COMMENTARIES

Acetylcholinesterase inhibitors for Alzheimer’s disease: anti-inflammatories in acetylcholine clothing!

N. Tabet

Postgraduate Medical School, University of Brighton, Falmer, Brighton, BN1 9PH, UK

Address correspondence to: N. Tabet. Email: n.t.tabet@brighton.ac.uk

Abstract

The pathogenesis of Alzheimer’s disease (AD) has been linked to a deficiency in the brain neurotransmitter acetylcholine. Subsequently, acetylcholinesterase inhibitors (AChEIs) were introduced for the symptomatic treatment of AD. The prevailing view has been that the efficacy of AChEIs is attained through their augmentation of acetylcholine-mediated neuron-to-neuron transmission. However, AChEIs also protect cells from free radical toxicity and β-amyloid-induced injury, and increased production of antioxidants. In addition, it has been reported that AChEIs directly inhibit the release of cytokines from microglia and monocytes. These observations are supported by evidence showing a role for acetylcholine in suppression of cytokine release through a ‘cholinergic anti-inflammatory pathway’. Based on the accumulating research data so far, it is no longer appropriate to consider that the sole action of AChEIs in AD is through direct acetylcholine-mediated enhancement of neuronal transmission. Evidence points to a possible anti-inflammatory role for these agents as well.

Keywords: Alzheimer’s disease, treatment, anti-inflammation, cytokines, acetylcholinesterase inhibitors, elderly

For a quarter of a century, the pathogenesis of Alzheimer’s disease (AD) has been linked to a deficiency in the brain neurotransmitter acetylcholine. This was based on observations that correlated cholinergic system abnormalities with intellectual impairment [1]. Subsequently, the ‘cholinergic hypothesis’ of AD gained considerable acceptance. It stated that a serious loss of cholinergic function in the central nervous system contributed to cognitive symptoms [2]. Over the years, both evidence for and challenges to the relationship between acetylcholine dysfunction and AD have been put forward [3]. In essence, it has been argued that acetylcholine dysfunction is not a primary pathological cause for AD but rather a consequence of the disease. Hence, in addition to cholinergic dysfunction, a role for β-amyloid deposition, oxidative stress and inflammation have been investigated in the aetiology of AD, and currently, trials are underway to test disease-modifying agents. Nevertheless, attempts at correcting acetylcholine deficiency in the brain of affected individuals produced the first licensed medication for the symptomatic treatment of AD in the form of acetylcholinesterase inhibitors (AChEIs). Although the benefits of these agents are modest, three (donepezil, rivastigmine and galantamine) are licensed in the UK. Current guidelines by the National Institute of Clinical Excellence support the use of these agents, although possible changes to the guidelines are presently awaited. AChEIs are widely available for the treatment of mild-to-moderate AD, and they are well tolerated in the majority of patients. Although their main use has been in the stabilisation of cognitive decline, there is evidence linking them with improvement in behavioural and psychological symptoms of dementia [4].

It has been the prevailing view that the symptomatic efficacy of AChEIs is attained through their augmentation of acetylcholine-mediated neuron-to-neuron transmission. However, there is evidence that AChEIs may slow disease progression and hippocampal atrophy and may have disease-modifying effects [5–7]. In addition, symptomatic improvement in AD patients is not restricted to agents that enhance acetylcholine function in the brain, as is the case for memantine which acts on another neurotransmitter. Interestingly, memantine, whose benefits also appear to be modest, and is licensed in Europe for moderate-to-severe AD, has been recently linked to modulation of inflammation [8]. Further research is needed to establish an anti-inflammatory role for memantine; overall however, inflammatory pathways in general are being recognised as an important contributor to cell death in AD [9]. In cell cultures and animal studies, as well as in human epidemiological surveys, agents
known to dampen down inflammation such as vitamin antioxidants, herbal extracts with antioxidant properties (e.g. Gingko Biloba) and long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) have shown some protective effect against AD pathology. There is also current interest in statins for the treatment of AD. Significantly, their suspected role in cognitive enhancement appears to be mediated through an anti-inflammatory effect, independent of their cholesterol-lowering properties [10]. To date, none of these agents have shown clear benefit to AD patients. In the case of NSAIDs, although strong evidence from epidemiological studies seems to point towards a protective role for these drugs in relation to the development of AD, randomised controlled trials have failed so far to show any benefit [11, 12]. The efficacy of anti-inflammatory agents may be limited by the fact that inflammation appears to be interlinked with other pathological events in AD, including β-amyloid deposition and cholinergic dysfunction [13]. However, this interrelationship and the central role of inflammation along with evidence that symptomatic improvement in AD can be achieved independent of acetylcholine raise the possibility that the mechanism of action of AChEIs may not be restricted to direct neuron-to-neuron signalling. Indeed it has been speculated that these agents might offer a degree of neuroprotection in AD [14]. Hence, it may be reasonable to consider that the efficacy of AChEIs is, at least in part, because of the anti-inflammatory effects. However, for an anti-inflammatory mechanism of action to be confirmed for AChEIs, two essential requirements are to be satisfied. They are the following: (i) direct link between the cholinergic system and inflammation (i.e. a direct role for acetylcholine in attenuating inflammation) and (ii) data showing clear effect of AChEIs on inflammatory mediators of toxicity and inflammatory processes. Recent research and discoveries allow for evidence for both to be presented below.

