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Amyloid β oligomers (AβOs) in Alzheimer's disease

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Abstract
The causative role of amyloid β 1–42 (Aβ42) aggregation in the pathogenesis of Alzheimer's disease (AD) has been under debate for over 25 years. Primarily, scientific efforts have focused on the dyshomeostasis between production and clearance of Aβ42. This imbalance may result from mutations either in genes for the substrate, i.e., amyloid precursor protein or in genes encoding presenilin, the enzyme of the reaction that generates Aβ42. Currently, it is supposed that soluble oligomers of amyloid beta (AβOs) and not fibrillar Aβ42 within neuritic plaques may be the toxic factors acting on a very early stage of AD, perhaps even initiating pathological cascade. For example, soluble AβOs isolated from AD patients' brains reduced number of synapses, inhibited long-term potentiation, and enhanced long-term synaptic depression in brain regions responsible for memory in animal models of AD. Concentrations of AβOs in the cerebrospinal fluid (CSF) of AD patients are often reported higher than in non-demented controls, and show a negative correlation with mini-mental state examination scores. Furthermore, increased Aβ42/oligomer ratio in the CSF of AD/MCI patients indicated that the presence of soluble AβOs in CSF may be linked to lowering of natively measured monomeric Aβ42 by epitopes masking, and hence, concentrations of AβOs in the CSF are postulated to as useful AD biomarkers.

Keywords Amyloid-β oligomer · Protein aggregation · Biomarkers · Cerebrospinal fluid · Alzheimer's disease · Neurodegeneration

Introduction

Alzheimer's disease (AD) epidemiology

There are approximately 47 million people with dementia worldwide. The number of new cases increases by almost 10 million every year (http://www.who.int/mediacentre/factsheets/fs362/en/). It is estimated that the total number of people with dementia can reach about 75 million by 2030 and might almost triple by 2050 to 132 million (http://www.who.int/mediacentre/factsheets/fs362/en/). The most frequent cause of dementia is Alzheimer's disease (AD) which constitutes 60–70% of all dementia cases (http://www.who.int/mediacentre/factsheets/fs362/en/) affecting about 6% of people over the age of 65. According to Global Burden of Disease Study 2015, there were approximately 29.8 million people worldwide with AD in 2015 (GBD 2015 Disease and Injury Incidence and Prevalence, Collaborators 2016). In 2015, dementia resulted in about 1.9 million deaths (GBD 2015 Mortality and Causes of Death, Collaborators 2016). This makes AD one of the main healthcare problems nowadays and the sixth-leading cause of death in the United States and other industrialized countries (AD Facts and figures, http://www.alz.org/facts/overview.asp 2017).

Pathophysiology of AD

AD belongs to a large group of neurodegenerative diseases (NDs) characterized by cognitive impairment and progressive synaptic damage accompanied by neuronal loss. The

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histopathological changes in the brain include the presence of extracellular amyloid plaques consisted of various peptide variants of amyloid β (Aβ) and accumulation of intracellular neurofibrillary tangles (NFTs) composed mainly of phosphorylated Tau proteins (pTau), localized predominantly in neurons (reviewed by Serrano-Pozo et al. 2011). Synaptic dysfunction in AD brain, such as reduced transmission and loss of dendritic spines, most probably precedes formation of Aβ plaques and neuronal loss. In early stages, these pathological changes are primarily seen within medial temporal lobe, and then progress subsequently to brain regions associated with neocortex (Braak and Braak 1996; de Leon et al. 1993). These alterations may start even two decades before manifestation of the first cognitive symptoms (Beason-Held et al. 2013). According to numerous human biomarker studies, decreased levels of Aβ42 in CSF and increased amyloid load in the brain, visualized by PET, precede other alterations: neurodegeneration (reflected by increased CSF Tau/pTau concentrations), impaired cerebral metabolism of glucose, brain atrophy, and finally clinical symptoms (Lewczuk et al. 2017a; Jack et al. 2013).

The risk factors of AD include: increasing age, vascular factors such as smoking, obesity, and diabetes (Reitz and Mayeux 2014) as well as genetic mutations. Majority of cases of sporadic AD are not related to any autosomal-dominant inheritance. However, a significant risk of AD development is related to certain genetic changes: the sporadic form of AD can be associated with the presence of apolipoprotein E (APOE) ε4 genotype (Holtzman et al. 2012; Spinney 2014), whereas the familial Alzheimer's disease (FAD) can be linked to mutations in presenilin1 (PS1), presenilin2 (PS2), and amyloid precursor protein (APP) genes (reviewed by Hardy and Gwinn-Hardy 1998).

AD is a complex, multifactorial disease. Despite over 100 years passing from the first description of its symptoms (Alzheimer 1907), the precise etiology of AD remains unknown, with the exception of 1–5% of cases, where the presence of genetic factors has been identified (Reitz and Mayeux 2014). Attempts to clarify AD etiopathogenesis have resulted in several different, partially complementary hypotheses. The presence of amyloid deposits, as the main factor leading to damage of the nerve tissue (amyloid hypothesis) has been postulated for over 25 years (recently reviewed in Selkoe and Hardy 2016). It seems that in the very early stages of AD, the altered equilibrium occurs between the production of amyloid proteins and its clearance. Moreover, this imbalance may often be the initiating factor in AD. Amyloid hypothesis is supported by the fact that progressive Aβ deposition is observed in early, preclinical stages of AD and, finally, in all AD patients. Aβ deposition is followed by surrounding neuritic and glial cytopathology in brain regions responsible for cognition and memory.

Although recently revisited (Selkoe and Hardy 2016) amyloid hypothesis of AD seemed initially very consistent in its assumptions, the sequence of failures of clinical trials targeting the accrual of Aβ has been confusing and caused the necessity of reevaluation of the hypothesis. Some concerns have arisen since the inception of this theory. The first question was why the degree of cognitive impairment and the neuronal loss are often better reflected by amount and distribution of NTF than by burden of Aβ senile plaques in brain (Arriagada et al. 1992; Gómez-Isla et al. 1997). A possible explanation may be the fact that Aβ deposits seem to be a very early event in AD development that precedes the symptomatic dementia by many years. These Aβ deposits lead to subsequent molecular and cellular alterations, such as NTFs, neuronal dystrophy, or microgliosis, i.e., pathological events that are closer to dementia and more relevant to neuronal dysfunction.

