Drugs for Alzheimer’s

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Abstract

Five drugs are currently approved for the treatment of Alzheimer’s disease; nevertheless, we have faced the challenge to respond to family members of these patients the reason why they observe a limited improvement from these treatments. Although both acetylcholinesterase inhibitors and memantine are correctly designed and they show an adequate performance, we believe the neuronal conditions resulting from the pathophysiology of the disease difficult their proper working in brains affected with Alzheimer’s. Patients should therefore undergo a neuronal rehabilitating therapy that enables these drugs for a more effective performance.

Introduction

Five drugs have been so far approved for the treatment of Alzheimer’s disease (AD) by the Food and Drug Administration (FDA), the most popular amongst them being the acetylcholinesterase inhibitors such as donepezil (aricept), galantamine (razadyne) and rivastigmine (exelon). Some of the more outstanding clinical characteristics of this drugs are that, for example, donepezil (aricept) is the most widespread used because it presents reduced side effects with a once a day dosage [1] and, importantly it can be used for treating severe AD cases [2]; galantamine (razadyne) with a twice a day dosage taken with meals, has proved to be involved in the inhibition of β-amylloid (Aβ) aggregation and citotoxicity [3], also showing a protective role against oxidative stress [4]; and rivastigmine (exelon) is only used at very low dosages because of the risk of severe gastric damage and hepatotoxicity associated with its chronic consumption [5]. We should also mention in this group tacrine which associated hepatotoxicity has left it out of the common clinical practice.

Aside acetylcholinesterase inhibitors we find memantine, a NMDA receptor antagonist [6] drug that is the only of its kind approved by the FDA for the treatment of moderate to severe AD [7].

Despite all the beneficial effects these drugs have shown on the cognitive and behavioral states of AD patients, it is noticeable that the treatment for AD does not come helpful to stop the cognitive decline in patients with AD [15].

Recent studies of postmortem brains from Alzheimer’s disease (AD) patients and transgenic mouse models of AD suggest that oxidative damage, induced by amyloid beta (Aβ), is associated with mitochondrial dysfunction early in AD progression. Furthermore, accumulation of Aβ at synaptic terminals might contribute to synaptic damage and cognitive decline in patients with AD [15].

Mitochondrial dysfunction is observed in Alzheimer’s disease (AD) brain, and the amyloid-beta (Aβ) peptide is known to induce mitochondrial dysfunction. The relative degree of mitochondrial dysfunction in different regions of the brain in AD is not completely understood. Moreover, the relationship between levels of synaptic mitochondrial Aβ and mitochondrial dysfunction has not been clearly established. It has been showed that hippocampal and cortical mitochondria showed the highest levels of mitochondrial dysfunction, while striatal mitochondria were moderately affected, and amygdalar mitochondria were minimally affected. Synaptic mitochondria were more impaired than non-synaptic mitochondria in the AD mouse models. The AβPP/PS1 mice showed more impairment in the cognitive interference task of working memory than the AβPP mice. The association between mitochondrial Aβ levels and mitochondrial dysfunction in mouse models of AD supports a primary role for mitochondrial Aβ in AD pathology. Moreover, the degree of cognitive impairment in AD transgenic mice can be linked to the extent of synaptic mitochondrial dysfunction and mitochondrial Aβ levels, suggesting that a mitochondrial Aβ-induced signaling cascade may contribute to cognitive impairment. Therapeutics that target this cascade could be beneficial in the treatment of AD [16,17].

Loss of synapses and synaptic damage are the best correlates...
of cognitive decline identified in patients with Alzheimer’s disease (AD), and mitochondrial oxidative damage and synaptic pathology have been identified as early events in the progression of AD. The progressive accumulation of amyloid β (Aβ) in synapses and synaptic mitochondria are hypothesized to cause synaptic degeneration and cognitive decline in patients with AD [18].

**Microtubule Associated Protein Tau (MAPT)**

This protein owes its name to its function as it associates to microtubules to provide stability [19,20], giving neurons their characteristic morphology. Thus, when tau expression is inhibited the neuronal morphology dramatically changes [21-24].

Tau’s mRNA transports anterogradely directed by the presence of a uracil rich 3‘-UTR (Un-Translated Region) [25]. A protein HuD binds to this region to stabilize the RNA molecule and then attaches to a kinesin which will transport the formed RNA-protein complex along the axon [26,27] (Figure 1).

Tau’s translation occurs in several sites along the neuronal axon; this implies a movement of the RNA-protein complex together with those proteins involved in the translation process [28]. The hyperphosphorylation and the subsequent detachment of tau from microtubules disturb the antero- and retrograde transports in growing axons because of a displacement of the transporter protein [29]. These hyperphosphorylated, microtubule dissociated tau proteins then form paired helical filaments (PHFs) which will constitute neurofibrillary tangles inside neurons with a destabilized membrane [30,31] and lost polarity [32]. It is thought that a disregulation of tau transport might be the cause for PHF generation [33].

