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Review

Current Approaches Against Alzheimer's Disease in Clinical Trials

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Alzheimer's disease (AD) is a progressive degenerative brain disease which causes mental and physical decline, gradually resulting in death. Currently, this disease represents one of the uppermost human issues, both from the medical and economic point of view. Interest in the discovery of a drug for AD is enormous. However, despite the long-term and worldwide effort for a more effective therapy, the only available treatment is a symptomatic use of acetylcholinesterase inhibitors (AChEIs) and memantine. New therapeutic approaches as well as those based on cholinergic or amyloid theory have not brought the desired benefits yet. Thus, the question is whether an effective drug for this progressive disease will ever be developed or whether people will have to rely only on prevention and minimize risk factors of AD.

Keywords: Alzheimer's disease, treatment, tacrine, rivastigmine, galantamine, donepezil, huperzine A, arecoline, AC-42, encenicline, ABT-126, rosiglitazone, pioglitazone, atorvastatin, thalidomide, minocycline, semagacestat, epigallocatechin gallate, etazolate, tramiprosate, valproic acid, tideglusib, methylene blue, immunotherapy

1. Introduction

The current demographic trend, especially in the developed countries, but also globally, is characterized by an aging population. The proportion of people over 80 years will be doubled according to the estimates for 2050.[1] A similar ratio applies to seniors older than 65 years (Figure 1).

Old age is the main factor that affects the occurrence of dementia in the population. According to the World Health Organization (WHO), the number of people with dementia worldwide was estimated to be 35.6 million in 2010. This number will probably be doubled by 2030 and by 2050 it will rise probably three times. The number of new cases of dementia *per* year (incidence) is approximately 7.7 million. That is one new case every four seconds.

When considering individual continents, 3.6 million (46%) people live in Asia, 2.3 million (31%) in Europe, 1.2 million (16%) in North and South America and

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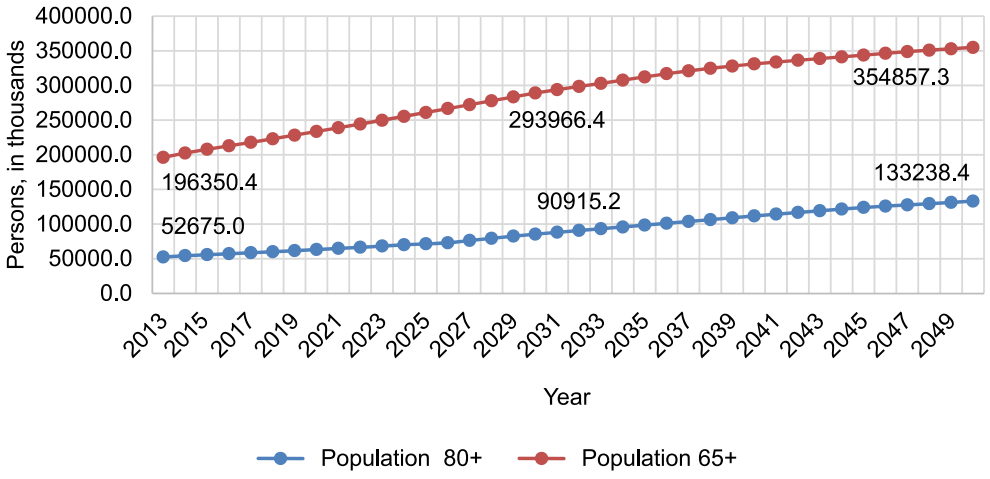

Figure 1. Number of people in the age 80+ and 65+ in the period 2013-2050. Source: OECD.[2]

0.5 million (7%) in Africa.[3] The data for 2015 and the forecasts are shown in Figure 2.

This significant growth of people with dementia brings an increased demand on healthcare and on public budget.[4,5] The total worldwide costs of dementia are US $ 818 billion in 2015, which represents 1.09% of global gross domestic product (GDP). Costs include informal care (as indirect costs) and direct costs of social and medical care.

