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Review Article

Down syndrome, beta-amyloid and neuroimaging☆

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ABSTRACT

This review focuses on the role of Aβ in AD pathogenesis in Down syndrome and current approaches for imaging Aβ in vivo. We will describe how Aβ deposits with age, the posttranslational modifications that can occur, and detection in biofluids. Three unique case studies describing partial trisomy 21 cases without APP triplication, and the occurrences of low level mosaic trisomy 21 in an early onset AD patient are presented. Brain imaging for Aβ includes those by positron emission tomography and ligands (Pittsburgh Compound B, Florbetapir, and FDDNP) that bind Aβ have been published and are summarized here. In combination, we have learned a great deal about Aβ in DS in terms of characterizing age of onset of this pathology and it is exciting to note that there is a clinical trial in DS targeting Aβ that may lead to clinical benefits.

1. Introduction

Improved medical care for people with Down syndrome (DS) has led to a significant extension in lifespan and improved quality of life [1–3]. However, as people with DS reach their 40's and 50's, they are vulnerable to the development of Alzheimer disease (AD). Increased frequency of AD in DS may be related to two key factors: (1) aging, which is a risk factor for AD in the general population and; (2) trisomy in genes associated with AD, particularly the APP gene.

AD was first described by Alois Alzheimer in 1901 (see [4] for an excellent review). We have since learned that a key protein engaged in AD pathogenesis is beta-amyloid (Aβ). One of the current working hypotheses is that Aβ is a critical initiator of AD [5,6]. Although this original hypothesis has been revised over time, due in part to the outcomes of recent clinical trials in AD targeting Aβ leading to little improvement in cognition [7], it is still considered a major contributor in the disease [8]. This review discusses the more recent developments regarding the role of Aβ in DS both at a molecular level and through neuroimaging as several reviews on both of these topics have been published elsewhere [9–11].

2. APP and chromosome 21

Aβ is produced from a longer amyloid precursor protein (APP) [12,13], which is present on chromosome 21 and thus triplicated in DS [14,15] (Fig. 1). It is interesting to note that one of the first descriptions of the biochemical properties of Aβ were from samples isolated from DS brain [16,17]. In the nonamyloidogenic processing pathway, APP is first cleaved by α-secretase to form sAPPα and subsequently cleaved by γ-secretase to produce p3 and AICD (APP intracellular domain). This form of APP processing prevents the production of Aβ. However, in the amyloidogenic pathway, APP is first cleaved first by β-secretase to produce sAPPβ followed by γ-secretase cleavage yielding Aβ and AICD. The β-secretase enzyme has been identified as beta-site APP cleaving enzyme or BACE1 [18] and γ-secretase consists of a complex that includes presenilin 1, nicastrin, PEN 2 and APH-1 [19].

In DS, the levels of brain Aβ are significantly higher when compared to controls at young ages [20] and Aβ increases exponentially with age [21,22] after 40 years. Increasing age-dependent Aβ in DS could be hypothesized as due to increasing APP production with age, increased β- or γ-secretase activity or reduced degradation (discussed later). In an autopsy study of 36 cases with DS, α-secretase activity appears to be relatively stable except in cases over 40 years of age who show a decline [22]. In contrast, studies of β-secretase activity show an increase with age [22] or show modest increases in protein level [23]. Further, total APP levels do not appear to change with age despite being higher in DS overall, suggesting that APP overexpression may be the primary driver of Aβ plaque accumulation [24,25].

A protein homologous to BACE 1, BACE2, can also cleave APP at the β-secretase site [26]. BACE-2 is also located on chromosome 21 and

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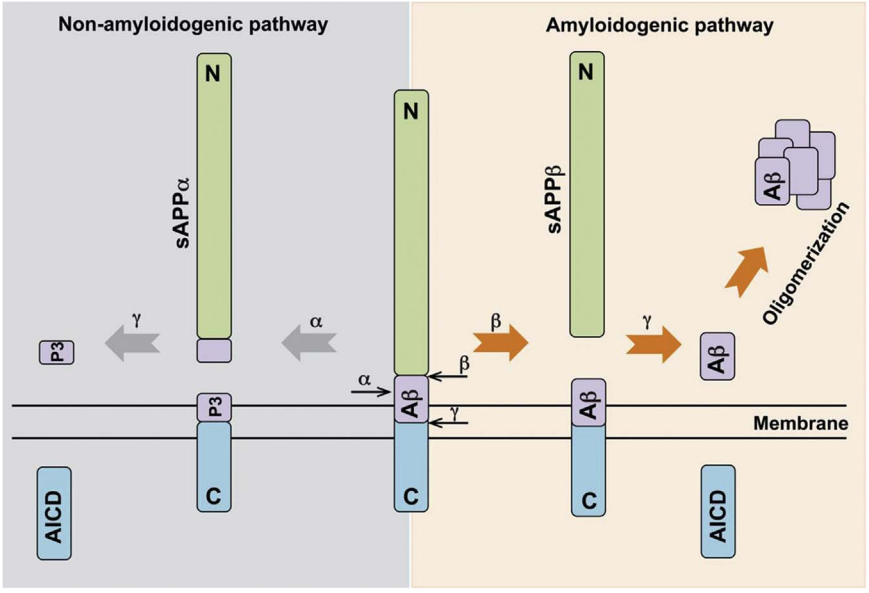

