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Review article

Amyloid cascade in Alzheimer's disease: Recent advances in medicinal chemistry

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ABSTRACT

Alzheimer's disease is of major concern all over the world due to a number of factors including (i) an aging population (ii) increasing life span and (iii) lack of effective pharmacotherapy options. The past decade has seen intense research in discovering disease-modifying multitargeting small molecules as therapeutic options. The pathophysiology of Alzheimer's disease is attributed to a number of factors such as the cholinergic dysfunction, amyloid/tau toxicity and oxidative stress/mitochondrial dysfunction. In recent years, targeting the amyloid cascade has emerged as an attractive strategy to discover novel neurotherapeutics. Formation of beta-amyloid species, with different degrees of solubility and neurotoxicity is associated with the gradual decline in cognition leading to dementia. The two commonly used approaches to prevent beta-amyloid accumulation in the brain include (i) development of beta-secretase inhibitors and (ii) designing direct inhibitors of beta-amyloid (self-induced) aggregation. This review highlights the amyloid cascade hypothesis and the key chemical features required to design small molecules that inhibit lower and higher order beta-amyloid aggregates. Several recent examples of small synthetic molecules with disease-modifying properties were considered and their molecular docking studies were conducted using either a dimer or steric-zipper assembly of beta-amyloid. These investigations provide a mechanistic understanding on the structural requirements needed to design novel small molecules with anti-amyloid aggregation properties. Significantly, this work also demonstrates that the structural requirements to prevent aggregation of various amyloid species differs considerably, which explains the fact that many small molecules do not exhibit similar inhibition profile toward diverse amyloid species such as dimers, trimers, tetramers, oligomers, protofibrils and fibrils.

Contents

Abbreviations: AD, Alzheimer's disease; Aβ, Beta amyloid; NFT, Neurofibrillary tangles; APP, Amyloid precursor protein; CNS, Central nervous system; CTF, C-terminal fragment; AICD, Amyloid intracellular domain; BACE-1, Beta-site APP cleaving enzyme.

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1. Introduction

Proteins, in all their structural forms, are high value macromolecules in cellular systems. From metabolism to catabolism, replication to apoptosis, signaling and regulation, proteins rely on their intricate folding arrangements to achieve biological outcomes [1]. The consequences from the collapse of that intricate folding structure can range from minor disruptions in biological output to various complex diseases [2–5]. Proteopathies can elicit multiple metabolic (e.g. type-II diabetes), functional (e.g. cystic fibrosis, glaucoma and sickle cell anemia) and neurological (e.g. Huntington's, Parkinson's and Alzheimer's diseases) impairments. While the impact of proteopathic diseases varies, the culprit is the presence of amyloid/abnormal protein deposits [6–16] (see Table 1).

When it comes to neurological disorders, Alzheimer's disease (AD) ranks high on the platform of complexity and pathophysiology. At the core of its pathology, AD is a protein misfolding disease [17–20]. While clinical symptoms are defined by cognitive impairment, the causes leading up to the observations of memory decline are strongly tied to deposits of misfolded protein aggregates [21–24]. Amyloid beta (Aβ) or beta amyloid and neurofibrillary tangles (NFTs) are the hallmark amyloid deposits in AD brains [25]. These aggregates derive from naturally occurring and highly crucial protein structures in the brain [26–35]. While the pathophysiology of AD is not fully understood, numerous studies have, and continue to, shed light on the aggregation mechanisms and impact of both Aβ and NFTs on brain health and cognitive ability.

This review will focus on the amyloid cascade of AD and highlight recent advances in medicinal chemistry research aimed at preventing Aβ aggregation as a therapeutic strategy to treat AD and related cognitive decline.

2. Amyloid precursor protein (APP)

In order to comprehend the Aβ cascade and its link to AD pathology, one must examine the functional biology of its precursor protein. The amyloid precursor protein (APP) is a highly conserved, integral membrane protein whose expression is mainly localized around the synapse of neuronal tissue. While its primary role is not fully understood, it is crucial for neuronal plasticity and synapse formation [26,36]. The APP gene, containing 18 exons and spanning over 170 kbp, resides on chromosome 21 and through alternative splicing, its isoforms range from 365 up to 770 amino acids [37,38]. Among the most common isoforms, APP695 is the more dominant form present in the CNS and, unlike APP751 and APP770, it lacks the Kunitz protease inhibitor (KPI) domain [37,39].

The biological incorporation of APP into the cellular membrane yields a much larger extracellular domain compared to the intracellular, C-terminal portion (as seen in Fig. 1). The primary proteolytic events on APP, whether pro- or anti-amyloid, occur at or around its transmembrane region by a group of secretase enzymes (α, β and γ) [26,40]. A number of missense mutations have been identified that negatively impact the metabolic pathway of APP and those are part of the larger designation, including presenilin mutations, for familial AD [39–42].

2.1. Non-amyloidogenic

In the metabolic pathways of APP, the anti- or non-amyloidogenic route is that initiated by α-secretase as showcased in Fig. 2. The term *non-amyloidogenic* is meant to refer to their non-aggregating nature unlike amyloidogenic proteins which tend to aggregate [43].

Briefly, α-secretase is part of a large group of proteolytic proteins referred to as ADAM (a disintegrin and metalloprotease domain). These are membrane-bound, multi-domain metalloenzymes that play a crucial role in non-AD physiology as well. Of its multiple subtypes, ADAM10 is of greater importance in AD pathology [44,45]. The APP cleavage site for α-secretase is very close to the cell membrane surface and occurs between Lys-16 and Leu-17 (based on the Aβ-peptide numbering), thus clearly disrupting the release of full length Aβ-40/42. The outcome of α-secretase proteolysis is the extracellular release of a large, soluble APP-alpha fragment (α-APPs) and a membrane-held C-terminal fragment (CTF-83). The α-APPs fragment is not subjected to further secretase metabolism and is documented for its neurotrophic/neuroprotective effects [29,30].

Following the initial cleavage by α-secretase, the CTF-83 is processed by γ-secretase to release an amyloid intracellular domain

Table 1
Listing of a few proteopathic diseases along with their amyloid protein.

Proteopathy	Amyloid protein
Type-II Diabetes	Islet Amyloid Polypeptide (IAPP)
Cystic Fibrosis	Cystic Fibrosis Transmembrane Conductance Regulator (CFTR)
Glaucoma	Amyloid-β
Sickle Cell Anemia	Hemoglobin
Huntington's	Poly-glutaminated/Mutated Huntingtin
Parkinson's	α-Synuclein
Alzheimer's	Amyloid-β