The most common form of dementia is Alzheimer's disease (AD),[6] which accounts for approximately 60-70% of all cases.[1] Other major types of dementia include vascular dementia, dementia with Lewy bodies and a group of diseases that contribute to frontotemporal dementia. The boundaries between the various subtypes are unclear and mixed forms of dementia often occur.[7]

AD is a progressive degenerative brain disease which causes mental and physical decline, gradually resulting in death. The first symptoms of this disease are mostly minor behavioral changes. Consequently, patients have difficulties with short-term memory, learning, counting or decision-making.[8] AD has the greatest impact on mental abilities. Patients have difficulties with remembering, thinking, understanding and communication. In addition, loss of memory is a progressive character and it proceeds fast.[9]

Nevertheless, despite the long-term and worldwide effort for a more effective therapy, the only available treatment is a symptomatic use of acetylcholinesterase inhibitors (AChEIs) and *N*-methyl-*D*-aspartate receptors antagonist-memantine. Such treatment is not, however, effective enough, and most importantly, it is short-term.[10] Furthermore, discovery of new therapeutic approaches is connected with the fact that the etiology of AD is still unknown and rather than finding the cause of this disease,

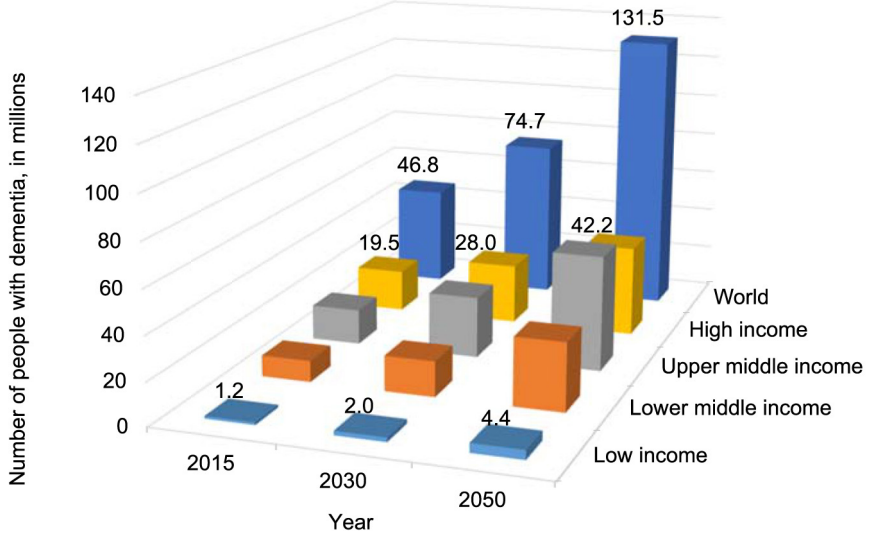

Figure 2. Number of people with dementia (millions), according to World Bank income classification. Source: Alzheimer's Disease International, 2015.[3]

the improvement of the situation focuses on its risk factors and prevention.

In this review article, several important approaches which have recently been under investigation are presented.

2. Cholinergic Hypothesis

The treatment with AChEIs is based on the cholinergic hypothesis, which at present is already considered as classic. The cholinergic hypothesis takes into consideration the key role of acetylcholine (ACh) in human cognitive functions. According to this theory, the activity of choline acetyltransferase (ChAT) and pyruvate dehydrogenase (PDH) complex, the key enzymes in the synthesis of ACh, is considered to be decreased.[11,12] Moreover, the decrease of cholinergic transmission is supported by impaired function of the muscarinic receptors, in particular subtype M1 which is mainly present in brain. Rather than by the decline in number of receptors it is caused by diminished intercellular transmission.[13] On the contrary, the authors of this study observed a lower number of nicotinic receptors (subtypes α7 a α4β2). It was also observed that toxic amyloid beta (Aβ) has high affinity towards nicotinic receptors, which is most likely connected with the functional decline of these receptors and accumulation of Aβ.[14] Thus, it is obvious that the cholinergic and amyloid theories are mutually intertwined cascades. It is then logical that research still focuses on the drugs which stimulate the cholinergic transmission by inhibition of decomposing ACh or the activation of central M1 muscarinic and nicotinic receptors.

