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PERSPECTIVE

Reconsidering and Reforming the Amyloid Cascade Hypothesis

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Alzheimer's disease (AD) is the most common form of dementia characterized by the accumulation of intracellular amyloid-β (Aβ) plaques and extracellular neurofibrillary tangles in brain regions responsible for memory, language, and other cognitive functions [1]. The amyloid cascade hypothesis was suggested in 1992 and is considered a basis of AD [2, 3]. This theory states that the accumulation of Aβ protein is the leading causative agent of AD [4]. Aβ peptide is derived from the metabolism of amyloid precursor protein (APP) by β- and γ-secretase [5] (Fig. **1**). Insoluble fibrillar assembly of Aβ, a key neuropathological trait of AD, is indispensable for exact diagnosis but is associated poorly with cognitive impairment [6] and AD [7]. AD patients whose Aβ plaques in the brain were substantially diminished by anti-Aβ immunotherapy did not display cognitive benefits [8]. Such results have inspired further analysis of other Aβ accumulations in AD patients [9, 10]. Various forms of Aβ aggregates have been recognized together with Aβ oligomers as well as Aβ fibrils. Aβ oligomers comprise tiny oligomers, medium-sized oligomers, and high-molecular-weight oligomers. Soluble oligomers form an intricate balance, including the 8 nm fibrils of Aβ, identified in the amyloid plaques [11]. They adhere to the cell membranes of neurons, and glial cells, eliciting transmembrane signals, as well as irregular intracellular alterations [12]. Aβ oligomers may block neural activities by triggering synaptic dysfunction along with mitochondrial dysregulation and influencing microglial activity [13]. Neurons exposed to Aβ oligomers cannot develop new synapses, which leads to learning disabilities [14]. So, the latest hypothesis of amyloid cascade reveals that the soluble form of the oligomer is liable for the neurotoxicity of Aβ rather than insoluble aggregates [15, 16]. Nevertheless, Aβ oligomers displayed a dynamic nature that provides a less efficient measure in body fluids and tissues [17]. Also, perspectives vary concerning the type and size of oligomers having disease-related potential. Based on some studies, large soluble oligomeric Aβ represents the maximum portion of soluble Aβ deposits in case of AD brain but exhibits the least cytotoxicity [11]. In contrast, soluble dimers exert somewhat excessive cytotoxicity [11]. Several studies showed that the midsized oligomer such as Aβ*56 causes a particular alteration in neural signaling, resulting in phosphorylation of tau as well as accumulation, whereas dimers and trimers do not possess such feature [18]. In the past twenty years, numerous medications that minimize the formation of Aβ or enhance Aβ brain clearance have been reported. To date, surprisingly, these clinical trials have been unsuccessful in ameliorating cognitive dysfunction despite decreasing brain Aβ as shown in Table **1**.

Table 1. Major failed clinical studies of anti-Aβ therapeutics in Alzheimer's disease.

Therapeutic Agent	Therapeutic Class	Mechanism of Action	Disease Status	Clinical Trial Phase	Clinical Efficacy	References
Atabecestat	BACE1 inhibitor	Blocks the first enzymatic step of Aβ formation	Early AD	Phase II/III	No	[19-21]
Lanabecestat			Mild-to-moderate AD	Phase III	No	[22-24]
Verubecestat				Phase III	No	[25, 26]
Avagacestat	γ-secretase inhibitor	Blocks the final enzymatic step of Aβ generation	Prodromal AD	Phase II	No	[27]
Semagacestat			Probable AD	Phase III	No	[26, 28]
Tramiprosate	Aβ aggregation inhibitor	Inhibits the formation of neurotoxic Aβ aggregates	Mild-to-moderate AD	Phase III	No	[29-31]
Bapineuzumab	IgG1 humanized anti-Aβ mAbs	Clears aggregated Aβ species	Mild-to-moderate AD	Phase III	No	[32, 33]
Crenezumab				Phase II	No	[34]
Gantenerumab			Prodromal AD	Phase III	No	[35]