On the contrary, in some studies, the abundant amyloid plaques were detected *post mortem* in brains of cognitively normal people at death (reviewed by Nelson et al. 2012). This raised the second question, why Aβ deposits occur in brains of humans without any evidence of their cognitive impairment. It may be elucidated partly by the assumption that these deposits could be non-AD-related, neurite-free diffuse plaques. Moreover, this type of plaques is associated with much lower levels of oligomeric forms of Aβ than typical amyloid plaques from AD brains (Esparza et al. 2013). These apparently normal persons, who have abundant plaques, may actually have low plaque-associated soluble oligomers of Aβ (AβO) levels, what suggests that plaques can effectively sequester oligomers in a non-diffusible form, potentially less neurotoxic.

As it was mentioned above, the amyloid hypothesis has so far failed to offer any causative treatment. Numerous trials with anti-amyloid targeted therapeutic agents have not met their assumed endpoints that led to the conclusion that amyloid hypothesis has certain inconsistencies and controversies, which should be critically discussed to expand our view of pathogenesis beyond Aβ and Tau pathology. The failure of these trials presumably might result from inappropriate preclinical data in studies that enrolled many subjects in the later stages of AD. The prodromal stage patients would most likely respond to the treatment. Unfortunately, currently, there is a lack of reliable and early AD diagnostics which would allow to select those presymptomatic stage AD subjects.

Furthermore, some of the agents tested could have poor brain penetration or low therapeutic indices. What is more important, these clinical failures can be attributed to the wrong targets of drugs tested (Selkoe 2011). Therefore, the amyloid hypothesis has been reevaluated in recent years. Currently, extensive studies suggest AβOs as the correct

target (reviewed by Viola nad Klein 2015 and by Montoliu-Gaya and Villegas 2016).

Soluble Aβ oligomers in AD

Protein aggregation is observed in a variety of NDs, also known as amyloid disorders, including AD. While monomers of Aβ are harmless, they become neurotoxic after their self-association, which has been verified in central nervous system (CNS) slice cultures (Lambert et al. 1998). Despite the fact that mature Aβ fibrils within senile plaques have long been supposed to be the cause of AD, recent evidence suggests that the intermediate oligomeric forms produced during fibrillization are the toxic factors (Verma et al. 2015). These soluble forms of Aβ, also termed Aβ-derived diffusible ligands (ADDLs), may affect neurons, but escape detection by measurements of solid amyloid.

It was hypothesized that soluble AβOs are sequestered within Aβ plaques until they reach certain physical limit of Aβ, then they can diffuse onto synaptic membranes and other hydrophobic cell surfaces (Hong et al. 2014). Moreover, it was postulated that AβOs may trigger a harmful cascade damaging neurons and synapses (Morris et al. 2014). The levels of soluble AβOs in human brain have been reported to correlate better with the severity of the disease than amyloid plaques do (da Rocha-Souto et al. 2011). It was also demonstrated that fibril-free AβO solutions are essential for memory loss (Brito-Moreira et al. 2017), while the fibrillar Aβ in amyloid deposits is not the active factor affecting the cognition (Martins et al. 2008).

Various species of AβOs include small, globular particles, and elongated protofibrils (PFs) that represent chains of these spherical fragments (Kayed et al. 2003). The formation of AβOs starts from alterations in the conformation of monomeric Aβ, resulting in low molecular weight (LMW) dimers and trimers, followed by aggregation to soluble spherical oligomers consisted of 12–24 monomers. LMW elongate to high-molecular-weight (HMW) oligomers with curvilinear strings or PFs, which finally become insoluble fibrils (Glabe 2008). These different Aβ conformations may be produced by several pathways and vary in their toxic effects, although it remains uncertain which types are actually the pathogenic factors (Ladiwala et al. 2012).

The tissue localization of soluble AβO-specific immunostaining in human AD brain is distinct from fibrillar amyloid (Kayed et al. 2003). In very early stages of AD pathology, before the appearance of amyloid plaques, oligomers assemble perisomatically, rather than intracellularly, surrounding individual diffuse neurons. It was shown that AβO-specific immunoreactivity in human AD brain was observed as clusters of deposits distributed in the same regions of fibrillar Aβ stains, although they were separate and spatially distinct (Kayed et al. 2003). Interestingly, no AβO-specific immunoreaction was seen in brain samples from age-matched non-demented reference group (Kayed et al. 2003).

It was also widely discussed whether AβOs are extra- or intracellular proteins (reviewed by Kayed and Lasagna-Reeves 2013). Currently, there is convincing evidence for both localizations. Although extracellular associations of AβOs with surface membranes were observed already at very early stages of AD pathology (Baker-Nigh et al. 2015), the intraneuronal Aβ accumulation appears prior to extracellular amyloid plaque formation (Wirths et al. 2001). This Aβ localization may result not only from intracellular production, but also from an uptake and internalization of extracellular Aβ pool through various receptors and transporters. Moreover, intracellular AβOs were identified in cholinergic neurons, suggesting their role in cholinergic deficiency either (Baker-Nigh et al. 2015). It appears that AβOs undergo a dynamic exchange and are able to dislocate between the extracellular space and inside the cells (Gaspar et al. 2010).

Neurotoxic effects of AβOs

The early cognitive symptom of AD is an inability to form new memories. The reason of this early memory loss is assumed to be related to a synapse failure caused by soluble AβOs. Toxic influence of AβOs was widely examined in AD brain tissues, cell cultures, and transgenic animal models (Table 1). It was demonstrated in series of experiments that neuronal changes may be generated by amyloid oligomers of various origin, i.e., by synthetic peptides or Aβ species secreted in cultured cells as well as by AβOs extracted from the brains of AD patients or animal models of this disease (reviewed by Viola and Klein 2015).

Soluble Aβ oligomers may cause a highly selective neuronal death accelerated by increasing exposure to AβOs (Lambert et al. 1998). It was also shown that soluble AβOs may directly trigger dysfunction of neural signaling, which leads to early memory loss and the progression of dementia in AD. Moreover, in brain slices, AβOs rapidly inhibited long-term potentiation (LTP) of synapses (Klein et al. 2001). Harmful activity of AβO may induce certain aberrations in synapse composition, shape, and their density (Lacor et al. 2007).