AChEIs were the first drugs approved for the treatment of AD. Besides the obsolete tacrine, these drugs include rivastigmine, galantamine, which also enables potentiation of nicotinic receptors, and apparently the most used drug-donepezil.[15] Another well-known drug, particularly in eastern medicine, is huperzine A, which combines distinctive affinity towards AChE with strong antioxidant and anti-inflammatory characteristics.[16] Chemical structures of clinically used AChEIs are depicted in Figure 3 and the PDB[17] structure of human AChE (HssAChE) complexed with huperzine A is shown in Figure 4.

Despite an enormous interest from pharmaceutical companies, none of the M1 agonists have been introduced as a therapeutic of AD yet. Substances such as arecoline (Figure 5) and its derivatives cevimeline, xanomeline, tazomeline and talsaklidine were studied in the second and third phases of clinical trials. Their efficacy was confirmed, however, due to the incidence of side effects in higher doses, further trials were stopped.[17,18] The major problem is a lack of selectivity towards M1 receptors in comparison with

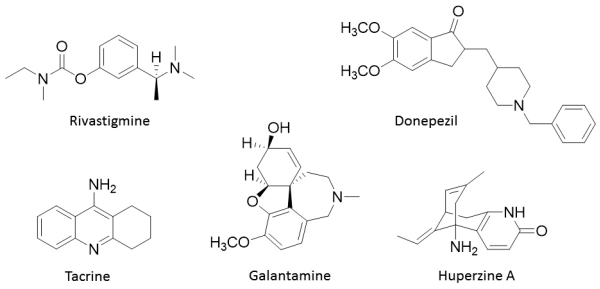

Figure 3. Clinically used AChEIs.

Figure 4. Structure of human AChE complexed with huperzine A. PDB code 4EY5.[19]

other subtypes. The development of novel drugs gradually shifted towards searching for positive allosteric modulators (PAMs) of M1 receptors. Substances such as AC-42 (Figure 5) binds to the allosteric site which is specific for the M1 receptor.[20] Thus, a chance of the incidence of peripheral side effects mediated by other receptor subtypes is decreased. In this way, PAMs only support the usual activation of ACh receptors. Unfortunately, no such modulator, which would be getting closer to the clinical practice, has been discovered yet in comparison with the substances aimed at nicotinic receptors. The clinical trials with nicotinic agonists confirm an increase of patients' attention and improvement of some of their verbal and non-verbal skills.[21] Encenicline (*syn*. EVP-6124, MT-4666, Figure 5) is a promising compound from the group of agonists of α7 nicotinic receptors, which in the first and second phases of clinical trials, showed good tolerance and improvement of cognitive functions. Currently, the third phase is running and it should be finished by 2016.[22] Another α7 agonist ABT-126 (Figure 5) developed to inhibit cognitive deficits in schizophrenia is in Phase IIb for the treatment of AD in the USA and in the third phase for the treatment of cognitive disorders in schizophrenia in the European Union.[23,24] Similar substances such as ABT-408 and ABT-08 developed as nootropics and for the treatment of hyperactive children, were eliminated in the second phase of clinical evaluation due to side effects upon the heart and gastrointestinal tract (GIT).[25]

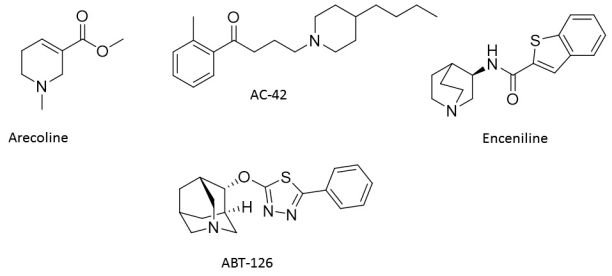

Figure 5. Chemical structures of muscarinic and nicotinic agonists that launched clinical trials.

