Acetylcholinesterase inhibitors: novel activities of old molecules

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Abstract

The therapeutic approach for improving the cognitive function in patients with Alzheimer’s disease (AD) is mainly based on the potentiation of central cholinergic activity and is achieved clinically by the use of acetylcholinesterase (AChE) inhibitors such as tacrine, donepezil, rivastigmine, galantamine and other drugs currently in clinical trials. These are, by their pharmacology, only symptomatic drugs yet recently these molecules have shown some potential also in the modulation of amyloid precursor protein (APP) processing. We explore in this review the experimental evidence that suggests a role for AChEIs in APP processing and point to multiple complex mechanisms involving either a cholinergic agonist effect, coupled to multiple signal transduction pathways, or post-transcriptional effects that modulate the expression of cellular APP.

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1. Introduction

Alzheimer’s disease (AD) is one of the most common form of dementia affecting approximately 10% of the population over the age of 65 years. Besides the neuropathologic hallmarks of the disease, namely neurofibrillary tangles and neuritic plaques (see details below), AD is characterized neurochemically by a consistent deficit in cholinergic neurotransmission, particularly affecting cholinergic neurons in the basal forebrain[1,2]. The evidence stems from data of several authors that demonstrated the reduction in activity of enzymes involved in the synthesis (choline acetyltransferase (ChAT)) or degradation (acetylcholinesterase (AChE)) of acetylcholine[3–5].

While the evidence for ChAT alterations is more consistent, the data concerning AChE are complicated by the complexity of AChE molecular forms. These can be divided into asymmetric forms and globular forms, with the latter existing as monomers, dimers or catalytic tetramers either secreted as soluble forms or anchored to the membrane by a hydrophobic domain. In spite of the inconsistencies in the literature concerning the nature and extent of the cholinergic system, alterations in the overall observation of a cholinergic deficit in AD patients led to the cholinergic-boosting strategies in the treatment of AD. In a field of several theoretical options, the best (clinically relevant) approach has been the use of AChE inhibitors (AChEIs) which led to the introduction of 1,2,3,4-tetrahydro-9-aminoacridine (tacrine) as the first AChEI specifically approved for the treatment of AD, in 1993[6]. Currently, several kinds of AChE inhibitors, such as donepezil[7], galantamine[8] and rivastigmine[9] are available for the symptomatic treatment of patients with mild-to-moderate AD. Cholinesterase inhibitory therapy may be considered, by its pharmacological nature, as a simple symptomatic short term intervention. However, the data emerging from long term mostly open label trials is that the maintenance of the clinical effect can be prolonged to at least 1 year. In some clinical studies, the data indicate that beneficial effects can be maintained for up to 36 months; results that were obtained with four inhibitors (donepezil, metrifonate, rivastigmine, and galantamine) reviewed in [10–12]. These effects of stabilization of the cognitive status of the patients suggest conceivably a structural effect of the treatment on pathological features of the disease; Giacobini suggested that the effects may arise from the interaction of these drugs with the amyloid cascade, influencing the