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Recent Developments in Treating Alzheimer's Disease

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Abstract

Early diagnosis and efficient treatment for sporadic Alzheimer's disease (AD) are urgently needed as the condition becomes an increasing burden within aging societies. We collected recent data on the progress towards effective treatments of AD, from targeting Aβ aggregation, passive immunization with anti-Aβ antibodies, fighting acute and chronic inflammation, modulating autophagy to balancing metals ions. We argue that from successful model studies and pre-clinical trials, insights into the critical pathogenic mechanisms at the molecular and cellular levels are confirmed. They in one way or another seem to support the modified amyloid cascade hypothesis, in which Aβ oligomers are believed to impair intracellular membranes, possibly resulting in mitochondrial and lysosomal dysfunctions that may lead to oxidative stress and impairment in protein clearance by autophagy, respectively. In accordance, chronic inflammation due to activation of microglia, is also consistently observed in AD brains.

Keywords: Alzheimer's disease; Aβ oligomers; Autophagy; Cure; Inflammation; Microglia; Mechanisms of neurodegeneration; Prevention; Treatment

Means for Early Diagnosis of AD

At the present time diagnosis of AD is typically obtained when the brains of patients are already severely affected, based on clinical signs of mental decline. Therefore, early diagnosis, possibly at a stage of mild cognitive impairment and selecting those at higher risk to develop the disease, is highly desirable. An early event in AD is over-production of the more toxic amyloid β (Aβ) peptide Aβ42, as opposed to Aβ40. Various imaging techniques enable one to detect and quantify extracellular Aβ plaques in living patients [1] offering a less invasive approach to performing a puncture of cerebral spinal fluid (CSF), in order to analyze the ratio of Aβ40 and Aβ42 peptides. A more convenient approach would be to detect a biomarker in peripheral blood and follow changes in its level upon disease progression. Such an approach has been recently reported by researchers at Rockefeller University who measured the contact systems activation levels in patient serum. The contact system cascade starts with factor XII and bradykinin peptide released downstream. The study showed activation of the inflammation cascade, especially in those patients who demonstrated high levels of Aβ42 in their CSF. Importantly, the Tg6799 mouse model of AD reproduced the findings observed with human blood samples. The authors Zamolodchikov et al. [2] propose that chronic activation of the contact system by Aβ42 results in constant low levels of bradykinin-mediated inflammatory processes in the blood of AD patients (i.e. chronic inflammation). This in turn leads to increased blood–brain barrier permeability and cytokine up-regulation [2]. A review of peripheral biomarkers of AD has been written [3].

Another approach to detect a biomarker in peripheral blood was reported by researchers at the University of Melbourne [4]. They focused on differences in micro-RNAs (miRNA) between AD patients and healthy controls. The miRNA in serum and other biological fluids resides in exosomes. Using next-generation deep sequencing they profiled exosomal miRNA from serum and validated the results by quantitative reverse transcription PCR (qRT-PCR). Additional risk factors for AD including clinical, medical and cognitive factors and amyloid neuroimaging were assessed. An AD-specific 16-miRNA signature was then selected, which together with other risk factors, among them apolipoprotein ε4 (APOE ε4) allele status, resulted in a sensitivity and specificity of 87% and 77%, respectively, for predicting AD [4].

Trials towards a Successful Treatment for AD

Understanding the molecular and cellular mechanisms of neurodegeneration and neural repair go hand-in-hand with the search for new treatments. The molecular and cellular mechanisms which underlie AD and neurodegenerative diseases in general are essentially a response to protein misfolding and aggregation. As evident from genetic cases the diseases often start with loss of function of the mutated protein, accompanied by toxic effects of protein aggregation. Inflammation, due to innate immunity response, is also important and it is not always clear what comes first [5].

If we start with the modified amyloid cascade hypothesis of AD, it states that Aβ oligomers are responsible for the neuronal and synaptic damage. These oligomers are believed to impair intracellular membranes [6], likely resulting in mitochondrial and lysosomal dysfunctions, which furthermore would lead to oxidative stress and impairment in protein clearance by autophagy, respectively. These events are presumably upstream of hyper phosphorylation and aggregation of Tau. Consequences of aberrant protein aggregation are elevated oxidative stress, impairments in mitochondrial energy levels [7] and autophagic flux with accumulation of auto phagosomes [8].

