Butyrylcholinesterase: Potential Importance for the Symptoms and Progression of Cognitive Decline in People with Dementia

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Abstract- Cholinesterase inhibitors have produced the best evidence of clinical efficacy for treating patients with Alzheimer's disease (AD). As AD progresses, BuChE may become increasingly important in the regulation of Ach. In addition there is accumulating evidence that BuChE may be an important factor in determining the rate of disease progression, perhaps because of a role in accelerating plaque maturation; with potential implications for treatment.

Key Words: Alzheimer's disease, Dementia with Lewy bodies, Butyrylcholinesterase, Cholinesterase inhibitors

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INTRODUCTION

Alzheimer's disease (AD) is a chronic illness that develops slowly and is characterized by a progressive decline in patients' cognitive and functional abilities[1]. Up to 24 million people world-wide have AD[2] and, as the world's population ages, the increasing prevalence of the condition has become an important public health issue[3]. This potential crisis has stimulated considerable research into developing effective treatments over the past couple of decades. There has been rapid progress in understanding the genetics, risk factors and pathogenic mechanisms of AD.

As with any type of dementia, irrespective of the underlying aetiology, the symptoms of AD are to a considerable extent related to the impaired neurotransmission and degeneration of neuronal circuits in the specific brain areas affected. Since the cholinergic hypothesis was first proposed[4,5], a large body of evidence has grown to support the view that impairment of cholinergic function is of central importance in the pathogenesis of AD[6-9]. In patients with AD, cholinergic neuronal loss is particularly noticeable in the neocortex and hippocampus, with a global impact on higher cognitive functions such as learning, memory and executive functioning as well as behaviour and emotional responses[10].

Building upon these studies, a number of therapeutic approaches were developed with the aim of enhancing cholinergic function, the most successful of which has been the use of cholinesterase inhibitors. Large, placebo-controlled, double-blind trials have demonstrated that cholinesterase inhibitor therapy results in signifi-

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cant improvements in cognitive, functional and global performances of patients with AD[11]. Three cholinesterase inhibitors are commonly used to treat patients with mild-to-moderate AD: donepezil, rivastigmine and galantamine. Donepezil and galantamine are selective acetylcholinesterase (AChE) inhibitors. Rivastigmine inhibits both AChE and butyryl-cholinesterase (BuChE) from degrading Ach.

In the current review, the potential importance of BuChE in the symptoms and progression of AD and the possible implications for clinical treatment are considered.

Structures of AChE and BuChE

AChE is a 76 kD protein and a member of the α/β-hydrolase fold family[12]. It contains an active catalytic centre that is found within a gorge. At the entrance of the gorge there is a peripheral anionic site that may serve as a 'landing-site' specific for AC[12]. The catalytic centre is lined with 14 amino acid residues, which interact with the ACh quaternary group. BuChE has a similar structure to that of AChE, sharing 65% amino acid sequence homology despite being encoded by different genes on human chromosomes 9 (7q22) and 3 (3q26), respectively, and BuChE also has it's active catalytic centre within a gorge. There are however some differences, for example BuChE lacks the peripheral anionic site at the entrance to the gorge and six of the aromatic residues[12]. Once in the gorge of either enzyme, ACh is cleaved and its neurotransmitter action is terminated[13]. While AChE is selective for ACh hydrolysis, BuChE accommodates and degrades several other substrates, including various neuroactive peptides[14].

The potential importance of BuChE

Cholinergic therapy for AD initially focused on AChE inhibition because this is the main enzyme involved in the breakdown of ACh in the normal brain. However, it is now evident that ACh is also a substrate for BuChE. For example, in rodent studies, it has been demonstrated that BuChE is able to hydrolyse ACh and plays an important role in cholinergic transmission[15]. In mice with no AChE activity (AChE knockout mice), an absence of AChE was compatible not only with survival for 3-4 months, but also with the structural integrity of cholinergic pathways. However, these mice were highly sensitive to the toxic effects of a butyryl-specific inhibitor[15]. The results indicate that BuChE is capable of compensating for some functions of AChE. Moreover, during a study of wild type and AChE knockout mice, traditional extraction buffers significantly inhibited BuChE activity resulting in a gross underestimation of activity by up to 15-fold[16], indicating that BuChE activity may be more widespread than previously acknowledged.