AβOs bind mostly to neurons in hippocampal cultures, whereas in cortical and cerebellar cultures, this binding occurs in a lesser degree (Chromy et al. 2003). It was revealed that anti-AβO antibodies labelling gave diffused immunostaining around neuronal cell bodies, with dendritic pattern (Lacor et al. 2004). It was also demonstrated that AβOs were bound to neuron surfaces in clusters

Table 1 AD-associated alterations attributed to AβO activity

Effect of AβO activity	References
Selective neuronal degeneration and nerve cell death	Lambert et al. (1998)
Neuritic dystrophy in cultured neurons	Shankar et al. (2008)
Synaptic dysfunction	Wirths et al. (2001) Lacor et al. (2007) Shankar et al. (2008)
Synaptic damage, changes of synapses composition, shape and density	Lacor et al. (2007)
Dysfunction of synaptic plasticity, inhibition of LTP and enhancement of LTD	Klein et al. (2001) Shankar et al. (2008)
Activation of metabotropic and ionotropic glutamate receptors	Lambert et al. (1998)
Ion channel activity	Kayed et al. (2003)
Ligand-like activity	Chromy et al. (2003)
Inactivation of insulin receptor and insulin resistance	Townsend et al. (2007)
Disrupted Ca^{2+} homeostasis	Zhao et al. (2004) Lazzari et al. (2015)
Induction of Tau hyperphosphorylation at AD-specific epitopes	Shankar et al. (2008)
Activation of microglia and astrocyte response	Sondag et al. (2009)

confined almost entirely with a subpopulation of synaptic spines (Lacor et al. 2004). Furthermore, this accumulation of AβOs in cultured rodent hippocampal neurons was similar to their brain distribution in early stages of human AD pathology (Lacor et al. 2004). The changes in dendritic spines in cultured hippocampal neurons after exposition to toxic AβOs were also similar to those in human brain affected by AD (Lacor et al. 2007). These findings indicate that AβOs are closely associated with impaired function of memory-related synapses and may offer a molecular basis for loss of connectivity and impaired memory function in early AD.

In normal rats, impaired memory of a learned behavior was observed after intraventricular application of soluble oligomers of Aβ42 isolated directly from human AD brains (Shankar et al. 2008). Furthermore, AβO injections resulted in reduction of a synapse number and their function in dose-dependent manner. It also led to the inhibition of LTP and enhancement of long-term synaptic depression (LTD) in rodent hippocampus (Shankar et al. 2008). These various effects were specifically recognized as exerted by Aβ dimers. On the contrary, when insoluble Aβ plaque cores were isolated from the same AD cortices, they did not affect LTP after application to rodents. The toxic effects of plaque cores on synapse function were seen only after their solubilization to release Aβ dimers, what suggests that Aβ plaques are largely inactive but sequester synaptotoxic Aβ dimers (Shankar et al. 2008). These results are in line with findings of Koffie et al. (2009), who revealed that AβOs surrounding plaques contribute to synapse loss in a mouse model of AD. In h-APP transgenic mice, synaptic density was decreased in close proximity of plaques, where soluble AβOs have a specific penumbra, whereas synapse number increased with the distance from edge of the plaque core (Koffie et al. 2009).

AβOs may be the link between the two major pathologies in AD, i.e., amyloid plaques and neurofibrillary tangles. It was shown that soluble oligomers of Aβ42 can drive Tau alteration. AβOs can trigger changes in Tau protein characteristic for AD (Shankar et al. 2008). They induce hyperphosphorylation of Tau at AD-specific epitopes and cause neuritic dystrophy in cultured neurons. Moreover, crossing h-APP with h-Tau transgenic mice enhanced Tau-positive neurotoxicity (Lewis et al. 2001).

Furthermore, it was demonstrated that AβO may not only injure the neurites of brain neurons, but also activate microglia and astrocyte response (Sondag et al. 2009). The influence of LMW AβOs on memory, astroglial cell response, and number of neurons was examined in double-transgenic human APP–Tau mice (da Rocha-Souto et al. 2011). An exponential increase of brain levels of AβOs in aging mice was observed. In addition, the load of AβO deposits significantly correlated with fibrillar Aβ plaque deposition as well as with neuronal loss and numbers of astrocytes, although not with memory deficits. The astrocyte response, as represented by number of glial fibrillary acidic protein-positive cells, was related to memory impairment and neuronal cell loss. On the contrary, no relationship between total Aβ plaque burden and number of astrocytes or neurons was found (da Rocha-Souto et al. 2011). According to their results, an assumption can be made that the astrocytic response is possibly initiated by accumulation of AβOs in the brain and might also affect cognition in these mice model of AD (da Rocha-Souto et al. 2011).

Cellular receptors related to AβO activity

Although it is known that extracellular AβOs are able to bind to the surface of neurons, resulting in synaptic dysfunction and neurodegeneration, precise mechanism of Aβ oligomers' activity remains uncertain. Binding of AβOs to cell membranes is probably mediated by particular cell surface proteins that act as toxin receptors, resulting in numerous alterations in various signaling pathways. There are over 20 candidates for AβO receptors, including glutamate and adrenergic receptors as well as prion-like proteins and others (Fig. 1). Unfortunately, no single candidate receptor protein has been shown yet to be responsible for all features of AβO activity.

Glutamate is one of the main excitatory neurotransmitters in human CNS with signaling through ligand-gated ion channels or through metabotropic receptors (reviewed by Petroff 2002). The *N*-methyl-D-aspartate receptor (NMDAR) belongs to glutamate receptors with ion channel activity that plays a role in controlling of synaptic plasticity and synapse formation in CNS (Li and Tsien 2009). Excessive activation of NMDAR by soluble AβOs triggers disproportionate influx of Ca^{2+} into neurons, which leads to excitotoxicity, mitochondrial dysfunction, and loss of synapses (Zhao et al. 2004). By modulation of NMDAR-dependent signaling pathway, AβOs induce also the decrease in spine density (Shankar et al. 2007).

