Alzheimer therapeutics—what after the cholinesterase inhibitors?

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The first generation of Alzheimer therapeutics

In the 1970s and early 1980s, biochemical and neuropathological evidence emerged, implicating the degeneration of basal forebrain acetylcholinergic neurons in Alzheimer’s disease (AD) [1]. The ‘cholinergic hypothesis’ of AD held that cholinergic dysfunction causes cognitive decline and that dementia therefore might be mitigated by the augmentation of acetylcholine activity in brain. The logical therapeutic objective was to boost the levels of the transmitter by inhibiting its catabolic enzyme, acetylcholinesterase. Today, several cholinesterase inhibitors are marketed for the treatment of mild-to-moderate dementia. They have been demonstrated to improve, relative to placebo, various cognitive and functional capacities [2], and there is evidence that they may slow the pathogenesis of AD [3]. Additionally, an inhibitor of ionotropic neurotransmitter receptors (memantine) recently was approved for use in moderate-to-severe dementia [4]. However, because multiple neuronal systems are severely damaged in AD, the benefits of agents that selectively target the activity of certain transmitters are small. The limitations of the current generation of AD therapies led, in 2005, to a tentative proposal by the National Institute of Clinical Excellence (NICE) not to recommend donepezil, rivastigmine, galantamine or memantine for the treatment of mild-to-moderate dementia [5]. Although these drugs offer hope, and probably some benefit, to many patients, the improvements are modest and mainly symptomatic, and the patients and their families must eventually face the reality that the drugs cannot halt the relentless deterioration of mental capacities. Fortunately, recent research on the fundamental pathogenesis of AD reveals promising new strategies for arresting or preventing the disease.

The proteopathic basis of neurodegenerative diseases

A century ago this year, Alois Alzheimer first described unusual lesions in the autopsied brain of a demented patient, including the deposits of a ‘peculiar substance’ in the cerebral parenchyma and odd, tangled fibrils within nerve cells [6]. We now know that the ‘peculiar substance’ is an aggregated, fibrillar form of the β-amyloid protein (Aβ), which forms the cores of senile plaques, and that the neurofibrillary tangles consist of abnormally polymerised tau protein. For unknown reasons, Aβ and tau undergo a conformational conversion that renders the proteins prone to self-aggregation into plaques and tangles, respectively [7, 8]. Interestingly, multiple disorders of the brain and systemic organs entail the aberrant accumulation of disease-specific proteins, suggesting that diverse protein conformational disorders, or ‘proteopathies’, share similar pathogenic mechanisms [7].

By convention, an abundance of plaques and tangles in a patient with dementia is diagnostic of AD, but how the lesions contribute to the signs and symptoms of AD has been controversial. Although tauopathy is vital for the clinical manifestations of AD [9], genetic and clinicopathological findings indicate that tau dysfunction is downstream of Aβ in the proteopathic cascade. Specifically, all known risk factors for AD augment the production and/or accumulation of Aβ in brain [8]. Hence, most current research into the arrest or prevention of AD centres on Aβ, although tau is undoubtedly a viable therapeutic target, both for AD and other tauopathies [10, 11]. Importantly, a growing body of data supports the view that small, soluble oligomeric forms of Aβ are the main toxic agents, rather than the amyloid fibrils that comprise the cores of senile plaques [12, 13]. Preventing the formation or toxicity of these Aβ oligomers may be the ultimate key to halting the progression of AD pathogenesis.

The next generation of Alzheimer therapeutics: targeting the Aβ cascade

Currently, the most compelling approach to treating AD is based on the hypothesis that the build-up and pathogenicity of Aβ are fundamental to the progression of the disease. At some point, other pathological events become part of the cascade, including tauopathy and inflammation. The centrality
of Aβ in this process suggests several disease-modifying strategies: (i) block the cellular production of Aβ, (ii) prevent the self-assembly of Aβ, (iii) promote the catabolism of Aβ, (iv) stimulate the removal of Aβ and (v) counteract the cytotoxicity of multimeric Aβ.

**Block the production of Aβ**

Beta-amyloid precursor protein (BAPP) usually is cleaved within the Aβ sequence by the enzyme α-secretase, which splits Aβ, rendering it non-amyloidogenic. Alternative cleavages by β-secretase (β-amyloid cleaving enzyme, or BACE) and γ-secretase at the Aβ N- and C-termini, respectively, yield monomeric Aβ. Most pharmacological efforts to reduce the production of Aβ have been directed towards inhibiting β- or γ-secretase [14]. Experimental evidence confirms the therapeutic potential of this approach [15, 16], but developing safe and effective inhibitors of the secretases has been challenging. γ-Secretase is an intramembranous enzyme complex that also is critical for cleaving (and thereby activating) the transmembrane receptor/signalling protein Notch; blocking γ-secretase lowers Aβ formation in experimental systems, but reducing Notch activity could interfere with important cellular proliferation and differentiation pathways [17]. In this regard, R-flurbiprofen (Flurizan™), the R-enantiomer of the anti-inflammatory agent flurbiprofen, selectively lowers Aβ42 production via allosteric modulation of γ-secretase activity [18], preserving the activity of γ-secretase on Notch and other substrates. The agent is well tolerated, and limited efficacy recently was reported in mild, but not moderate, AD subjects [19]. More study of this strategy is warranted [20], but one implication of the clinical findings is that early treatment will be critical to reaping optimal benefit from disease-modifying therapies.