Both AChE and BuChE break down ACh and terminate its neurotransmitter action, and it has been hypothesised that they may co-regulate levels of ACh[17]. The inhibition of BuChE may be expected to enhance cholinergic activity in the brain, and represents a legitimate target for AD treatment. Cytochemical studies have demonstated that in certain key neuronal pathways BuChE predominates, suggesting that cholinergic pathways can be regulated by BuChE alone[18].

Over the course of AD, AChE activity progressively decreases in certain brain regions, while in contrast, BuChE activity progressively increases[19]. For BuChE, there is an approximate 30-60% increase in the G1 form of the enzyme in AD[20], and as AD progresses the G1 forms of AChE and BuChE become increasingly located in plaques and tangles[20]. The elevation of BuChE observed with disease progression is probably due to an increase in the numbers of BuChE-positive glia in the brains of patients with AD, although it has been hypothesized that glial BuChE may play an important role in the breakdown of acetylcholine in the neuronal synapse[21].

BuChE and progression of cognitive decline in dementia

Preliminary studies in Newcastle have indicated that BuChE may play an important role in disease progression. This evidence comes from 2 lines of investigation. First from a study of genetic polymorphisms. There are 2 common polymorphisms (K variant, atypical variant) of the BuChE gene, involving single amino acid substitutions, which appear to be related to reduced activity of the enzyme. In a study of 58 people with operationalized clinical diagnoses of dementia with Lewy bodies

(McKeith criteria[22]) or moderate-severe probable Alzheimer's disease (NINCDS ADRDA criteria), the presence of a K or atypical variant was associated with a significantly slower rate of cognitive decline[23]. Within this preliminary cohort, people without the K or atypical variant had an annual decline which was 60% greater than those with these variants (16 points per year v 9 points per year on the CAMCOG schedule). These data are illustrated in Fig. 1. There was however no relationship between the K variant and the rate of decline in people with mild AD. In the second study, BuChE enzyme levels were measured in Brodmann area 20 of the temporal grey matter in a preliminary series of 9 patients with neuropathologically confirmed dementia with Lewy bodies who had received annual cognitive evaluations during life. There was a highly significant positive correlation between the annual rate of decline on the Mini-Mental State Examination during life and the level of the BuChE enzyme at post-mortem examination [[24]-Fig. 2]. Although requiring confirmation in larger studies, both lines of evidence indicate a relationship between higher levels of BuChE and more rapid cognitive decline.

BuChE and maturation of amyloid plaques

Amyloid deposits exist in the brain as diffuse deposits or compact plaques for many years before leading to neuritic degeneration and dementia. Therefore, it seems that some amyloid deposits are relatively benign while others lead to progressive neuronal damage. AChE and BuChE are both associated with amyloid plaques and neurofibrillary tangles in the brains of both individuals suffering from AD and elderly individuals without significant cognitive impairment[25-28].

The factors that contribute to the transformation of a relatively inert plaque to a pathogenic one may involve interactions with additional plaque constituents. One such constituent is BuChE. Advanced plaques show as much as 87% BuChE reactivity, compared with less than 20% reactivity in early, diffuse deposits[29]. The presence of BuChE appears to distinguish the neurotoxic plaques seen in the AD brain from those observed in normal ageing[29]. In tissue culture, addition of BuChE to β-amyloid results in an increase in aggregation[30] and neurotoxicity[31]. Based upon these observations, it seems that BuChE may play a role in the transformation of benign plaques to a malignant form associated with neuritic tissue degeneration and clinical dementia. The mechanisms of this effect are unclear, but given the accumulation of BuChE in glial cells with advancing AD, we would hypothesise that glial actions may be important.

These studies are consistent with the clinical data indicating an association between incrased BuChE and accelerated decline, and provide the beginnings of a possible mechanistic framework.