The α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) is also a glutamate ionotropic transmembrane receptor. Tetrameric AMPAR is composed of four subunits, which of GluA1 and GluA2 play an important role in synaptic plasticity and LTP (Boehm et al. 2006). Soluble AβOs, but not monomers, mediate the internalization of the GluA1/GluA2 subunits by endocytosis (Zhang et al. 2011), leading to synaptic dysfunction (Hsieh et al. 2006). GluA1 subunit functions in brain are also associated with another receptors signaling pathway, β_2-adrenergic receptors (β2ARs) (Joiner et al. 2010). Activation of β2ARs is essential for normal learning and memory (McIntyre et al. 2012) and promotes synaptic LTP (Qian et al. 2012), whereas degradation of these receptors may be induced by AβOs (Li et al. 2013a). LMW oligomers led to a decrease in the neuronal levels of β2ARs, activated brain microglia, and induced impaired hippocampal LTP in mice in vivo (Yang et al. 2017). Moreover, the deficits of AMPAR signaling induced by AβOs are mediated by hyperphosphorylation and abnormal distribution of Tau protein in dendritic spines, resulting in early cognitive impairment (Miller et al. 2014).

Although additional receptors may contribute to mediation of AβO action, more recent evidence indicate that significant part of AβO toxicity may be related to interaction with cellular prion protein (PrP^C) on the neuronal surface. PrP^C was identified as AβO co-receptor, which mediates an impairment of synaptic plasticity by AβOs, although the infectious form PrP^{Sc} conformation is not necessary (Lauren et al. 2009). The mediation of the signal transduction of AβOs requires formation of complexes between PrP^C and transmembrane receptors such as NMDAR (You et al. 2012) or metabotropic glutamate receptor 5 (mGluR5) (Um et al. 2013; Haas et al. 2016). Soluble extracellular AβOs bind to lipid-anchored PrP^C with high affinity and specificity (Chen et al. 2010). AβOs, together with PrP^C, interact with the membrane receptors, forming annular amyloid pores and ion channels to induce aberrant cytoskeletal changes in dendritic spines (Sivanesan et al. 2013). It was demonstrated that Aβ42 oligomers, but not monomers, significantly altered Ca^{2+} release from intracellular stores (Lazzari et al. 2015), what induced intracellular Ca^{2+} increase in neurons via the complex PrP^C–mGluR5, with harmful effects on synaptic transmission (Beraldo et al. 2016). Moreover, PrP^C inhibits

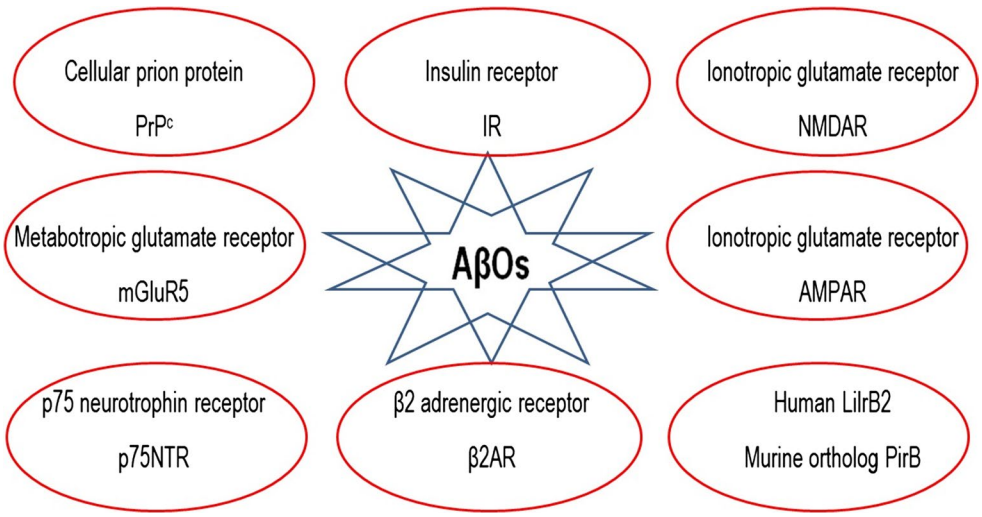

Fig. 1 Candidates for receptors of Aβ oligomers

formation fibrillary form of Aβ, trapping Aβ in an oligomeric state (Younan et al. 2013).

It was suggested that AβOs may also induce neuronal death via nerve growth factor (NGF) receptor (Yamamoto et al. 2007). NGF mediates cell loss through a low-affinity p75 neurotrophin receptor (p75NTR) (Kayed and Lasagna-Reeves 2013). Synapse targeting of AβOs involves activation of p75NTR. The toxic effects of AβOs mediated by p75NTR depend on a "death domain" in the cytoplasmic part of this receptor molecule (Zhang et al. 2003; Costantini et al. 2005).

Toxic activity of AβOs may be linked with impaired insulin receptors (IR) signaling and brain insulin resistance (De Felice et al. 2014). AβOs bind to neuronal IRs and affect their insulin-induced autophosphorylation, preventing activation of specific kinases required for LTP (Townsend et al. 2007). In cultures of mature hippocampal neurons, soluble AβOs caused a rapid, substantial loss of surface IRs, especially on dendrites (Zhao et al. 2010). It indicates that AD is sometimes called a "brain-specific form of diabetes" or "type 3 diabetes" (de la Monte 2014).

Human leukocyte immunoglobulin-like receptor B2 (LilrB2) and its murine orthologue paired immunoglobulin-like receptor B (PirB) belong to leukocyte immunoglobulin-like receptors (LIR) expressed on immune cells. Both LilrB2 and PirB are thought to be nanomolar affinity receptors for Aβ oligomers (Kim et al. 2013), which also participate in the process of synaptic plasticity and neurite growth in CNS (Kim et al. 2013).

AβOs as potential neurochemical biomarkers of AD

CSF concentrations of Aβ42, also combined with Aβ40 in a form of Aβ42/40 ratio, together with Tau proteins, are well established neurochemical biomarkers used in the diagnostics of AD (Lewczuk and Kornhuber 2011; Lewczuk et al. 2017b). Despite enhanced Aβ42 accumulation in AD brain (Lewczuk et al. 2003), concentrations of monomeric Aβ42 in the CSF of AD patients are decreased. Amyloid burden in brain may also be visualized by positron emission tomography (PET) imaging using the ligand ^{11}C-PIB, which binds to fibrillar Aβ (Klunk et al. 2004), not detecting AβOs or diffuse plaques that are found in the earliest stages of AD process (Cairns et al. 2009).