Fig. 1. The proteolytic processing of APP. APP can be cleaved by α-, β- and γ-secretases; the cleavage sites of these proteases are indicated in the full-length APP shown in the center of the figure. APP can undergo amyloidogenic (right) or non-amyloidogenic (left) processing. In the amyloidogenic pathway, cleavage by β-secretase results in the formation of soluble APPβ (sAPPβ) and βAPP-CTF. The subsequent action of γ-secretase on βAPP-CTF releases Aβ from the amyloid precursor protein intracellular domain (AICD). In the non-amyloidogenic pathway, cleavage by α-secretase prevents the formation of Aβ; α-secretase cleaves within the Aβ sequence, giving rise to sAPPα and the membrane-tethered αAPP-CT, which in turn is cleaved by γ-secretase resulting in release of the P3 peptide and AICD.
Reproduced with permission from Nicolas and Hassan [125].

may potentially contribute to increased Aβ production in DS. In DS fetal tissue, BACE-2 RNA levels are significantly higher relative to controls [27]. In addition, in cultured fibroblasts from adults with DS, BACE-2 mRNA (i.e. protein expression) was 2.6 fold higher than normal controls. In 13 individuals with DS ranging in age from 27 weeks to 37 years, frontal cortex BACE-2 immunoreactivity was observed only in neurons of adults with DS and AD. BACE-2 immunoreactivity was not observed in younger individuals [28]. However, several studies comparing DS brain to similarly aged control brains do not find higher levels of BACE2 protein overall [24,29]. Similarly, no differences in DS as compared to controls was observed for BACE2 in the intracellular compartment [27]. It is therefore possible that despite increased RNA for BACE2 in DS, there may be posttranscriptional regulatory mechanisms that lead to normal levels of BACE 2 or that increase the degradation of this enzyme [25]. Thus, APP overexpression and production of Aβ may be the primary driver of accumulation with age in DS [24,25].

3. Soluble Aβ and oligomers in DS

Once Aβ is cleaved from APP it appears in soluble forms that can be detected either within neurons or in the extracellular space. Higher levels of soluble Aβ are observed in DS fetal tissue relative to tissue from controls [20]. Aβ can assemble into oligomers, protofibrils and Aβ-derived diffusible ligands (ADDLs) [30,31] (Fig. 2). Importantly, Aβ oligomers cause neuronal dysfunction prior to overt neuron loss [32]. Both biochemical and immunohistochemical experiments reveal significant amounts of oligomeric Aβ in the AD brain [33–35].

In DS frontal cortex, the amount of soluble Aβ40 and Aβ42 is higher in DS relative to controls [36,37]. Interestingly, phosphate buffered saline (PBS) extracted soluble Aβ40 in the frontal cortex increases in an exponential function with age in DS, particularly after age 40 years [21]. However, soluble Aβ42 declines with increasing age but with a parallel increase in insoluble Aβ42 suggesting sequestration into plaques [21]. PBS soluble Aβ40/42 was also not different between DS and control cases in a study by Miners et al.[23]. Water soluble Aβ also appears to include modifications to N-terminal glutamates [38].

Oligomeric Aβ also accumulates exponentially after the age of 40 years [21]. Further, increasing amounts of oligomeric Aβ in DS frontal cortex is associated with lower synaptophysin protein levels, suggesting impaired synaptic function [39]. Soluble and insoluble Aβ fibrils are also present in higher levels in aged DS cases with AD neuropathology compared to similarly aged control cases [40]. Thus, oligomeric Aβ may play a critical role in causing neuron dysfunction during both development and aging in DS. Indeed, a recent study in the Ts65Dn mouse using environmental enrichment, led to reduced hippocampal oligomers and improved cognition [41].

4. Intracellular Aβ in DS

Although a large amount of Aβ exists in a soluble form, insoluble deposits also begin to progressively form over time. However, the subcellular location for these events is less well understood [42], particularly in DS, which has been discussed in a previous review and is updated here [10]. Gyure et al. report intracellular Aβ1-40 but not Aβ1-42 [43]. In contrast, other studies report intracellular Aβ1-42 but not Aβ1-40 [44,45], which in one study was clearly distinguished from intracellular APP immunoreactivity [44]. A report by Hirayama et al. found neither Aβ1-40 nor Aβ1-42 but observed intracellular Aβ1-43 [46]. Each length of Aβ has different properties. Aβ1-40 is more rapidly degraded within lysosomes than the longer, more toxic Aβ1-42/43 [47,48]. The reasons for observations of different length Aβ species in intracellular deposits in each of these studies may therefore be due in part to technical differences.

A common observation in the majority of the studies of intracellular Aβ in DS is the early age of onset; both infants and children with DS accumulate intracellular Aβ. In addition, intracellular Aβ is consistently observed prior to the accumulation of extracellular Aβ deposits [44], which parallels reports in transgenic mouse models of AD [49,50]. These findings suggest that prior to extracellular Aβ deposition there is an accumulation of intracellular Aβ within neurons in DS at a much earlier age than in the general population. Thus, intracellular Aβ accumulation may be important in the developmental course of DS and occurs prior to and contributes to age-associated extracellular Aβ deposition. The accumulation of neuronal Aβ may be associated with caspase cleavage products leading to increased apoptosis [51], which in turn may partially account for observed brain atrophy and neuronal loss. Intracellular Aβ is localized to endosomes, intracellular organelles responsible for degrading and turning over proteins within cells [52,53]. Interestingly, partially reducing BACE1 in the Ts2 mouse model of DS leads to a reduction in endosomal abnormalities [54] typically observed in the DS brain [53]

5. Aβ plaques

There is a well established literature that Aβ accumulates within