβ plaques or neurodegeneration [90,91]. However, although the reductions in CBF and CGU were coupled, the coupling differed between Tg2576 and wild-type mice: for any measured level of CGU, CBF was about 30% lower in Tg2576 than wild-type mice, indicating that the reduction in blood

flow in Tg2576 mice was not simply a reflection of lower metabolic activity.

4. Aβ acts on the endothelin system to cause reduced CBF

There is evidence that Aβ may contribute to the reduction in CBF in AD: CBF was reduced by 20–40% in mice that over-express *APP* [81,92] and regulation of CBF was most impaired in transgenic mice with highest intracerebral levels of Aβ [81]. Several experimental studies have shown $A\beta_{1-42}$ and $A\beta_{1-40}$ to induce endothelial dysfunction (defined as impaired endothelium-dependent relaxation and enhanced endothelium-dependent vasoconstriction) *in vivo* and *in vitro* [93–101]. For example, exposure of isolated vessels to $A\beta_{1-40}$ or $A\beta_{25-35}$ for 24–48 h altered endothelial function without changing cell morphology or inducing apoptosis [102]. In these studies of isolated vessels, Aβ peptides act directly on cerebral arteries to cause cerebral smooth muscle cell contraction (Fig. 1). This direct action of Aβ was associated with $A\beta_{1-40}$, not $A\beta_{1-42}$ or the highly neurotoxic fragment $A\beta_{25-35}$, suggesting that the factors responsible for direct mediation of Aβ vasoactivity are distinct from those mediating Aβ cytotoxicity. The precise mechanism of enhanced vasoconstriction is not entirely clear. It may be partly mediated through the production of free radicals [93,95,98,99,103]: interaction of Aβ with endothelial cells of rat aorta produces an excess of superoxide radicals, which inactivate endothelium-derived relaxing factor [104], leading to enhanced vasoconstriction [98]. However, in some studies vasoconstriction was reported not to be caused by enhanced production or biological activity of free radicals during Aβ incubation [100,102,105]. A pro-inflammatory pathway involving upregulation of COX-2 has also been suggested [106–108].

Our own research has focused on the contribution of the endothelin system to vascular dysfunction in AD. Endothelin-converting enzymes-1 and -2 (ECE-1 and -2) expressed, respectively, by endothelial cells [109] and neurons [110] within the CNS [111], convert the inactive precursor 'big-endothelin' to the potent vasoconstrictor endothelin-1 (ET-1). ECE-1 and -2 are also capable of degrading Aβ [112], and *ECE-1* heterozygous and *ECE-2* homozygous knock-out mice [113] have significantly elevated levels of $A\beta_{1-40}$ and $A\beta_{1-42}$ [114], attributed to decreased Aβ degradation. In addition, *ECE-2* homozygous knock-out mice are deficient in learning and memory [115]. However, we found expression of ECE-1 to be unchanged [109] and ECE-2 to be significantly elevated [110] at both the mRNA and protein level in post-mortem (PM) brain tissue from patients with AD compared to that from normal controls and patients with vascular dementia (VaD). The fact that ECE-2 expression was unchanged in VaD despite neuronal damage and gliosis, suggested that the elevated expression in AD might be secondary to the accumulation of Aβ. 24 h exposure of SH-SY5Y cells to monomeric or oligomeric $A\beta_{1-42}$ caused marked upregulation of ECE-2 mRNA and protein [110], supporting this hypothesis. The upregulation of ECE-2 may be a physiological feedback or protective mechanism that serves to increase degradation of Aβ and reduce its accumulation. Immunostaining of ET-1 was found to be elevated in frontal, temporal, parietal and occipital cortex in AD compared to control brains [116] and ET-1 expression was elevated in the cerebral vasculature of mice that had been infused with Aβ [117]. We have recently extended these observations and shown that the levels of both *EDN1* mRNA and of ET-1 itself are significantly elevated in temporal neocortex in AD, and that $A\beta_{1-42}$ induces the production and release of ET-1 by neuroblastoma cells *in vitro* [118,119]. ET-1 was shown to be present in perivascular nerves surrounding cerebral vessels [120], providing further support for the idea that release of neuronally derived ET-1 is a cause of vasoconstriction [121]. We suggest that the cerebrovascular dysfunction in AD reflects not only a direct action of $A\beta_{1-40}$ on cerebral blood vessels but also the indirect effects of $A\beta_{1-42}$, mediated through upregulation of neuronal ECE-2 and increased production and release of ET-1, causing a chronic reduction in CBF.