Inverse correlation between amyloid load on PET imaging and CSF Aβ42 concentrations (Fagan et al. 2006; Forsberg et al. 2008) as well as Aβ42/40 ratio (Lewczuk et al. 2017a) has been reported, which suggested that Aβ aggregation and sequestration into plaques may be responsible for this observation. In addition, the decrease of CSF concentrations of Aβ42 in AD may be partly explained by oligomerization of amyloid peptides. It is possible that AβOs can interfere with diagnostic tests causing underestimation of Aβ levels due to epitope masking (Englund et al. 2009). Combining denaturing and non-denaturing quantifications of Aβ42 into an "oligomer ratio" allowed for the estimation of AβOs in biological samples. Indeed, natively measured Aβ42 in AD and MCI samples displayed the expected decrease in the concentration, as well as increased Aβ42/oligomer ratio, but not when analyzing under denaturing conditions. These results confirm that the lowering of natively measured Aβ42 is caused by oligomerization (Englund et al. 2009).

Assuming an important role of AβOs in the pathogenesis of AD, their detection and measurement in body fluids would be extremely valuable. As AβOs accumulate in a very early stage of the disease, and perhaps, they are the first indicators of AD pathology, AβO assays would be useful for capture the onset the disease, especially in families carrying AD-related mutations (Lacor et al. 2004). In contrast to monomeric Aβ42 peptide, soluble AβOs are not routinely established as neurochemical biomarkers yet, although they are presumably more specific for AD. However, commercially available assays for the determination of AβOs already exist. The concentrations of AβO species in CSF seem to be 10^3 times lower, with picomolar (or fg/mL) range, in comparison with Aβ monomers, which concentrations are in pg/mL range (Hölttä et al. 2013). This requires development of very sensitive assays, allowing for the detection such low concentrations of analyte. Further investigations to develop high-sensitivity analytical platforms for AβO determination as well as rigorous methods of developing stable assay standards are necessary before implementation these assays as a routine diagnostic method for the evaluation of AD patients.

Studies concerning detection and quantification of AβO levels in CSF gave diverse results (Table 2). CSF AβOs in AD were reported to be elevated, decreased, unchanged, or not measureable (reviewed by Viola and Klein 2015). These differences may be explained by various techniques used for the measurement of AβOs, differences in patients' cohorts or inconsistent preanalytical samples treatment. Moreover, amyloid oligomers are heterogeneous and instable compounds that may vary in their molecular mass, composition, and molecular conformation.

Despite the heterogeneity of methods used and oligomers assayed, majority of authors reviewed in this paper report increased concentrations of AβOs in AD. As it was described by Georganopoulou et al. (2005), the assay based on monoclonal anti-AβO antibodies coupled to DNA-tagged nanoparticles was able to capture AβOs using PCR amplification. Detection of AβOs in CSF collected shortly postmortem from patients with AD revealed a higher assay signal than in CSF from healthy age-matched controls (Georganopoulou et al. 2005). Likewise, Savage et al. (2014) have developed a competitive enzyme-linked immunosorbent assay (ELISA)

Table 2 Soluble oligomers of Aβ as biomarkers of AD—summary of results

References	Method	Results
Englund et al. (2009)	Sandwich ELISA (Innotest® β-Amyloid 1–42, Innogenetics), specifically constructed to measure full-length Aβ1–42	AD and MCI samples: a decrease in natively measured Aβ42 in comparison with healthy controls and FTD No significant differences between groups in analysis of denatured Aβ42 AD and MCI had a higher CSF Aβ42 "oligomer ratio" than control group
Gao et al. (2010)	Misfolded protein assay detection of soluble oligomers of Aβ x-40 and x-42 peptides in CSF	Presence of aggregated Aβ40 in the CSF of AD patients Diagnostic sensitivity and specificity of aggregated Aβ40 with Aβ42 > 95 and 90%, respectively
Fukumoto et al. (2010)	ELISA test specific for high-molecular-weight (HMW) AβOs of 40–200 kDa	HMW AβOs of 40–200 kDa significantly higher in CSF samples from AD or MCI patients compared to controls ROC curve analysis: AUC for the CSF HMW AβOs (0.8440) was larger than for Aβ42 (0.7120) A negative correlation of HMW AβO CSF levels with MMSE scores in the AD/MCI group
Santos et al. (2012)	Flow cytometry assay for CSF Aβ-oligomer levels	CSF Aβ-oligomer levels in AD patients elevated in comparison with the non-AD group Ratio AβOs/Aβ42 significantly elevated in AD subjects compared to non-AD subjects A negative correlation between the amount of AβOs and MMSE score in AD patients
Wang-Dietrich et al. (2013)	Surface fluorescence intensity distribution analysis (sFIDA)	Homogenously low AβO levels in all control subjects Significantly higher levels of AβOs in AD group than in controls AβO numbers correlated with MMSE score
Bruggink et al. (2013)	ELISA specific for Aβ oligomers the same capture and detection antibody recognized relatively small oligomers (10–25 kDa) and not monomers.	AβO levels in brain tissue increase with age of APP/PS1 transgenic mice AβO concentration in HAMA-depleted human AD hippocampal extracts was significantly higher than in non-demented controls No difference detected between AD and control groups in AβO levels in pre-treated CSF samples
Herskovits et al. (2013)	Monoclonal single antibody sandwich ELISA assay for the detection of oligomerized Aβ42 and sAPPα fragments adapted to a Luminex platform	Significantly elevated AβO CSF levels in AD patients compared to control subjects Significantly elevated ratio of AβOs to Aβ42 in AD patients compared to control subjects
Hölttä et al. (2013)	Highly sensitive AβO ELISA with the same N-terminal monoclonal antibody 82E1 for capture and detection specific for AβOs, with a lower limit of quantification of 200 fg/mL	CSF AβO levels in AD patients higher than in controls Large overlap in AD-control comparisons and poor separation of AD from controls Increased AβO levels in patients with MCI who later converted to AD
Savage et al. (2014)	A two-site ELISA using 19.3 monoclonal antibody against AβO bead-based fluorescent platform able to detect single photons of emitted light	A significant three- to fivefold increase in CSF levels of AβOs in AD compared with comparably aged controls Range of CSF levels of AβOs 0.1–10 pg/mL Inverse correlation of AβO levels with MMSE score ROC curve analysis: AUC for AβOs 0.860, diagnostic sensitivity 80% and diagnostic specificity 88%