3. Amyloid Cascade Hypothesis

At present the amyloid cascade hypothesis is the most studied hypothesis based on the incidence of characteristic extracellular Aβ plaques. This toxic protein is formed by the proteolytic cleavage of β- and γ-secretase, from the so-called amyloid precursor protein (APP) by an amyloidogenic way.[26] Two main forms of the Aβ exist: (*i*) $Aβ_{1-40}$, which often occurs in AD patients' brains and the more toxic; (*ii*) $Aβ_{1-42}$, which shows greater tendency to aggregate and subsequently form senile, extracellular plaques.[27] These plaques are then responsible for the death of nerve cells. Findings about Aβ are still insufficient. It was, for example, discovered that a degree of dementia did not correlate to the amount of senile plaques and their removal did not lead to the improvement of patient's cognitive competences.[28] Thus, the responsibility for pathological processes has been attributed to the imbalance in the representation of $Aβ_{1-42}/Aβ_{1-40}$ or to the presence of soluble forms of Aβ in the brain than to the representation of senile plaques.[29]

None of the so far studied drugs, aiming to target the pathophysiological processes connected with Aβ, has found its use in the clinical practice, although a few of them are already in the advanced stages of clinical trials. An interesting group is formed by the compounds modulating an activity of β-secretase (BACE-1), which is inhibited by the compounds or regulated at the level of expression of nuclear receptors activated by peroxisome proliferators (PPAR-γ).[30] It is this second group which is closely connected with the regulation of glycemia and insulin resistance, presumed risk factors for the development of AD.[31] From the commonly prescribed drugs influencing PPAR-γ it was rosiglitazone (Figure 6), which proceeded into the third phase of clinical trials. However, this drug showed serious side effects to cardiovascular system and incidence of edemas in higher doses. Currently, pioglitazone (Figure 6) is being investigated in the third phase of clinical trials. In comparison with rosiglitazone, it passes the blood-brain barrier (BBB) more easily.[32] Similarly, statins were intensively studied with respect to the fact that a lower level of cholesterol (another risk factor of AD) is connected with a lower incidence of Aβ in the brain.[33] However, tests of this group, represented by atorvastatin (Figure 6), was stopped in the third phase of clinical evaluation after it had been discovered that atorvastatin did not show any benefit at administration longer than 18 months.[34] The 3D structure of BACE-1 complexed with thalidomide is shown in Figure 7. Out of BACE-1 inhibitors it is thalidomide (Phase II/III of clinical trials, Figure 6) and minocycline (Phase II, Figure 6) which have proceeded furthest so far.[35,36]

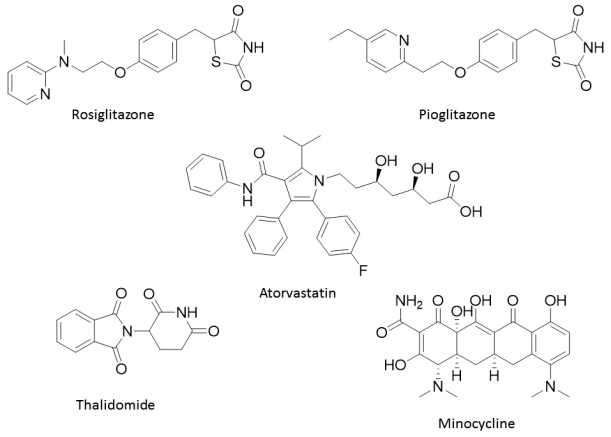

Figure 6. Compounds interacting directly or indirectly with BACE-1.