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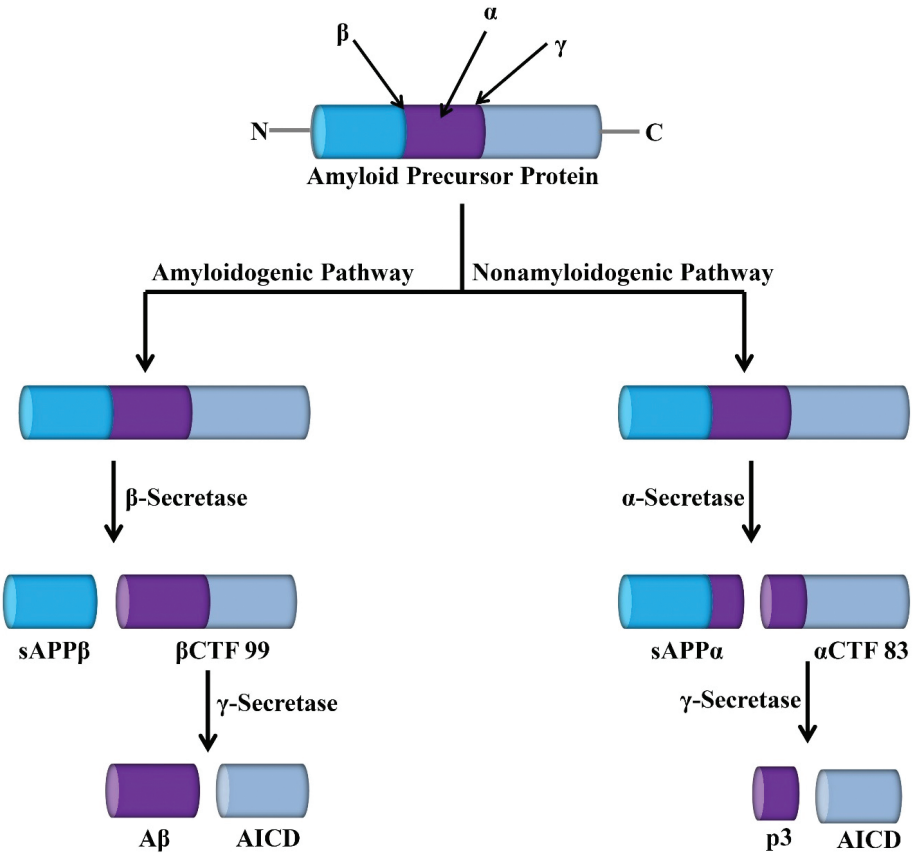

Fig. (1). The metabolism of amyloid precursor protein processing leads to the formation of Aβ peptides. sAPPβ, soluble amyloid precursor protein beta; βCTF 99, beta C-terminal fragment 99; sAPPα, soluble amyloid precursor protein alpha; αCTF 83, alpha C-terminal fragment 83; AICD, APP intracellular domain. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Surprisingly, certain medications like tarenflurbil, scylloinositol, LY-450139, AD02, CAD106, MK-8931, JNJ-54861911, and AZD3293 appeared to deteriorate the cognitive or clinical condition in comparison to placebo; it needs to be clarified whether such deteriorated outcomes are due to nonspecific side effects which overcome the definitive impacts on cognition. In case of plaque-containing and plaque-free experimental animals (mice) in which human APP is abundantly expressed, the introduction of anti-Aβ monoclonal antibodies impairs neuronal malfunction by raising the frequency of calcium ion transients, triggering abnormal neural synchronicity as well as over-activation of neurons [36]. Supporters of the Aβ cascade hypothesis oppose that these unsuccessful clinical trials do not contradict the hypothesis, but the given treatments must be more efficient and must be administered earlier Aβ has induced neuronal and synaptic damage. Moreover, they proclaim that the individuals involved in these failing clinical trials had no record of brain amyloid pathology [37]. Nonetheless, several anti-Aβ drugs have been analyzed in the initial phase of AD as well as in biomarker verified AD, and that concept has not proven as efficient yet. For instance, phase III clinical trial of LY2062430 (EXPEDITION 3) in participants with mild AD provided discouraging findings, and the phase II/III study of gantenerumab (SCarlet RoAD) in participants having prodromal AD was terminated for inefficiency. Likewise, the phase III clinical trial of verubecestat (APECS) in participants with prodromal AD was canceled due to deterioration of cognitive function and the undesirable ratio of risk-benefit assessment. Scientists are currently attempting to target Aβ oligomers directly. Immunization with Aβ antibodies can lessen the severity of AD [38]. Studies reported that immunotherapy that effectively erases the Aβ monomers or Aβ fibrils would be predicted in an extended period to change the balance of several Aβ species comprising Aβ oligomers. Aβ fibrils could form Aβ oligomers owing to solubilization through immunotherapy [39, 40].