Table 2 (continued)

References	Method	Results
Jongbloed et al. (2015)	A validated in-house AβO-specific ELISA assay	No difference between AD, MCI and non-demented controls in AβO concentrations at baseline or follow-up MCI patients that develop AD and stable MCI patients—similar baseline AβO levels in CSF An annual decrease in AβO levels in MCI and AD patients Strong association of decrease in AβO levels over time with severity of cognitive decline in AD patients

to quantify AβOs in CSF using 19.3 monoclonal antibody, coupled to a highly sensitive, fluorescent, bead-based assays (Savage et al. 2014). This assay distinguished HMW Aβ oligomers in human brain from monomers. The authors have shown a significant, three-to-fivefold increase in CSF AβOs in AD patients in comparison with age-matched controls, with oligomer range between 100 and 10000 fg/mL. AβO levels revealed also an inverse correlation with mini-mental state examination (MMSE) score. Moreover, area under AβO ROC curve was 0.860, with 80% sensitivity and 88% specificity, what suggests reasonable utility of oligomers as a diagnostic marker for AD.

Similar result was obtained by Herskovits et al. (2013), who adapted a monoclonal single antibody sandwich ELISA assay to a Luminex platform for detection HMW AβOs in CSF of AD patients. The authors found significantly elevated levels of AβOs as well as the ratio of AβOs to Aβ42 in CSF samples from AD patients when compared with age-matched control subjects. When analyzed associations between Aβ oligomers and cognitive status, only the ratio of AβOs to monomeric Aβ42 shown an inverse correlation with MMSE score in the entire sample pooled, but not when computed for AD or control cases separately (Herskovits et al. 2013).

Increased levels of AβOs were also described by Fukumoto et al. (2010), who employed an assay based on the monoclonal antibody BAN50 both for capture and detection and synthetic AβO as standard. This kit allowed for detection of HMW of 40–200 kDa in CSF. The levels of HMW AβOs in AD or MCI patients were significantly higher than in normal controls and correlated inversely with MMSE score. The AUC for the AβOs (0.844) was greater than that for CSF Aβ42 (0.712), suggesting that AβOs may serve as a test for discriminating between AD/MCI patients and cognitively normal control.

Another study showed also significantly higher value of the AβO readout in 14 AD patients than in 12 age-matched non-demented controls, using surface fluorescence intensity distribution analysis (sFIDA) (Wang-Dietrich et al. 2013). The authors demonstrated a clear difference between AD patients and control group, allowing for a distinction between both groups. Although AD group exhibited high variations among samples, almost all AD samples characterized with significantly elevated sFIDA readouts in comparison with homogenously low levels of AβOs in the control group, which resulted in a sensitivity of 93% and a specificity of 100% (Wang-Dietrich et al. 2013). Furthermore, the authors demonstrated significant, negative correlation of AβO number with the MMSE scores, what indicates that sFIDA readout seems to reflect the severity of AD, similar to the results described above.

Of particular interest are reports suggesting that elevated AβO levels may not only be helpful in the diagnosis of AD, but they also can predict if an MCI would eventually

progress to AD dementia. Using a highly sensitive AβO-specific ELISA with the same N-terminal monoclonal antibody 82E1 for capture and detection, Hölttä et al. (2013) demonstrated not only increased levels of AβO in CSF of AD patients in comparison with healthy controls, but also elevated AβO concentrations in subgroup of MCI patients who later converted to AD. Their results indicate that the presence of high or measurable AβO levels in CSF may be associated with increased risk of AD development.

It was shown that not only oligomers of Aβ42 may be elevated in CSF of AD patients. Using a novel misfolded protein assay for the detection of soluble oligomers composed of Aβx-40 and Aβx-42 peptides, Gao and co-workers demonstrated also increased levels of oligomeric Aβ40 in CSF, which may be a potential biomarker for the diagnosis of AD (Gao et al. 2010). The authors achieved diagnostic sensitivity and specificity greater than 95 and 90%, respectively. Moreover, Aβ40 oligomers were not only found in individuals with more advanced stage of AD, but also in AD patients with higher MMSE scores, at early stage of the disease (Gao et al. 2010). These results suggest that circulating Aβ40 oligomers, and not only Aβ42 oligomers, could be a potential new biomarker in early AD.

On the contrary, some studies revealed that AβO levels were unchanged in AD patients. For example, in the work of Santos and colleagues, CSF AβOs, as determined in flow cytometry, displayed only a tendency to be increased in AD patients in comparison with the non-AD group (Santos et al. 2012). However, the ratio of AβOs to Aβ42 was significantly elevated in AD subjects compared to non-AD subjects. Moreover, there was a significant negative correlation between the AβOs and MMSE score (Santos et al. 2012).

Similarly, no significant differences between study groups were observed for AβO levels in the work of Jongbloed et al. (2015), who assessed the prognostic utility of AβO levels in CSF as indicators of AD progression and conversion from MCI to AD in comparison with age-matched non-demented controls, using a validated in-house AβO-specific ELISA test. Levels of CSF AβOs did not differ between the groups of non-demented, MCI, and AD neither at baseline, nor at follow-up. However, an annual rate of AβO decrease was higher in MCI group than in AD patients. This decrease in concentrations of oligomeric Aβ over time was strongly associated with severity of cognitive decline in AD patients (Jongbloed et al. 2015).

The study of Bruggink et al. (2013) points out that the differences in concentration of AβOs may be related to interference of human anti-mouse antibodies (HAMA) in CSF collected from AD patients. The authors developed an ELISA assay specific for AβOs, which predominantly recognized relatively small, 10–25 kDa oligomers. While AβO levels increased with age in brain homogenates in mouse model of AD, the determination of AβOs in human brain samples required a pretreatment to remove HAMA. Aβ oligomer levels in HAMA-depleted human hippocampal extracts were significantly increased in AD compared with non-demented controls. Furthermore, Aβ oligomer levels were quantified in pretreated human CSF samples with no difference detected between AD and control groups. These results prove the influence of HAMA interference in assays and suggest that LMW oligomers might not be suitable as biomarkers for AD.