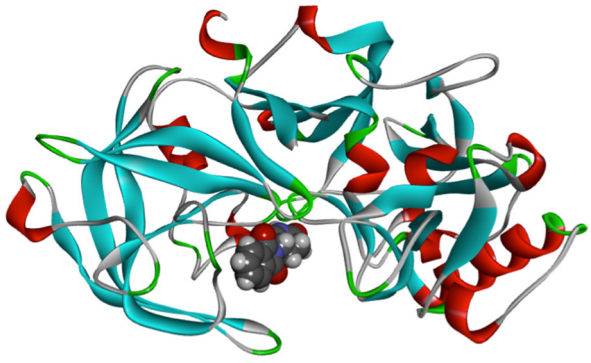

Figure 7. Structure of human BACE-1 complexed with thalidomide.[19]

γ-Secretase participates in the last step of cleavage of Aβ from APP.[28] The inhibitors of this enzyme are frequently represented in the clinical trials. In addition, semagacestat (Figure 8) reached the Phase III. However, it did not show an adequate benefit for the delay of progression of AD in comparison with the group controlled by placebo. Furthermore, its administration increased the risk of skin cancer.[37] α-Secretase participates in the so-called non-amyloidogenic decomposition of APP.[27] Thereafter, the so-called soluble form of APP with neuroprotective and memory enhancing effect originates.[38] Stimulation

of this enzyme, for example, with the help of etazolate (originally developed as a selective modulator of $GABA_A$ receptors, Figure 8) is currently in the third phase of clinical evaluation.[39] Tramiprosate (*syn.* homotaurine, Figure 8) represents the group of drugs binding to monomers $A\beta_{1-42}/A\beta_{1-40}$ and in this way it prevents conformational changes leading to the aggregation of Aβ in oligomers and fibrils.[40] This drug reached the Phase III of clinical trials. However, further research was stopped due to ambiguous results.[41] Likewise to tramiprosate, epigallocatechin gallate (Figure 8) shows affinity to $A\beta_{1-42}$. In addition, it decreases neurotoxicity induced by Aβ.[42] This compound is currently in the second and third phases of clinical trials.

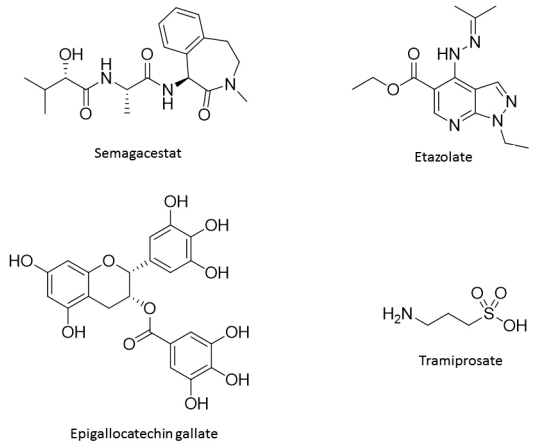

Figure 8. Chemical structures of compounds with anti-amyloid properties.

4. Hypothesis of Hyperphosphorylated Tau Protein

Tau protein is a protein which under physiological conditions stabilizes microtubules of nerve cells axons. Its function is regulated by phosphorylation. A number of neurodegenerative diseases are connected with malfunction of this protein. In particular, it causes its hyperphosphorylation and aggregation, which eventually results in the death of neurons.[43] The deterioration of cognitive functions correlates with the amount of intracellular accumulated filaments of hyperphosphorylated tau protein.[44] A possible intervention for the therapy aimed at tau protein can be in form of inhibition of hyperphosphorylation or desegregation of the filaments of this hyperphosphorylated protein. In the clinical practice lithium (in form of carbonate salt) and valproic acid (Figure 9) found its use. Both act by the mechanism of glycogen synthase kinase 3β (GSK-3β) inhibition, which regulates the degree of phosphorylation of tau protein.[45] The administration of lithium was stopped in the second phase of clinical trials due to contradictory results. Valproic acid reached the third phase of clinical trials. However, it did not show any improvement of cognitive parameters in comparison with placebo controlled group.[46] Tideglusib (Figure 9), another inhibitor of GSK-3 β, completed the Phase IIb of clinical trials in which it did not show any efficacy for the improvement of cognitive parameters.[47]

