Neurobiology of Aging xxx (2013) 1–6

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Review

Why Alzheimer trials fail: removing soluble oligomeric beta amyloid is essential, inconsistent, and difficult

William I. Rosenblum*

VCU School of Medicine, Richmond, VA, USA
Icahn School of Medicine at Mt Sinai, Mt Sinai, NY, USA

ARTICLE INFO

Article history:
Received 17 September 2013
Received in revised form 14 October 2013
Accepted 16 October 2013

Keywords:
Alzheimer's disease
Clinical trial failures
Neurotoxic soluble oligomers
Soluble ABeta amyloid
Correlation of soluble oligomers with cognitive decline
Synapses
Cognitive decline
Autopsies
Senile plaques
Interrelationship of senile plaque amyloid and soluble oligomers
Tau
Neurofibrillary tangles

ABSTRACT

Before amyloid formation, peptides cleaved from the amyloid precursor protein (APP) exist as soluble oligomers. These are extremely neurotoxic. Their concentration is strongly correlated with synaptic impairment in animals and parallel cognitive decline in animals and humans. Clinical trials have largely been aimed at removing insoluble beta amyloid in senile plaques and have not reduced soluble load. Even treatment that should remove soluble oligomers has not consistently reduced the load. Failure to significantly improve cognition has frequently been attributed to failure of the amyloid hypothesis or to irreversible alteration in the brain. Instead, trial failures may be because of failure to significantly reduce load of toxic Aβ oligomers. Moreover, targeting only synthesis of Aβ peptides, only the oligomers themselves, or only the final insoluble amyloid may fail to significantly reduce soluble load because of the interrelationship between these 3 points in the amyloid cascade. Thus, treatments may fail unless trials target simultaneously all 3 points in the equation—"triple therapy". Cerebrospinal fluid analysis and other monitoring tools may in the future provide reliable measurement of soluble load. But currently, only analysis of autopsied brains can provide this data and thus enable proper evaluation and explanation of the outcome of clinical trials. These data are essential before attributing trial failures to the advanced nature of the disease or asserting that failures prove that the theory linking Alzheimer's disease to products of amyloid precursor protein is incorrect.

1. Introduction

Clinical trials have not yet succeeded in reducing or preventing cognitive decline in Alzheimer's disease (AD). Most trials have targeted elements of the beta amyloid (Aβ) cascade. The following article reviews explanations that have been given for the failures; ascribes the lack of success to the failure to remove sufficient amounts of neurotoxic soluble oligomers, the precursors of Aβ amyloid; explains why removal of oligomers is difficult; and suggests a therapeutic course of action that may succeed.

A focus on soluble oligomers reflects a change in the original hypothesis, which attributed AD to the presence of insoluble Aβ amyloid in senile plaques (Hardy and Higgins, 1992; Hardy and Selkoe, 2002; Joachim and Selkoe, 1992). It has been more than 10 years since the hypothesis was modified with the suggestion that soluble oligomers of Aβ peptides are the most toxic products produced by the processing of amyloid precursor protein (APP) (Klein, 2002; Selkoe, 2002). The term ADDL, for Aβ-derived diffusible ligands, was suggested for these toxic moieties (Klein, 2002) but has not come into widespread use.

Many investigators have suggested that soluble oligomers should be the target of therapies designed to ameliorate or prevent AD (e.g., Hefti et al., 2013; Lue et al., 1999; Walsh and Selkoe, 2007). But in spite of their work and the work of others, several trials have been directed at removing insoluble Aβ amyloid. When these trials have failed, some investigators have suggested that we abandon the hypothesis linking AD to products of APP (www.alzforum.org/new/detail.asp?id=3234). Alternatively, a number of investigators, as quoted in the popular press (Groopman, 2013) and elsewhere (www.alzforum.org/new/detail.asp?id=3234), have suggested that the treatment began too late, at a stage when there was significant and presumably permanent

* Corresponding author at: 200 East End Ave, Apt 9i, N.Y., N.Y. 10128. Tel.: +1 212 996 1772.
E-mail address: wirosenb@aol.com.

0197-4580/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neurobiolaging.2013.10.085

neuronal and synaptic loss. Thus, new trials will be directed at early stages of cognitive decline or at high-risk populations that have not yet developed cognitive decline (Groopman, 2013; www.clinicaltrials.gov). However, if treatments must significantly reduce the soluble Aβ burden to succeed, then failure to administer treatments that target the soluble oligomers may lead to premature abandonment of patients with more advanced AD or doom ongoing and future trials in that population to failure. Moreover, as pointed out in the following section, removal of soluble oligomers may be difficult because of the possible reciprocal interrelationship of several points in the amyloid cascade. Therefore, assumptions concerning the removal of soluble oligomers may not be valid, and an effort must be made in all trials to monitor the levels of soluble oligomers to properly interpret the reasons for either success or failure of the treatment.