The soluble Aβ oligomers are thought to be toxic to neurons by the above mentioned amyloid cascade. However, the Aβ peptide

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also accumulates outside neurons as amyloid-plaques and activates microglia, leading to chronic inflammation.

Decreasing Aβ

In accordance with the modified amyloid cascade hypothesis, many of the new trials in search of treatments for AD are based on reducing the levels of soluble Aβ peptide or clearing the amyloid plaques from the brain blood vessels. An innovative approach was recently applied in a mouse model of AD by the researchers at the University of Queensland, using ultrasound. High frequency sound waves activated the microglia cells, which in turn digested Aβ plaques. As reported by Leinenga and Gotz, memory loss was restored in these mice [9]. As will be described under "Preventive measures" some compounds from plants also reduce amyloid plaques and inhibit intracellular Aβ aggregation.

Immunization

Another means to reduce toxic Aβ oligomers is by immunization. We can differentiate between passive and active immunization, where active means that the body produces it's own antibodies against the peptide of choice. With dangerous species alike Aβ one cannot guarantee that its peripheral injection would not cause seeding effect in the brain leading to more amyloid plaques. As well, people with compromised immune system, which can be the case with AD patients, do not produce sufficient auto-antibodies. Passive immunization with an engineered, preferentially humanized antibodies, is therefore safer, even though, it should be repeated continuously.

Passive immunization trials with antibodies directed against Aβ have been performed for some time, as reviewed by Doris Lambracht-Washington and Roger N. Rosenberg [10]. Several of these had to be abandoned, due to serious side effects, among them aseptic meningoencephalitis [11]. A recent announcement about a possible cure for AD evaluated a high affinity naturally occurring human antibody against Aβ oligomers. These antibodies were isolated from people aged around 100 years, who still were cognitively intact, assuming that they produce powerful auto-antibodies against Aβ peptide. The biological medicine Aducanumab (by Biogen) is a high-affinity monoclonal antibody against Aβ based on the sequence of the auto-antibodies. It recognizes Aβ's N-terminal structural epitope that is present in the aggregated form of Aβ but absent in monomers. First clinical trials (phase 1b) of passive immunization with Aducanumab were seemingly successful, lowering Aβ plaques in the brain as seen by PET imaging but also improving cognitive performance. However severe side effects were observed such as brain swelling and headaches, especially at the highest, most efficient dose. Medium doses produced less side effects and were still moderately efficient. The trials are being repeated with a wider dose range and more patients.

Another antibody for passive immunization BAN2401: monoclonal antibody directed against Aβ that selectively binds and eliminates Aβ protofibrils is under clinical study. BAN2401 is a promising candidate for Aβ immunotherapy of Alzheimer patients at an early stage [12]. The clinical study (in progress) will evaluate the effect on cognition and biomarkers reflecting the progression of the disease.

Crenezumab is yet another monoclonal antibody used for passive immunization. It recognizes primarily aggregated Aβ, including oligomeric and fibrillar species and amyloid plaques. In order to avoid side effects such as vasogenic edema, this humanized antibody is prepared on IgG4 backbone, exerting activation of microglia [13].

Decreasing inflammation

Microglia are a unique CNS resident myeloid cell population, derived from primitive myeloid progenitors [14]. When microglial cells become over-activated they induce significant production of cytotoxic molecules such as superoxide [15], NO [16] and tumour necrosis factor-α (TNFα) [17].

In AD microglia are able to bind to soluble Aβ oligomers and Aβ fibrils via cell-surface receptors and this process participates in an inflammatory response. The inflammasome sensor NLRP3 is important for mediating neuroinflammation as it can sense a range of aggregated substances, including Aβ aggregates [18]. Recently several articles described the role of inflammation in AD progression [19,20]. NLRP3-deficient APP/PS1 mice (a mouse model of AD) have decreased deposition of Aβ [19].