Methylene blue (Figure 9) is a compound which is able to dissolve the filaments of hyperphosphorylated tau protein *in vitro*.[48] Its clinical relevance was validated in the second phase of clinical trials at patients with AD. However, in this phase it did not reach the desirable criteria for the improvement of cognitive functions. Another derivative of methylene blue, the so-called leucine methylthioninium is now in the third phase of clinical trials.[49]

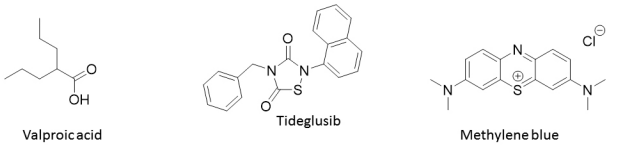

Figure 9. Anti-tau agents.

5. Immunotherapy in the Treatment of AD

One of the most promising approaches in the treatment of AD is immunotherapy. In the last ten years big effort has been devoted to the prevention of production and accumulation of Aβ in the brain. One of the most encouraging approaches for the active elimination of senile plaques from the brain seemed to be immunization against Aβ. Vaccines formed by antigen (active immunization by non-aggregated $A\beta_{1-40,}$ as well as by subunit $A\beta_{1-6}$) were clinically trialed (Phases I and II), but they had fatal side effects (microcerebral hemorrhages).[50] Furthermore, there were clinical trials (Phases I-III) of the approaches to the direct immunization by monoclonal antibodies against Aβ (passive immunization by humanized monoclonal antibodies against epitope $A\beta_{16-24}$-solaneuzumab and $A\beta_{1-5}$-bapineuzumab, respectively), or by human donor pooled polyvalent immunoglobulins (IVIG, e.g., Gammagard, Octagam, NewGam). While a decrease of deposits of Aβ in the brain was proved, unfortunately, the clinical trials did not prove any improvement of cognitive functions.[51]

Inability of immunotherapy to achieve the cognitive improvement can be caused by the fact that the load by senile plaques predominantly increases in the period before the manifestation of clinical displays of AD. Therefore it would be necessary to start immunization in the earlier phase of the disease, possible before its full breakout. On the contrary, it seems that the immunotherapy aimed at pathology of tau protein could have better results because

the progression of cognitive deterioration at patients with AD very strongly correlates with the increasing intracellular depositing of neurofibrillary tangles mainly composed by tau protein.[44,50]

In June 2013 the first clinical trial with substance AADVac1 began. It is an active immunization which targets tau peptide. Using 3D modeling, a peptide which mimics the site, where an interaction of tau-tau proteins takes place, was designed. This peptide is then conjugated with the immunogenic carrier for the attainment of higher efficacy. The results of preclinical trials showed efficacy on transgenic models of rats and mice. The pilot results of the first phase of clinical trial study after the first year show that the vaccine could be safe when used at humans.[52] However, as it was proved in case of immunization against Aβ, the results from the animal models are not fully transferable into clinical practice and therefore only future will show if this confirmation about the efficacy of the immunization strategy against tau will be valid.

6. Conclusions

In conclusion, it can be said that apart from the presented mainstream approaches in the treatment of AD, there are many more approaches which are only marginal in clinical evaluation and which are mainly found in preclinical trials or even before this stage. Such approaches involve, e.g., neuroprotective/neurorestorative substances, agonists of RAGE receptors, or metal chelators. In this connection, it is often mentioned that multifactorial diseases, such as AD, will require a multi-level intervention, which is presently known as MTDL (multi-target directed ligands) strategy,[53] which means that one drug is able to influence more targets. As it results from the information described above, it is not very probable that there will be a novel drug on the market for AD and the treatment should mainly focus on the prevention and minimization of risk factors of this disease.

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