It should be noted that there are also other ways in which Aβ may cause cerebral vasoconstriction in AD. $A\beta_{1-42}$ upregulates neuronal production of angiotensin-converting enzyme (ACE) [122], the activity of which is increased in the brain in AD. ACE is another

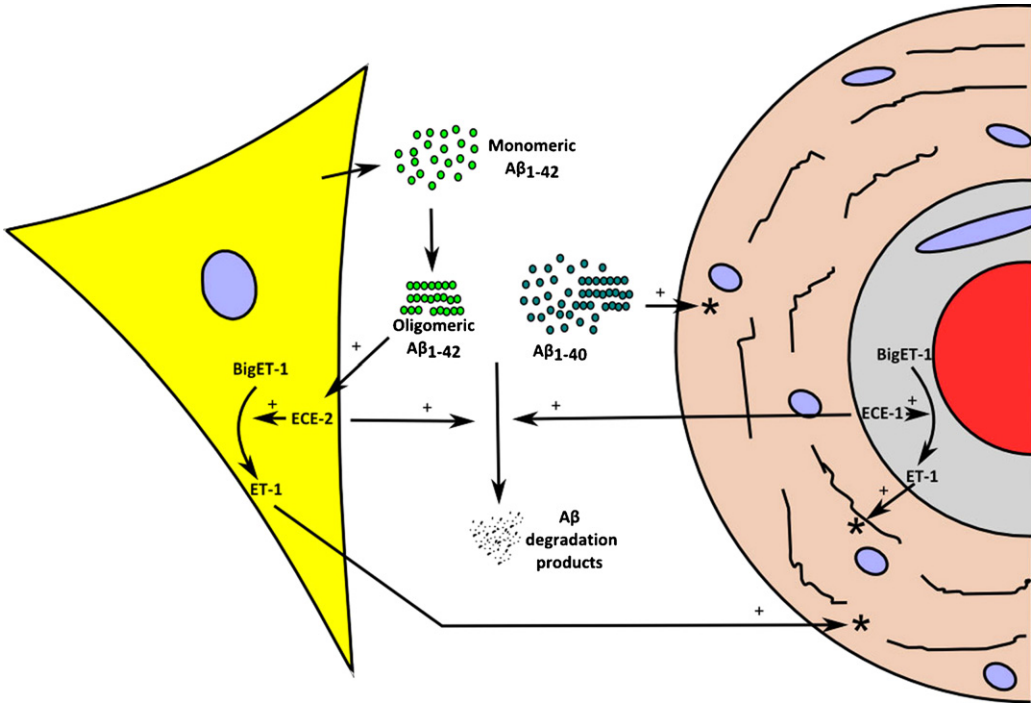

Fig. 1. Two of the mechanisms by which Aβ is thought to reduce cerebral blood flow in AD. $A\beta_{1-40}$ acts directly on cerebral arteries to cause cerebrovascular smooth muscle cell contraction. $A\beta_{1-42}$ acts on neurons to upregulate *ECE-2* and *EDN1* expression, increase cleavage of big ET-1 and release of ET-1. High levels of ET-1 cause chronic vasoconstriction by acting on ET_A receptors on cerebral smooth muscle cells (represented by asterisks *).

example of an enzyme that is capable of degrading Aβ [123,124] but may also reduce CBF, through the cleavage of angiotensin I to form the vasoconstrictors angiotensin II and III. This is a further mechanism through which Aβ may reduce CBF, potentially treatable through the use of ACE inhibitors and angiotensin receptor blockers [125].

5. Does the endothelin system hold therapeutic potential in AD?

At present, only a few symptomatic treatment options exist for AD. Acetylcholinesterase inhibitors (which prolong availability of ACh at synapses) and glutamate receptor (*N*-methyl-D-aspartate receptor) antagonists (which are thought to reduce glutamate-mediated neurotoxicity) are the only treatments approved by the National Institute for Health and Clinical Excellence for AD [126–131]. Many other therapies have been proposed and investigated, including anti-inflammatory drugs, antioxidants, selegiline, *G. biloba*, oestrogen replacement, statins, and compounds designed to inhibit aggregation or toxicity of Aβ or tau but trial data for all of these are lacking, negative or inconclusive [132].

Pathological changes and neuronal degeneration in AD begin many years before a clinical diagnosis can be made [133–136]. Once the disease has reached the middle to late stages, a cure for AD seems unlikely because of the degradation and loss of neuronal networks that control cognitive functions. Aβ immunisation (Elan AN1792 trial) resulted in significant plaque removal [137,138] in patients with AD. However, the relationship between neurodegeneration and plaque load is tenuous [139] and there was no improvement in survival or delayed progression to severe dementia in the AN1792 compared to the placebo group [138]. It has been suggested that drugs aimed at reducing the amount of Aβ in the brain need to be administered before significant neurodegeneration has occurred. However, the concentration of soluble Aβ in the brain is considerably higher in early than later life [140] which may reflect a physiological role in neuronal development and suggests a need for caution in attempting to lower Aβ level too aggressively at too early a stage. Modulation of other risk factors may be a more realistic strategy. de la Torre [141] proposed screening subjects at mid-life for vascular risk factors associated with AD, such as atherosclerosis, hypertension and cardiovascular disease, and treating those conditions before they become symptomatic; yet this should constitute normal good clinical practice for the prevention of stroke and other adverse vascular events irrespective of the potential beneficial impact of such screening on development of AD.