A recent study on the role of microglia in an AD animal model was conducted at Stanford University and its success announced early in 2015 [21]. The deterioration in microglial function with age and in AD is driven, in large part, by increased signaling activity of the prostaglandin receptor protein EP2, which resides both on the surface of microglial and neural cells. Activation of the EP2 receptor by prostaglandins E2 or PGE2 leads to inflammation. In more details, the authors Johansson et al. [21] examined peritoneal macrophages of young (4 months) and aged (21 months) C57B6/J mice. When exposed to soluble Aβ oligomers, macrophages from young mice produced a rather modest response, not causing inflammation. In contrast, exposure of macrophages from older mice to Aβ initiated a significant increase in EP2 activity, resulting in inflammation and a reduced amount of Aβ digesting enzymes. A molecule to block the down-stream activity of EP2 receptor, i.e. an inhibitor, would be most desirable. In fact non-steroidal anti-inflammatory drugs block two enzymes: COX-1 and COX-2, which produce prostaglandin PGE2 that triggers EP2 action. Non-steroidal anti-inflammatory drugs are widely used in the elderly yet no clear benefits in order to prevent or ameliorate AD symptoms have been observed in patients to date. Some improvements in cognition in animal models were observed for ibuprofen and mefanamic acid [22].

Clinical trials of anti-inflammatory substances (such as aspirin, naproxene…) mostly failed [23]. This seems consistent with recent studies indicating that inflammation is a transient and early phase of AD [5,22]. Inflamasome formation can also result from impaired processes of Beclin-1 dependent autophagy, which is reviewed elsewhere [24].

Metal ions balance

Metal ions balance is critically important for the brain physiology and may be disrupted in AD [25,26]. Cu2+ ion homeostasis was re-established by treating AD mouse model with mild metal chelators, such as clioquinol. Researchers at the University of Melbourne screened substances based on clioquinol backbone to be used as possible chelator drugs. Even though the drug PBT2 reversed memory loss in mice, phase III trial was not performed. Phase I and II clinical trials showed that PBT2 did not improve the burden of amyloid plaques significantly and the trial was stopped after the phase II, as reported by Prana. However recent evidence suggests that the same compound could be efficient to ameliorate cognitive decline accompanying aging [27,28] and even to reverse signs of Parkinson's disease [29].

Augmenting autophagy

Autophagy is a major route to clear protein aggregates, and may be

1. **Inhibit Aβ oligomerization/ fibrillation**:
a. antibodies – in clinical studies, Aducanumab, BAN2401, Crenezumab
b. recruit chaperones, and small heat shock chaperones:
c. Aβ binding proteins: prion, cystatins, crystallins
d. Aβ oligomerization inhibitors: polyphenols
e. dissagregases: chaperones Hsp70 and 104, polyphenols: among them resveratrol and curcumin
f. increase microtubules stability in order to improve transport of the oligomers: by histone deacetylase inhibitors (Asthana, Kapoor, Mohan, & Panda, 2013; Hahnen, et al., 2008)
2. **Dissolve amyloid plaques:** polyphenol compounds, antibodies, phagocytosis by microglial cells
3. **Augment degradation by autophagy** of the aggregates accumulated in aggresomes and endosomal inclusions: Examples of mTOR-dependent drug is a rapamycin analog *temsirolimus* (an approved anti-cancer drug) and mTOR-independent drug *rimendine* (anti-hypertension drug). Lithium has a more complicated action and so does sodium-valproate, which is an inhibitor of histone deacetylase.
4. **Establish metals ions balance**: mild metals chelators – also dissolve the Aβ aggregates, which bind Cu^{2+} ions; *PBT2* by Prana was omitted after clinical trial phase II
5. **Prevent chronic inflammation:** non-steroidal anti-inflammatory drugs, such as ibuprofen and mefanamic acid, block prostaglandin production. Resveratrol and curcumin also exert anti-inflammatory action.

*sometimes enhancing autophagy, especially at more developed phase of the disease, might be contra-productive

Table 1: Towards more rational AD treatment; chosen recent treatments.

impaired in AD [8] as well as other neurodegenerative diseases [30]: such as PD, and ALS [31,32]. Therefore, it is a viable therapeutic target also in AD, as recently reviewed by Friedman and co-workesr [33]. Autophagy is induced by several different signaling cascades; of which the best known is mammalian target of rapamycin (mTOR). Multiple mTOR-dependent and mTOR-independent drugs have been tested in AD models. Examples of mTOR-dependent drugs are rapamycin analog temsirolimus (an approved anti-cancer drug) and an mTOR-independent drug is rimendine (anti-hypertension drug). Another such drug is lithium, which inhibits inositol monophoshatase, which through down-regulation of IP3 signaling up-regulates autophagy. Lithium also inhibits glycogen synthase kinase (GSK)-3β, which ultimately suppresses autophagy [33]. Treatment by rapamycin has already been suggested as an approach to ameliorate toxicity by protein aggregates in Huntington's disease and other proteinopathies [34,35]. Rapamycin has been used in longevity studies and this suggests possible benefits for AD [36].