**Amyloid cascade**

The amyloid precursor protein (APP) is a type I membrane of small family with a large extracellular domain and a short cytoplasmic one, APP presents three main isoforms (695, 571 and 770 residues) and is the only protein containing the Aβ sequence. The 695 residues is the most abundant isoform in neurons, but other brain cells also express variable amounts of APP and non-neuronal cells express mainly the 751 and 770 residues APP isoforms. The APP gene is located in chromosome 21 and over 25 mutations to this gene have been described as responsible for familial forms of AD [34,35].

β-amyloid peptides generate from the amyloid precursor protein (APP), after it has been cleaved by the sequential actions of two membrane enzymes: the β- and the γ-secretases. γ-secretase is a tetrameric complex which cleaves APP within its transmembrane domain, releasing an intact 39 to 43 residues long β-amyloid peptide [36]. Most β-amyloid peptides are 40 aminoacids long (Aβ 40), while a minor proportion (~10%) are 42 (Aβ 42). Compared to Aβ 40, Aβ 42 is a little more hydrophobic, toxic and prone to aggregation; the latter variant is more widely found as a constituent of amyloid plaques in the AD brain [37]. According to the amyloid hypothesis, the excessive and chronic aggregation of Aβ, particularly Aβ 42, triggers a pathogenic cascade leading to the pathophysiology of AD [38]; however, the evidence shows that amyloid plaques are also associated with mild neuronal alterations in normal aging and no necessarily correlate with the level of cognitive decline in an AD mouse model. This suggests an independence of Aβ toxicity from its accumulation in the brain [39-41] (Figure 2).

**Drugs for AD Work at the Synapse Level**

There is no cure for AD, however drug treatments are available to help with the symptomatology in several aspects of the disease.

The drugs approved by the Food and Drugs Administration (FDA) for the treatment of AD, these are mainly divided into two groups: the acetylcholinesterase inhibitors and the NMDA receptor antagonists (this last represented by memantine). We should consider here that these drugs are designed to diminish the symptoms originated by neurodegeneration but that neither of them targets the plaques and/or tangles to destroy them or to stop the processes responsible for their formation and progress; they provide cognitive improvement by different means. It is also convenient here to say that these are not the only drugs that have shown beneficial effects on AD patients, nevertheless no other drug has been approved for AD treatment so far [42].

Acetylcholinesterase inhibitors allow a prolonged maintenance of acetylcholine in the synaptic cleft, which enables the neurotransmitter for a proper postsynaptic binding (Figure 3). When acetylcholinesterase is inhibited, cholinergic function rises by an increase of neurotransmitter concentration at the synapse. Acetylcholinesterase is the main degrading enzyme of acetylcholine in the brain; in AD, it has proved an increased activity in certain brain regions [43]. It has also been determined an association of acetylcholinesterase with amyloid plaques that may have an effect on brain regions [43]. It has also been determined an association of acetylcholinesterase with amyloid plaques that may have an effect on AD’s pathology [44].
Donepezil and galantamine exert a rapid inhibiting action on acetylcholinesterase, while rivastigmine works more slowly. AD patients present an increase in acetylcholinesterase levels during the first months of treatment [44].

Although acetylcholinesterase inhibitors potentiate the brain on normal conditions [45], in the deteriorated AD brain their function could get a lot more difficult due to a disturbance in protein transport along the neuronal axon [46,47]. The alterations on axonal transport that lead to the loss of synapses related with cognitive decline might be due to an axonal misdistribution of mitochondria resulting from Aβ aggregation [18,48]. It has been hypothesized that amyloid peptides could be responsible for the disruption of the cytoskeleton which would contribute to a malfunctioning of axonal transport and subsequent alterations in the processing of membrane proteins such as APP [49].

Glutamate activates several types of metabotropic and ionotropic receptors (AMPA, kainate and NMDA). This neurotransmitter is involved in Alzheimer’s neurotoxicity because it has been estimated that an increased activity of NMDA receptors in AD leads to neuronal loss [50] which might be exacerbated by the excitotoxicity of amyloid plaques. The progressive neuronal loss then increases cognitive impairment [51]. Memantine is a non-competitive, voltage-dependent, N-methyl-D-aspartate (NMDA) receptor antagonist with moderate affinity. In contrast to other competitive antagonists, memantine is well tolerated by patients [52]. A lot of research has been done to test the effects of memantine in animal models and clinical trials, data suggesting a neuroprotective effect in vascular dementia and its helpful use in the treatment of conditions such as CNS trauma and amyotrophic lateral sclerosis (ALS) [53]. Although memantine has been widely used for treating the symptoms of moderate to severe AD [54], we believe in the deteriorated AD brain it would exert a very limited improvement (Figure 4).