A link between the cholinergic system and inflammation has been established through the discovery of an anti-inflammatory role for a stimulated vagus nerve [15]. In an animal model of toxemia, acetylcholine suppressed proinflammatory cytokine release from peripheral tissue-activated macrophages. This resulted from the action of acetylcholine on specific nicotinic receptors expressed on these cells [16]. Hence, this ‘cholinergic anti-inflammatory pathway’ provides a physiological mechanism linking acetylcholine with inhibition of inflammation. Shytle et al. [17] have shown the presence of similar pathway in the brain linking the cholinergic system with the regulation of mouse-cultured microglial activation. Here again, acetylcholine acting on the same nicotinic receptors to those expressed on macrophages attenuated cytokine release from microglia (brain cells increasingly linked with AD pathology). These interesting results in the brain have also been confirmed in rat microglial cultures [18]. Furthermore, there is a growing body of evidence from animal and, recently, human studies directly linking AChEIs with an anti-inflammatory role. Pre-incubation of rat cells with tacrine and donepezil protected them from the effect of hydrogen peroxide, a toxic-free radical, and significantly produced an increase in catalase and glutathione peroxidase antioxidants [19]. Tacrine also prevented hydrogen peroxide-induced cell death possibly through inhibition of certain genes expression [20]. Free radicals are known to directly damage cells and appear to be involved in reciprocal induction of other mediators of toxicity in AD such as β-amyloid and as such contribute to inflammation [21]. Hence, blocking the action of toxic-free radicals helps in attenuating the inflammatory response. Data also show that AChEIs protected cells directly against β-amyloid-induced injury [22] and that donepezil was recently shown to protect rat septal neuronal cells against toxicity of β-amyloid [23]. Recent evidence also point to a direct role of AChEIs in the inhibition of the release of inflammatory substances from specialised cells. Galantamine, for example, attenuated release of cytokines from activated murine microglia [24]. In mice, peripheral administration of AChEIs almost completely blocked activated microglia’s cytokine production in hippocampus and blood [25]. Significantly, similar results have now been shown in humans. Donepezil treatment of AD patients for 1 month led to an attenuation of the release of cytokines from peripheral monocytes [26].

Increasing evidence now points towards an anti-inflammatory role for AChEIs through action against free radicals and amyloid toxicity and through decreasing release of cytokines from activated microglia in hippocampus and blood. More research is now needed to clarify the anti-inflammatory role of AChEIs in AD patients and to define the mechanisms involved. This undoubtedly will shed further light on the pathogenesis of AD and the interaction between the various pathological factors involved in its aetiology. However, based on the accumulating research evidence so far, it is no longer appropriate to consider that the sole action of AChEIs in AD is through direct acetylcholine-mediated enhancement of neuronal transmission.

**Key points**

- Acetylcholinesterase inhibitors are widely used for the treatment of Alzheimer’s disease.
- Prevailing view has been that efficacy of these agents is through acetylcholine-mediated neuron-to-neuron transmission.
- Acetylcholinesterase inhibitors protect against free radicals’ toxicity and β-amyloid-induced injury and attenuate cytokine release from microglia.
- Increasing evidence support an additional anti-inflammatory role for acetylcholinesterase inhibitors.

**Conflicts of interest**

The author has received speaker’s fees from Shire, Pfizer and Novartis and has obtained a research grant from Novartis.

**References**