This review first considers—section 2 in the following— the role played by neuronal loss in producing cognitive decline. Section 3 emphasizes the importance of synaptic loss and dysfunction and the possibility of some recovery. Section 4 shows that soluble oligomers cause synaptic dysfunction and that the concentration of soluble Aβ is highly correlated with cognitive decline and/or synaptic dysfunction in animal models and in humans. Preclinical studies cited in this section also show that recovery of synaptic function and cognition requires removal of soluble oligomers. Section 5 then presents studies showing the relationship of soluble oligomers to tau, neurofibrillary tangles, and senile plaques rich in Aβ amyloid, the insoluble end product of oligomer aggregation. Particularly important is the evidence that soluble oligomers may be released from such plaques. Section 6 points out the parallelism between the failure to reduce the burden of soluble oligomers and the failure to improve cognition in both preclinical and clinical studies in which insoluble Aβ amyloid was removed. Section 7 suggests that removal of soluble oligomers may be difficult because of the tendency of senile plaques to release oligomers into the extracellular space when either the plaque is attacked or the synthesis from APP is reduced. Therefore, a triple therapy is suggested which would attack synthesis, while scavenging both soluble and insoluble Aβ. Finally, section 8 points out that measurement of soluble oligomers in autopsied brains is essential to the analysis of all clinical trials, both successful and unsuccessful, and expresses disappointment with the failure of recorded trials to insist on this end point.

2. Neuronal loss and cognitive decline

It may be that patients with advanced AD have too much neuronal loss to benefit from treatment. There is no question that neuronal loss in selected areas of the brain is highly correlated with decline in mental functioning in patients with AD and in transgenic models of AD (Calhoun et al., 1998; Giannakopoulos et al., 2003; Gomez-Isla et al., 1996; Morris et al., 2001). But limited sampling of the brain precludes a definitive decision concerning the relationship of neuronal loss to decline of the various areas of mental function. Moreover, we now know that new neurons can be formed in the human brain, at least in the hippocampus, an important and early point of attack in AD (Eriksson et al., 1998; Spalding et al., 2013). In addition, sampling of the brain, limited although it may be, has provided evidence that decreased cognitive function can precede significant loss of neurons in transgenic models of AD and in patients (Cohen et al., 2013; Irizarry et al., 1997; Paula-Barbosa et al., 1986; Selkoe, 2002). None of these data detract from the importance of neuronal loss in explaining the symptoms of AD, but the same data does make it reasonable to look at additional loci of damage.

3. Synaptic loss and cognitive decline

A better corollary of cognitive decline than neuronal loss may be loss or dysfunction of synapses. Correlation of cognitive decline in AD with loss of synapses was reported by Terry et al. (1991). A decrease in the number of synapses and an increase in size of the remaining synaptic contacts were demonstrated by Dekosky and Scheff (1990). Moreover, an extensive examination of multiple brain regions in patients under the age of 65 years revealed a significant reduction in the number of synapses per surviving neuron (Davies et al., 1987). In transgenic AD mice, Kirkwood et al. (2013) found a decrease in dendritic spines. Dendritic spines play an important role in synapse formation. In another mouse model, intraneuronal Aβ amyloid accumulated before extracellular deposition and was accompanied by synaptic dysfunction (Oddo et al., 2003). It is clear that synaptic loss and remodeling is a critical factor in AD, but it is possible that some of these changes can be reversed. Thus, there is tremendous plasticity in the injured brain with remodeling at synapses and evidence of reinnervation in the hippocampus in transgenic models of AD and in patients with AD (DeKosky and Scheff, 1990; Geddes et al., 1985; Hyman et al., 1987).

4. Soluble oligomers and synaptic dysfunction

If synaptic loss or dysfunction is an important correlate of cognitive decline it is important to inquire as to its cause in AD. Synaptic dysfunction appears to be related to the concentration of soluble oligomers of Aβ (Lue et al., 1999; Selkoe, 2002). The synaptic damage may be related to the cognitive decline that parallels the accumulation of soluble oligomers. Several studies have shown that the soluble pool of Aβ is a better correlate of cognitive decline than the insoluble pool (McLean et al., 1999; Wang et al., 2002). In a transgenic mouse model spatial learning deficits develop as diffuse, soluble deposits of Aβ accumulate in the absence of plaque formation (Koistinaho et al., 2001). In a mouse model there was a 60% loss of excitatory synapses in the immediate vicinity of oligomers and a steep decline in this loss as the concentration of oligomers decreased (Koffie et al., 2009). The soluble Aβ from human brains disrupted memory in normal rats (Shankar et al., 2008). In humans the importance of soluble Aβ has recently been illustrated in studies, which image Aβ amyloid using Pittsburgh compound B (PIB), which binds to insoluble Aβ amyloid. Imaging predicted severity of disease but the amount of soluble Aβ was an even better measure (Niedowicz et al., 2012). In another study of people with AD, soluble $A\beta_{1\text{-}40}$ was the best correlate of synaptic degeneration (Lue et al., 1999).

Long term potentiation (LTP) is dependent on synaptic health. Oligomers inhibit LTP in the rat hippocampus (Klyubin et al., 2005; Wang et al., 2002). In a mouse model of AD the inhibition of LTP was demonstrated both in vivo and in vitro (Knobloch et al., 2007). Shankar et al. (2008) demonstrated in the rat hippocampus that insoluble plaque cores from human brains did not impair LTP unless the cores were first solubilized to release Aβ dimers. As noted previously, a gradient of soluble and apparently synapto-toxic oligomers were found adjacent to dense cored plaques in a mouse model of AD (Koffie et al., 2009).

If synaptic health is impaired by soluble oligomers of Aβ, then removal of the oligomers should prevent or reverse the impairment and its consequences. That is the case. The inhibition of LTP by the soluble dimers in rat hippocampus was