In rats, scylloinositol (an inhibitor of the Aβ aggregation) was found to abate the neurotoxic effects of the Aβ oligomers and synaptic damage caused by oligomers, memory deficit, and inhibition of long-term potentiation [41]. LY2062430 can function by stabilizing Aβ monomers, therefore protecting the production of neurotoxic Aβ oligomers [42]. In particular, crenezumab can bind to Aβ oligomers and fibrils with equivalent strong interaction [43]. Gantenerumab demonstrated twenty-fold stronger interaction in case of Aβ oligomers than the Aβ monomers [44]. Intravenous human immunoglobulin (IVIg) includes different classes of anti-Aβ antibodies, several of which recognize Aβ oligomers as well as fibrils [45]. IVIg antibodies have been found to influence the oligomerization and fibrillization of Aβ, thus preventing neurons from Aβ-modulated toxicological effects [46, 47]. All the therapeutic strategies were inefficient and did not show any beneficial impacts on AD patients. However, effective

anti-Aβ oligomer monoclonal antibodies, for example, aducanumab, exhibit improved clinical outcomes, and a Biologics License Application has been submitted to the FDA on 8 July 2020 [48]. Monoclonal antibody BAN2401 has shown selective binding to soluble Aβ protofibrils [49], displayed positive effects in an eighteen-month, phase IIb clinical trial in 856 patients with prodromal or mild AD. The administration of 10 mg BAN2401 (biweekly) reported a noticeable reduction of both clinical decline (ADCOMS) and brain Aβ aggregation in comparison to placebo [50]. However, the biases in case of study design could influence these inspiring findings. BAN2401 is scheduled to reach clinical trials in phase III very soon. A methodological problem responsible for the repeated failure of anti-Aβ treatments is that the screening and choice of the drugs to be evaluated in volunteers with sporadic AD are tested in experimental animals (i.e., transgenic mice) with human gene correlated with familial AD cases. The expectation is that the effectiveness of the targeted drug might be the same in case of both familial as well as sporadic AD cases. Surprisingly the selected therapeutics from several studies using transgenic animals are at the initial stage of examination in participants with AD-related gene mutations after a number of years of failure in sporadic AD cases. Several of the favorable evidence for the amyloid cascade hypothesis emerges from infrequent autosomal dominant forms of AD; however, overexpression of human familial mutated forms of APP in animal models develops Aβ plaques but not neurofibrillary tangles or severe neurodegenerative events. In case of transgenic mice expressing only Aβ peptide, in the deficiency of APP overexpression, it generates plaques without showing abnormal cognitive function [51].

Moreover, several pending issues regarding the amyloid cascade hypothesis are the function and biochemical nature of Aβ oligomers; the appearance of the Aβ accumulation in cognitively stable people; a poor linkage between Aβ plaques and intensive clinical symptoms; and inadequately defined underlying pathology (which is heterogeneous), and co-morbidities correlated to AD [52-54]. Nonetheless, one problem with the original amyloid hypothesis is that the amyloid deposition patterns in the temporal region do not correlate well with the cognitive impairments in affected individuals [55]. In AD mouse models, impaired synaptic plasticity was observed before deposits of Aβ are detected [56, 57]. This might be clarified by the presence of intraneuronal Aβ accumulations that have been stated in AD transgenic mouse models and individuals with AD and Down-syndrome [58, 59]. In transgenic models, these buildups associate with the onset of behavioral and synaptic abnormalities [60-63] and significant intraneuronal accumulation was linked with early ultrastructural pathology, particularly within synaptic compartments and distal processes [64]. Soluble Aβ oligomers have a direct synaptotoxic activity at nanomolar concentrations [65]. The surrounding area of amyloid plaques was characterized via extensive dysmorphic neurites and spine turnover caused a net loss of spines [66, 67]. Indeed, continuous Aβ overgeneration at axons or dendrites acts locally to decrease the plasticity and number of synapses [68, 69]. Soluble Aβ generated abnormalities in spine abundance, shape, and composition that strongly indicate the hypothesis that the soluble form of Aβ starts inflicting toxic effects in AD brains that constitute synaptic damage in hippocampal culture [70]. Continuous Aβ exposure resulted in a marked reduction in spine density and aberrant spine morphology [70]. In order to investigate the acute activities of intracellular and extracellular Aβ42 on synaptic transmission, Moreno *et al*. [71] conducted a study and observed suppression of synaptic transmission through nanomolar levels of intracellular Aβ42 oligomers rather than extracellular Aβ40 or Aβ42 oligomers. Therefore, local axonal and dendritic abnormalities linked with amyloid deposits resulted in synapse loss and destruction of axons and dendrites in AD [67, 72]. In a study, Parihar and Brewer [73] provided details of synaptotoxic activities of Aβ in AD. Moreover, numerous studies have suggested that Aβ can impair synaptic plasticity. Besides, inconsistent findings obtained from *in vitro* and *in vivo* studies have revealed that elevated synaptic function might trigger the secretion of Aβ [74-76]. This further indicates that even though the overproduction of Aβ is synaptotoxic, lower levels might play a role as a physiological molecule that controls normal synaptic plasticity and memory [77].

