The APP and PS1/2 Mutations Linked to Early Onset Familial Alzheimer’s Disease Increase the Extracellular Concentration of Aβ1-42(43)

S. G. Younkin

Introduction

The amyloid β protein (Aβ) is an ~4 kD secreted protein that is derived from a set of large, alternatively spliced precursor proteins collectively referred to as the amyloid β protein precursor (AβPP). Secreted Aβ is readily detected in cerebrospinal fluid (CSF), plasma, and medium conditioned by cultured cells (Seubert et al. 1992; Shoji et al. 1992; Haass et al. 1992; Busciglio et al. 1993). Most secreted Aβ is Aβ1-40, but a small component (5–10%) is Aβ1-42 (Dovey et al. 1993; Vigo-Pelfrey et al. 1993; Suzuki et al. 1994). A large amount of amyloid β protein (Aβ) is deposited extracellularly in the senile plaques that are invariably observed in the brains of patients with all forms of Alzheimer’s disease (AD). Aβ1-42 appears to be particularly important in AD because it forms insoluble amyloid fibrils more rapidly than Aβ1-40 in vitro (Hilbich et al. 1991; Burdick et al. 1992; Jarrett et al. 1993; Jarrett and Lansbury 1993) and is deposited early and selectively in senile plaques (Iwatsubo et al. 1995). Extracellular Aβ deposition could be 1) an essential early event in AD pathogenesis, 2) an “innocent” marker that is invariably associated with some other change that drives AD pathogenesis, or 3) an unimportant, end-stage consequence of AD pathology. To examine the importance of Aβ in AD, we have analyzed the effect of the amyloid β protein (APP; Goate et al. 1991; Mullan et al. 1992), presenilin 1 (PS1; Sherrington et al. 1995) and presenilin 2 (PS2; Levey-Lahad et al. 1995; Rogaev et al. 1995) mutations that are known to cause early onset familial AD (FAD) on extracellular Aβ concentration.

Swedish Aβ1PPK670N, M671L mutation

In 1992, Mullan et al. identified a large Swedish family in which the AD phenotype cosegregates with a double mutation that converts the lysine-methionine at AβPP670,671 to asparagine-leucine. The age of disease onset in this family is 53±4 years (mean ± SD) with a range from 44 to 61 years. Clinical progression is indistinguishable from other forms of AD, and the clinical diagnosis has been confirmed by neuropathologic examination of the brain of a deceased mutation.

* Mayo Clinic Jacksonville, 4500 San Pablo Rd. Jacksonville, FL 32224, USA

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Previous analyses of this mutation have shown 1) that $\beta$APP$_{K670N,M671L}$ undergoes altered processing in transfected cultured cells, releasing 5–6 times more Aβ1-40 and Aβ1-42(43) than wild type $\beta$APP (Citron et al. 1992; Cai et al. 1993; Suzuki et al. 1994), and 2) that fibroblasts from affected and pre-symptomatic individuals with the $\beta$APP$_{K670N,M671L}$ mutation secrete more 4 kD Aβ than fibroblasts from age-matched controls (Citron et al. 1994). Thus there is good evidence that this mutation causes AD by coordinately increasing secretion of Aβ1-40 and Aβ1-42(43), thereby increasing Aβ concentration in a way that fosters amyloid deposition.

We have developed sandwich ELISAs that specifically detect fmol amounts of Aβ1-40 or Aβ1-42 in plasma (Scheuner et al. 1996) and in medium conditioned by cultured cells (Suzuki et al. 1994). Since the $\beta$APP$_{K670N,M671L}$ family is quite large and well characterized, it provided an excellent opportunity to determine whether measurement of plasma Aβ is useful in identifying individuals who develop AD because of elevated Aβ concentration. Plasma samples from 43 individuals in this family were analyzed (Scheuner et al. 1996); 12 of these individuals carried the $\beta$APP$_{K670N,M671L}$ mutation and 31 were non-carriers. In each of the 12 carriers, the concentration of Aβ1-40 in plasma (Fig. 1) was substantially higher than in any of the 31 non-carriers. Plasma levels of Aβ1-40 were 511±124 pM (mean ± SD) and 178±29 pM (p<0.0001) in carriers and non-carriers, respectively. In the 12 carriers, Aβ1-40 ranged from 329–752 pM, and there was no significant difference between the seven pre-symptomatic carriers.

![Fig. 1. Plasma Aβ1-40 concentration in the Swedish FAD (βAPP$_{K670N,M671L}$) family. Non-carriers (○), pre-symptomatic carriers (▲), symptomatic carriers (■). Methods were as described by Scheuner et al. 1996.](image-url)