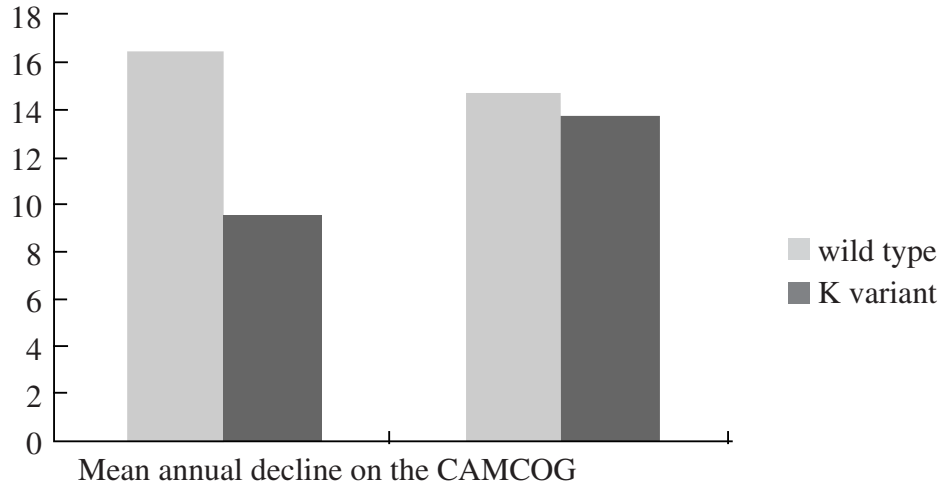

Figure 1. Mean annual decline on the CAMCOG in patients with moderate-severe AD/DLB and mild AD respectively.

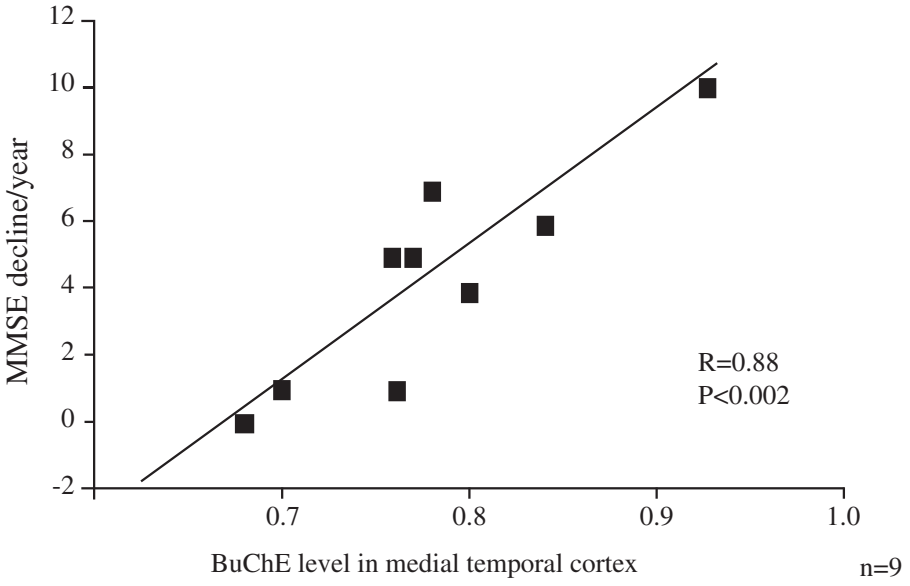

Figure 2. Rate of cognitive decline in DLB is correlated with BuChE levels in temporal cortex at autopsy.

Potential clinical utility for disease modification

Cholinesterase inhibitors have been shown to be effective symptomatic treatments for Alzheimer's disease and dementia with Lewy bodies, but whether they also modify disease progression is a key unresolved question. There are a number of different mechanisms by which these agents could possibly modify fundamental disease processes. The preliminary evidence reviewed in the current article indicates that there may be specific mechanisms related to BuChE, which may indicate that cholinesterase inhibitors such as rivastigmine which inhibit both acetyl and butyrylcholinesterase may have potential advantages specifically with respect to disease modification, particularly in people with moderate to severe neurodegenerative dementia, and is consistent with improvements seen in preliminary animal studies using specific BuChE inhibitors[32]. This however needs to be verified in long term human clinical trials, preferably with biological as well as clinical endpoints, and cannot be assumed from clinical data alone.

CONCLUSION

Further work is needed to clarify the potential mechanisms whereby BuChE impacts upon disease progression and long term studies comparing agents which inhibit BuChE and AchE to those inhibing AchE alone are essential before clear clinical recommendations can be made. However, because of the potential importance of BuChE, there are strong theoretical reasons to hypothesise that agents which inhibit not only AChE but also BuChE, such as rivastigmine, may have greater long term clinical efficacy. In addition clinical trials of specific BuChE inhibitors are merited.

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