Unlike γ-secretase, direct inhibition of β-secretase (BACE) appears to be comparatively safe in animal models, but the open binding pocket of β-secretase has thus far thwarted the development of potent, small molecule inhibitors [21]. Neutralising Aβ by enhancing α-secretase cleavage also is a plausible, if complicated, anti-Aβ tactic [22], and there is evidence that statins, which might reduce the risk of AD, act in this manner [23].

**Prevent the self-assembly of Aβ**

A second option is to interfere with the aggregation of Aβ into oligomeric and/or fibrillar assemblies [24]. Tramiprostone (Alzheimed™), a glycosaminoglycan mimetic developed to block the interactions of proteoglycans with amyloid fibrils and thereby impede amyloid aggregation, has been reported to reduce senile plaque load in a mouse model of β-amyloidosis [25]. Tramiprostone recently reached phase III clinical trials [25], the results of which will help determine the potential of aggregation inhibition in AD. Although theoretically attractive, impeding protein–protein interactions can be difficult pharmacologically [7]. Additionally, it may be necessary to interrupt the Aβ self-assembly process very early in the cascade, as inhibiting fibril formation conceivably could cause the accumulation of prefibrillar oligomers and thereby exacerbate cytotoxicity.

**Promote the catabolism of Aβ**

Aβ can be broken down by endopeptidases, notably nephrilysin and insulin-degrading enzyme (IDE) [26]. Increasing the activity of these enzymes in BAPP-transgenic mice reduces brain Aβ levels and senile plaque load [27]. Thus, pharmacological augmentation of Aβ-degrading enzyme function in the brain is an encouraging means by which one might slow the course of AD. However, selective up-regulation of enzymatic activity can be problematic, and it is important to be mindful of other substrates that might be adversely affected. For these reasons, blocking the enzymatic liberation of Aβ remains a more attractive Aβ-lowering approach.

**Stimulate the removal of Aβ**

An auspicious strategy for halting AD pathogenesis is to promote the elimination of Aβ, either immunologically or by enhancing the transcellular efflux of the peptide from the brain. Anti-Aβ immunisation reduces Aβ load and improves behavioural performance in BAPP-transgenic mice [28] and even has shown hints of disease-modifying efficacy in early AD [29, 30]. Unforeseen adverse events, particularly aseptic meningoencephalitis, have hindered the clinical application of Aβ-immunotherapy in AD [31], but the effectiveness of immunisation in preclinical models justifies the current intensity of research in this arena.

Aβ is a substrate for certain cellular transport systems, including LRP1 [32] and β-glycoprotein (Pgp) [33]. Pgp insufficiency in particular has been linked to a higher cerebral Aβ load [34, 35]. Several available drugs are known to enhance Pgp activity in humans; however, the functional importance of transporters in various organs suggests that their up-regulation should be undertaken cautiously.

**Block the cytotoxicity of multimeric Aβ**

How multimers of Aβ exert their cytopathic effects remains uncertain, although two possibilities that have surfaced are abnormal interactions of globular oligomers [36] with cellular elements, or the formation of membrane pores that act as anomalous ion channels [37]. If the production, assembly and elimination of Aβ prove to be refractory to the development of effective therapies, the downstream effects of Aβ aggregation on cell integrity represent another option. For instance, should Aβ pores be proven to form in membranes of degeneration-prone cells, selective Aβ-channel-blocking agents could be useful AD therapeutics.

**The road ahead**

The next generation of AD therapeutics will be judged by their ability to provide more than temporary, symptomatic relief from the dementia of Alzheimer’s disease. The burgeoning data implicating aberrant Aβ in the genesis of AD argue for a sustained and diversified research effort in this domain. Alzheimed and Flurizan, which specifically (if incompletely) target the Aβ cascade, are at the vanguard of potentially disease-modifying, small-molecule therapies for AD. Basic and clinical research on Aβ immunisation and direct secretase inhibition, perhaps the most promising
approaches, also is proceeding apace. A conspicuous void in our knowledge is a fuller understanding of the in vivo conditions that favour the initial corruption and propagation of Aβ, i.e. the ‘prime mover’ of the Aβ cascade. Several potentially tractable factors have been inculpated in the early pathogenesis of AD, including inflammation, oxidative stress, as well as changes in pH, temperature and metal-ion homeostasis [38–40]. Elucidation of the contribution of these factors to the Aβ cascade is a significant objective that could open alternative pathways to disease-modifying therapies for AD and other degenerative proteopathies.

References


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