Surprisingly, decreased concentrations of AβOs in CSF were also demonstrated by some authors. It was suggested that decline of AβO CSF levels may, similar to monomeric Aβ42, be an inverse AD biomarker (Sancesario et al. 2012). A simultaneous detection of LMW and HMW AβOs was performed using flow cytometry and fluorescence resonance energy transfer (FRET) methods. Different species of Aβ oligomers were evaluated in native CSF in AD group and compared with patients with other dementia (OD) diseases and in subjects with other neurological disorders (OND). AβO concentrations were also compared with levels of Aβ42 monomers, total Tau, and $pTau_{181}$. In AD patients, the CSF levels of AβOs and the ratio of AβOs to p-Tau_{181} were significantly lower than in other OD and OND patients, with diagnostic sensitivity of 75% and a specificity of 64%. Interestingly, levels of AβOs appeared higher in AD than in OND patients after the dilution of CSF in RIPA buffer, what may be caused by interference of dilution or partial disaggregation of oligomers by ionic and non-ionic RIPA detergents (Sancesario et al. 2012).

Reports have also been published on attempts to implement of blood-based measurement of AβOs. The possible use of plasma AβO levels was suggested by Zhang et al. (2014) who demonstrated results of a two-target assay measuring AβOs and soluble TNF-R. They revealed increases in AβOs and soluble TNF-R plasma levels that accurately differentiated mild AD patients from control subjects and to some extent from amnestic mild cognitive impairment (aMCI) patients. Similar results were obtained by Xia et al. (2009) who examined concentrations of AβOs and monomeric Aβ42 in plasma of AD patients, using ELISA assays with the same N-terminal anti-AβO antibody for the capture and detection of the antigen. They demonstrated that more than half of AD subjects had detectable plasma levels of AβO, while 70% of control subjects had AβO plasma concentration below the detection limit (Xia et al. 2009). Moreover, AβO plasma levels were closely associated with Aβ42 monomer levels across all of the subjects, whereas in analysis of sequential plasma samples from AD patients decreased both AβOs and monomeric Aβ42 levels were observed in follow-up period. Interestingly, both oligomer and monomer levels of Aβ were higher in brain tissue of AD cases (Xia et al. 2009).

Likewise, the potential use of serum AβO was suggested in the study of Kasai et al. (2013), who assayed HMW oligomers in matched pairs of human serum and CSF collected simultaneously from the same non-demented individuals. A single antibody ELISA assay employed a monoclonal antibody BAN50 for both capture and detection of AβOs. Unexpectedly, the assay detects positive signals in 60% of serum samples and in 80% of CSF samples obtained from non-demented subjects. Moreover, as the concentrations AβO were high in control serum, it suggests the possible detection of non-pathological Aβ complexes associated with serum carriers (Kasai et al. 2013). Furthermore, the authors revealed a significant positive correlation of serum AβOs with the levels obtained from matched CSF samples. These findings suggest that the levels of serum AβOs might be useful as a marker for AD, reflecting an intact smaller AβOs, which could be transported across the blood–brain barrier in contrast to large particles of fibrillar Aβ (Kasai et al. 2013).

Difficulties in the development of assays for AβOs—technical aspects and limitations

Based on the data presented above, AβOs are promising candidates for AD biomarkers. However, additional studies are needed before implementation of the analysis of AβOs as a diagnostically useful method for the routine clinical assessment of AD patients. The evaluation of the role of AβOs in AD is troublesome due to the lack of robust well-standardized, high-sensitivity assay, which would be confirmed on large cohorts of patients in critical multi-center comparison. Full validation of AβO assay should include also intra- and inter-assay variability, spike recovery, dilution linearity, and limit of detection (Savage et al. 2014). These inconsistent and conflicting results on AβO levels in CSF of above-presented studies may be due to a relatively small number of clinical samples, performed on a variety of diagnostic platforms with different antibody pairs with uneven avidity for LMW or HMW AβOs and, therefore, may differ from outcome of assays that are dedicated to all oligomeric forms.

Studying Aβ oligomers is also methodologically difficult because of their heterogeneity. An increasing number of varied size and structure AβOs have been implicated in the pathophysiology of AD. Although the chemical composition of AβOs is poorly defined, several lines of evidence suggest that AD-associated oligomers are mainly composed of Aβ42, although shorter and longer molecules are also involved (Gao et al. 2010). Moreover, the size of an AβO is directly related to the amount of Aβ peptides that form the oligomer and influences its properties in a pronounced degree. There are variegated species of oligomers, from dimeric AβOs to 10–20 mers and even larger aggregates in size (Fukumoto et al. 2010). Furthermore, the composition of the Aβ-oligomer, which could in theory be any combination of Aβ subtypes, also influences its conformation (Jongbloed et al. 2015). The use of different test systems leads to the detection of various oligomer species with different compositions, sizes, and molecular conformations. Therefore, the results of above-described studies varied in such a degree and led to conflicting conclusions.

The detection of AβOs can be challenging, because they are unstable and may disassemble or aggregate again during analysis. Furthermore, oligomerization of Aβ may be an artefactual consequence of certain experimental manipulations. Morris et al. (2014) indicated that it is not fully clear whether AβOs are present in the original specimens, or they rather emerge due to some detection techniques. It was suggested that sodium dodecyl sulphate (SDS) can promote formation of dimeric AβO during polyacrylamide gel electrophoresis (PAGE) (Watt et al. 2013). The findings that SDS may induce Aβ dimerization have significant implications for the putative role of low-order oligomers in AD pathogenesis (Watt et al. 2013). Furthermore, the dynamic equilibrium of monomers and oligomers of Aβ may be affected during some steps of assay protocol aimed to maximize interaction of capture antibodies with analyte, such as long-time, overnight incubation in Luminex assays, which may promote oligomerization and fibril formation in vitro, especially in supraphysiological concentrations of Aβ42 (Herskovits et al. 2013; Stine et al. 2011).

In addition, the interference of heterophilic antibodies (HA) in ELISA immunoassays should not be ignored. The positive results of detecting low concentrations proteins may be caused by interference from HA, which recognize immunoglobulins from other species and are present in human body fluids. HA may cause cross-binding of the capture and detection antibodies in enzyme-linked sandwich immunoassays and interfere the assay, generating a false-positive reactivity. The interference of HA should be taken into consideration, especially when measuring low levels of AβOs in human samples (Sehlin et al. 2010).