AD transgenic mouse models have associated tau as the main Aβ toxicity mediator with the dendritic spines and postsynaptic compartment [78]. APP transgenic mice crossing with tau transgenic mice mediated neurofibrillary tangles pathology [79-81] and antibodies-mediated immunization of APP/Psn/tau triple transgenic (3xTg-AD) mouse models against Aβ decreased the hyperphosphorylated tau levels [82]. In line with the previous study in cultured neurons [83], endogenous tau removal prevented Aβ-stimulated behavioral impairments in a mouse model of AD expressing human APP and blocked excitotoxin-stimulated neuronal impairment in both nontransgenic and transgenic mouse models [84]. Furthermore, synaptic physiological findings suggested reducing tau levels corrected multiple irregularities in several hippocampal subregions of hAPPJ20 mouse models [85]. These findings collectively suggest the concept that abnormalities in tau phosphorylation can play a role in disease pathogenesis [86] by mediating toxic Aβ accumulation [78]. It has also been suggested that phosphorylated tau may accumulate in dendritic spines where it might influence the synaptic trafficking and/or anchoring of glutamate receptors, which eventually influences postsynaptic activity. In contrast, Aβ may increase hyperphosphorylated tau production via activating various kinases including microtubule-affinity regulating kinase (MARK) [87-89], glycogen synthase kinase-3β (GSK-3β) [90], Fyn kinase [91, 92], and cyclin-dependent kinase-5 (CDK5) [93, 94]. The notion of Aβ pathology, operating by tau, is the key to neurodegeneration and becomes central to the amyloid hypothesis. Nevertheless, in the autopsy study (even for young people), tau pathology was found before noting Aβ accumulation [95].

Brain imaging indicates that the early appearance of AD-related characteristics, like the decline in hippocampal volumes as well as impairment in glucose metabolism, in cognitively stable individuals with preclinical AD never relies on Aβ amyloidosis [96]. The study of patients with genetic markers for neurodegeneration without Aβ deposition has gained significant interest; it remains to be elucidated whether suspected non-AD pathology exerts a different pathology from AD or describes the initial phase of AD in several persons. A study regarding cognitively stable elderly individuals demonstrated that the yearly rates of converting to mild cognitive impairment are the same in 10% of people with suspected non-AD pathology and 11% of patients have Aβ amyloidosis [97].

Numerous studies revealed that neuronal damage arises in cognitively stable elderly APOE*ε4 carriers [98, 99]. Longitudinal analysis of *APP* and presenilin (*PSEN*) mutation demonstrated that atrophy in medial and lateral temporal zones began before Aβ aggregation [100]. These shreds of evidence create arguments that Aβ biological markers gain abnormality first, accompanied by neurodegenerative biomarkers and cognitive manifestations [101, 102], and indicate that AD is a multifactorial disease to which tau could boost the Aβ toxicological effect. Longitudinal investigation suggests that Aβ plaques at baseline might be involved in future cognitive deprivation in cognitively stable people; however, this deprivation can be mild and clinically relevant [103-105].

Even if the deposition of amyloid in the brain of cognitively stable individuals decreases significantly in parallel, it may still be secondary to neuronal loss involving unknown factors. Aβ deposition results from an assembly process that begins with the ongoing accumulation of soluble oligomers and may hypothesize that Aβ-plaque containing patients have been exposed to Aβ oligomers for an extended time. The prevalence of dementia in these persons indicates that they are not vulnerable to the suspected toxicity of Aβ oligomers [106]. Also, Aβ may spread extensively across the brain and body, even in cognitively healthy people. Soluble Aβ plays a significant role in modulating synaptic activities and promotes neural growth [107, 108]. Aβ exists in the whole life and is present in all the vertebrates that have been tested yet, and their molecular sequence showed a highly conserved pattern among the distinct species. For example, Aβ prevents the brain against injury, repairs leaks in the blood-brain barrier, facilitates rescue from injury, and modulates synaptic activities [109]. Studies demonstrated that Aβ formation occurs rapidly inside cells regarding physical challenges and often declines in recovery [109]. These results are further advocated by the cognitive findings in several studies that have tried to diminish Aβ levels to treat AD patients.

Whether the accumulation of Aβ results in AD or is a byproduct of the AD process remains elusive. Findings from current studies in asymptomatic or preclinical AD stages and cognitively healthy people at risk of AD ought to give some answers. There is a possibility that AD is not only a brain disease but also a systemic disease with prevalent abnormalities beyond the brain. Therefore, systemic factors may interact with brain-associated factors to alter the AD process. Meanwhile, it is essential to consider and pursue alternative hypotheses.

AUTHORS' CONTRIBUTIONS

All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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