We proposed that the process of autophagy may also be relevant for progressive myoclunus epilepsies (such as Lafora disease) or neuropsychiatric disorders (such as depression and bipolar disease) [37,38], for which no clear protein inclusions have been shown as yet or they are transient.

Inhibition of autophagic flux causes neural death [39]. However it is not certain that enhancing autophagy would be beneficial in all cases of AD. Induction of autophagy seems appropriate at the early stages of AD, whereas later, when extensive accumulation of autophago-lysosomes is observed, it might be counter-productive to enhance autophagic flux [8].

Drugs stabilizing microtubule-trafficking or those promoting lysosomal fusion and lysosomal enzymes function can enhance the later stages of autophagic flux. Inhibitors of histone deacetylase, among them sodium valproate, contribute to tubulin acetylation and stabilize microtubules [40,41]. Fusion of autophagosomes with lysosomes is needed for final degradation of the aggregated substrates, taking place at acidic pH. An increase in activity of lysosomal cathepsins, especially of cathepsin B – one of the Aβ degrading enzymes [42] - can be achieved by deleting its protein inhibitor cystatin B and can reverse autophagy dysfunction in the TgCRND8 mouse model of AD [43]. However, cystatins C and B may be themselves neuroprotective [44], inducing autophagy by an as yet unknown mechanism [45]. Both cystatins are Aβ binding proteins [46-49]. Of interest, stefin B tetramers inhibit Aβ fibril formation but not so the monomers [49]. We suggested that stefin B may act as an amateur chaperone [50], similarly to crystallins. Thus, the role of cystatins in AD and neurodegeneration in general, remains somewhat controversial [51].

Preventive Measures

Because the costs to treat people with AD are enormous and the disease is a significant burden for the relatives and those directly affected, preventive measures are certainly welcome. Physical exercise has been proven as a way to reduce burden of Aβ plaques in patient studies [52,53].

Nutrition is an obvious source of health promoting substances. In a recent survey, the effect of some natural compounds on Aβ aggregation and implications for possible new AD treatments was reviewed [40,41,54] (Table 1). Among the best known plant compounds for their preventive effects on AD are resveratrol and curcumin. It was reported that resveratrol, like many other polyphenols, contributes to Aβ fibril disaggregation [55] and what is even more important to prevent toxicity, inhibits Aβ oligomerization [56]. Similar effects of resveratrol were observed on α-synuclein oligomerization, thus preventing synaptic dysfunction in both AD and PD [57,58].

It was previously shown that resveratrol did not inhibit Aβ production by the two (β and γ) secretases, instead it enhanced proteasome activity [59]. In accordance, the decrease of Aβ was prevented by selective proteasome inhibitors and by siRNA-directed silencing of the proteasome subunit β5 [59]. Curcumin's inhibitory action on Aβ fibrils formation is also well documented [60-62]. Of note, the same two compounds (reveratrol and curcumin) exert anti-inflammatory and antioxidant actions [63,64].

Conclusion

In recent few years several important break troughts in the search for treatment of Alzheimer's disease (or even a cure) have been made. The aim of this review is, on one hand, to describe these recent developments as illustrated by animal model studies as well as preclinical and clinical trials, and, on the other hand, to highlight the critical pathogenic mechanisms that these studies reveal/confirm.

Undoubtly, to truly treat AD and similar neurodegenerative

diseases at its source, a better understanding of the molecular and cellular, including glial, neuronal and synaptic mechanisms need to be understood. Here, we argue that modified amyloid cascade hypothesis presents a good basis for such an understanding, proven by success in reducing soluble Aβ oligomers by anti-Aβ oligomers antibodies or aggregation inhibitors (usually also anti-oxidants) derived from plants. Diminishing (dissolving) Aβ plaques and keeping in check accompanying inflammation proved of some help if started early at still mild cognitive impairment. Intensified clearance of the aggregates by autophagy and restoring metals ions balance may also be beneficial in certain (early) stages of disease.

Not at least, better understanding of prion-like templating, seeding and cell to cell spreading of the protein aggregates may be used to stop the routes of spreading [65], which is out of scope of this review.

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