As noted above, one of the earliest abnormalities in AD is a reduction in CBF [79–81,85] and both $A\beta_{1-40}$ and $A\beta_{1-42}$ induce endothelial dysfunction [103]. The cerebral hypoperfusion observed in AD is likely to impair neuronal function and reduce the clearance of Aβ and other solutes from the brain – whether by perivascular drainage or by transport across vessel walls into the circulation. Furthermore, hypoperfusion results in upregulation of BACE1 and so increases Aβ production [142,143]. Cerebral hypoperfusion may also lead to cerebral capillary damage, further reducing blood flow [144]. Intervention at an early stage may be of critical importance in preserving vascular function, neuronal metabolism and cognitive function [145,146].

Outside of the CNS several diseases are associated with abnormal activation of the endothelin system. These include pulmonary hypertension, some forms of renal disease, systemic arterial hypertension, heart failure, allograft rejection and diabetes/insulin resistance [147]. Substantial physiological and clinical benefit derives from the use of ET receptor antagonists, particularly selective ET_A receptor blockers, in these disorders [148–155]. ET_A receptor antagonists improve endothelium-dependent, NO-mediated vasodilatation [156], which is blocked by selective ET_B receptor antagonists [157].

In keeping with our own observations on the upregulation of the ECE-2-ET-1 axis by Aβ, Elesber et al. [158] demonstrated that bosentan (Tracleer®), a dual ET_A/ET_B receptor antagonist, preserved aortic and carotid endothelial function in Tg2576 mice, which overexpress *APP*. This provides additional evidence of the involvement of ET-1 in the pathogenesis of endothelial dysfunction associated with elevated Aβ and demonstrates the therapeutic potential of drugs such as bosentan in this context. Several selective ET_A receptor antagonists have been used for the treatment of pulmonary hypertension, including ambrisentan (Letairis®, Volibris®), darusentan and sixaxsentan (Thelin®) [147]. Experimental and clinical studies have shown beneficial effects of treating pulmonary hypertension with both ET_A receptor-selective and non-selective ET_A/ET_B receptor antagonists [159] but not selective ET_B receptor antagonists [148,150–153]. In view of the opposing functions of the ET_A and ET_B receptor in the maintenance of vascular tone, and the probable role that endothelial ET_B receptors play in the clearance of excess ET-1 from the circulation [159], it seems likely that selective ET_A receptor inhibitors would be most beneficial in maintaining CBF in AD.

6. Enhancement of ECE activity for treatment of AD: need to evaluate risk of vascular dysfunction

Reduction of Aβ accumulation is a major objective of treatment in AD, and enhancement of the activity of Aβ-degrading enzymes is a potential therapeutic approach [160]. The ECEs have Aβ-degrading potential [39,161–163]. Intracranial administration of serotype 5 recombinant adeno-associated viral vector containing the *ECE-1* synthetic gene resulted in an ~50% reduction in the total Aβ load in the cortex and hippocampus in transgenic mice overexpressing *APP* and *PSEN1* [162]. This led to the suggestion that increasing the expression of the ECEs is a promising therapeutic approach for the treatment of AD [162,163]. In these studies, the Aβ load was assessed by immunohistochemistry of PM brain tissue, and no measurements of blood pressure, CBF or cognitive function were made antemortem, so it remains to be investigated whether measures that increase ECE activity affect the production of ET-1, cerebral perfusion or cognition.

The corollary of the concern that enhanced ECE activity might reduce CBF is that the use of ECE inhibitors to improve CBF might exacerbate the accumulation of Aβ. The advantage of using ET-1 receptor antagonists rather than ECE inhibitors is that the former would be expected to prevent the cerebrovascular dysfunction caused by excess ET-1 without the potentially deleterious effect on ECE-2-mediated degradation of Aβ.

7. Conclusions

Many patients with AD have concomitant white matter pathology, attributed to ischaemia caused by cerebral hypoperfusion [164,165]. Current data indicate that increased levels of Aβ in the brain may have a significant influence on CBF but the precise mechanism of Aβ-mediated vasoconstriction remains to be established. Little is known about the normal function of Aβ, which is present in the normal brain and is produced throughout life but accumulates in excess in AD [166]. Aβ starts to accumulate decades before the onset of AD and is likely to influence cerebral perfusion from as early as mid-life in a much wider context than solely in patients with AD. This influence could extend to conditions such as neurogenic hypertension and all of its systemic consequences [167,168] including stroke and cerebral ischaemic damage.

The relationship between vascular risk factors and AD is difficult to interpret from review of the scientific literature, as the pres-

ence of significant cerebrovascular disease was long considered an exclusion criterion for the diagnosis of AD. However, recent experimental studies have strengthened the 'vascular hypothesis' of AD, in which dysfunction of the cerebral microvasculature contributes directly to the development of AD [74]. There is also a growing body of evidence that Aβ contributes to cerebrovascular insufficiency, by both direct and indirect actions on the cerebral vasculature, the latter mediated through the influences of Aβ on neuronal function and signalling.

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