The reliable detection and quantification of AβOs in ELISA methods depend also on the use of appropriate oligomer-specific antibodies with sufficiently high sensitivity. This can be achieved by application of the same AβO epitope-specific capture and detection antibodies in a single ELISA assay (Bruggink et al. 2013; Hölttä et al. 2013; Herskovits et al. 2013). These ELISAs do not react with monomeric Aβ, because the capture antibody reacts with the only epitope available. Instead, the employment of the same antibodies for capture and detection paves the way for the determination of molecules holding at least two copies of the same epitope. Moreover, higher specificity of assay methods may be achieved by means of antibodies specific for certain tertiary conformations of oligomers, such as

globular (Barghorn et al. 2005) or protofibrillar forms of AβO (Schupf et al. 2008). Furthermore, both above-mentioned strategic approaches may be combined into an assay in which an oligomer-specific antibody was used as both capture and detection antibody (Englund et al. 2007).

AβOs as therapeutic targets of AD

Currently, available therapies of AD allow ameliorating of the symptoms but do not treat the underlying causes of the disease. Despite research efforts, no effective cure, which could successfully pass Phase III of clinical trials, has been identified to date. Although numerous factors contributing to AD pathogenesis may become therapeutic targets, the disturbed processing of Aβ appears as the most extensively studied and validated among them. As the pathology of AD involves the progressive accumulation of Aβ protein, various anti-amyloid approaches were studied for the prevention and treatment of the disease. Furthermore, finding the specific pathogenic activity and toxicity of AβOs in AD led to direct attempts of targeting these species. It is now under discussion that anti-amyloid therapy requires focusing on the early stages of Aβ cascade, especially on the oligomerization of amyloid or aggregation into protofibrils (Lannfelt et al. 2014). Removal of oligomeric Aβ forms from AD brains seems to be the most promising therapeutic target.

The recent trials include use of immunotherapy for its supposed ability to reduce the accumulation and oligomerization of Aβ (Spencer and Masliah 2014). This aim may be achieved either by active or passive immunization. Active vaccines aim to stimulate B cells to synthesize specific antibodies, using synthetic Aβ peptide or its fragment, which should result in the destruction of plaques and would inhibit further deposition of Aβ in the brain (Li et al. 2013b).

Although active immunotherapy seems an attractive solution because of its relative lower cost (Lemere 2013; Wang et al. 2010), it can induce long-term production of polyclonal antibodies with variable specificity and in varying degrees. Moreover, the use of strong adjuvants to boost antibody generation may increase the risk of undesirable immune responses. In addition, age-related attenuation of the immune system may also lead to the production of antibodies in meaningless titres and affect the effectiveness of this therapy. Unfortunately, an active vaccine trial was terminated after few doses due to the occurrence of a T-cell-mediated aseptic meningitis in the Phase II patients (Gilman et al. 2005; Orgogozo et al. 2003). Furthermore, follow-up studies revealed that immunization resulted only in a reduction of Aβ plaques, but it did not influence the progression of cognitive impairment in AD patients (Holmes et al. 2008).

Another approach to anti-amyloid immunotherapy is passive immunization based on the administering of ex vivo produced monoclonal antibodies (mAbs). These antibodies act through binding to extracellular Aβ, which results in the blockade of amyloid incorporation into Aβ plaques. Many of anti-amyloid antibodies do not discriminate between Aβ species. Some of mAbs react preferably with monomeric Aβ but they still recognize larger aggregates, while others are plaque-targeted and able to join with smaller species too. For example, solanezumab is a monoclonal antibody which has high affinity for mid-region of Aβ monomer. This mAb binds predominantly to soluble monomers and perhaps low-n AβOs but not to plaques (Siemers et al. 2010). Another mAb, bapineuzumab has low affinity for monomers, but binds AβOs and also attaches to amyloid fibrils (Kerchner and Boxer 2010).

Passive immunotherapy may stop seeding AβO pathology in new regions and constrains inflammatory response in brain (Valera et al. 2016). Moreover, it was shown on animal model of AD that systemic vaccination with anti-oligomeric mAbs may improve the cognitive function by reducing Aβ deposition and tau pathology (Rasool et al. 2013). Although intravenous administration of mAbs is more way expensive than use of polyclonal antibodies and requires long-term administration, the advantage of passive immunotherapy over active vaccines is targeting a specific epitope. In addition, passive immunization by mAbs seems to be safer and more controllable than active immunization, allowing for discontinuation of the treatment whenever any adverse effects occur.

To date, one amyloid-targeting human mAb, BIIB-037, or aducanumab has shown promising effects in a Phase I clinical trial (Sevigny et al. 2016). It is human monoclonal IgG1 that selectively targets N-terminal and mid-domain aggregated Aβ, including AβO and fibrils but not monomers. It was shown that 1 year of monthly intravenous infusions of Aducanumab reduced PET amyloid brain levels in a dose- and time-dependent manner in patients with prodromal or mild AD (Sevigny et al. 2016). Moreover, Aducanumab administration was accompanied by a slowing of clinical decline measured in two tests (Clinical Dementia Rating-Sum of Boxes and MMSE scores). The main safety and tolerability findings are amyloid-related imaging abnormalities (ARIA) in approximately 20% of the participants (Sevigny et al. 2016). Aducanumab entered the necessary Phase III studies in 2015 (http://www.alzforum.org/therapeutics/aducanumab, https://clinicaltrials.gov/ct2/show/NCT02477800).

Conclusions

This paper is a review on Aβ oligomers in Alzheimer's disease. We discuss amyloid hypothesis of AD pathology, indicating the role of oligomeric amyloid species as the main

toxic factors leading to loss of synapses and damage of neurons. Moreover, we describe candidate receptors of AβO that could be related to its harmful influence on neurons. Furthermore, this review summarizes recent data regarding CSF levels of AβOs, technical aspects of their measurement, and the possible use as neurochemical biomarkers of AD. Finally, we mention therapeutic options for AD related to anti-amyloid agents, especially AβOs targeted monoclonal antibodies, although this issue requires further investigation. Taken together, it seems that synaptotoxic activity of AβO may constitute a molecular basis for the ethiopathology, diagnosis, and treatment of AD.

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Compliance with ethical standards

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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