**Neuroprotection and Potential New Drugs**

There is currently no cure for AD and no treatment capable of...
eradicate its symptomatology, therefore our best weapons against the disease might be neuroprotection and the maintenance of a healthy neuronal state. As an old Hindu proverb says: “the fish dies by its mouth”, dietary habits importantly participate in several pathologies and AD is not the exception; thus, a healthy diet could be helpful to prevent AD as much as other diseases. AD presents a higher prevalence in industrialized countries, which might be the result of several environmental, dietary and social factors [55].

In order to keep neurons in a healthy state it is important to maintain the integrity of the plasma membrane and to avoid oxidative stress [56]. On this matter, attention has been turned to omega-3 acids as they are essential for neurogenesis [57] and the maintenance of cell membranes [58, 59]. They also reduce the oxidative stress-induced damage and take BDNF back to its normal levels [60].

Other commonly used drugs for the treatment of several symptoms of AD have shown some extra advantages and other drugs are currently being developed for this purpose. Examples are the antidepressants of the selective serotonin reuptake inhibitors (SSRIs) group such as escitalopram, used to treat depression in AD patients, which could also help to create neuronal connections in the AD brain [61, 56]. Antipsychotic agents are useful to treat the associated psychotic symptoms of AD. Recently, agonists of the metabotropic glutamate receptors (mGlus) have been developed as novel antipsychotic agents lacking of the adverse effects of conventional antipsychotics. Selective positive allosteric modulators (PAMs) of mGluz2 receptors mimic the antipsychotic activity of mGluz2/3 receptor antagonists in animals. Experiments performed in mixed and pure neuronal cultures exposed to synthetic Aβ to investigate the distinct influence of mGluz2 and mGluz3 receptors indicate that a selective potentiation of mGluz2 receptors enhances neuronal vulnerability to Aβ toxicity while the dual activation of mGluz2 and mGluz3 receptors is protective against it [62].

Nowadays, several research groups focus their efforts on the development of new multitargeted drugs against AD [62–65] such as memooquin, an acetylcholinesterase inhibitor, free-radical scavenger and inhibitor of Aβ aggregation [66], and other quinone derivatives that are being widely used to develop new drugs which are effective simultaneously towards BACE1 activity, inhibition of Aβ aggregation and disaggregation of preformed Aβ fibrils [67].

Commentary

In our experience with AD patients, family members have repeatedly manifested their worry about treatments appearing to be ineffective despite their accuracy following physician’s instructions. It is known that AD drugs have a limited period of efficacy in these patients and that they do not stop the neurodegeneration process, reason why the cognitive decline keeps progressing over time. We believe a neuronal rehabilitation would enable these drugs to function in a better manner and thus become more effective to treat the disease, prolonging their positive effects over cognitive decline on AD patients.

We previously proposed a neuronal rehabilitation therapy which considers several aspects involved in the pathophysiology of AD [56]. This therapy first considers the repair of plasma membranes, which are very important because they are responsible for maintaining the cellular contents organized. Although there is no drug serving this purpose, fatty acids such as the omega-3 found in fish are capable of incorporating into membranes, being highly important for the cerebral cortex development [68]. Unsaturated fatty acids like decosahexaenoic acid (DHA) are a great example of the relevance fatty acids have on health. DHA is particularly abundant in brain and retinal tissues; it corresponds to nearly 50% of all membrane acylated chains, thus a reduction in DHA affects membrane physical properties such as the domains involved in signaling processes, called rafts [69]. These rafts or cholesterol and sphingolipid rich microdomains are the major regulators of membrane organization. Because lipid rafts can move laterally and cluster into larger patches, they have been proposed to play a role in the redistribution of specific molecules to specialized cellular structures. Rafts have shown to favor formation and maintenance of synaptic receptor clusters in neurons of the CNS [70] and they are altered in AD patients [71].

Another important aspect to consider is oxidation. Resveratrol is a polyphenol with a great antioxidative activity and it has also demonstrated an ability to reduce amyloid plaques [72, 73]; therefore, it is believed resveratrol could be beneficial for AD patients [74, 75]. To restore memory processes, ginkgo biloba could be useful and provide some improvement for the AD patient’s quality of life [76, 77] despite controversial results obtained from different studies. Neuronal rehabilitation also involves the reestablishment of neuronal connections and for this purpose we consider fluoxetine or escitalopram could be useful as they have demonstrated a role in the formation of new synapses and neuronal reconnection [78, 79].

In AD, neuro-inflammatory processes are of great importance. Non-steroidal anti-inflammatory drugs (NSAIDs) have a protective effect on these patients, as shown by studies performed on rats where quisqualic acid was injected into the right nucleus basalis, excitotoxin-induced cholinergic degeneration, an intense glial reaction and production of inflammatory mediators, but seven days of treatment with nimesulide (10 mg/kg/day, i.m.) strongly attenuated the microglial reaction, reduced the number of inducible nitric oxide synthase positive cells and completely abolished increase in prostaglandin-E2 formation [80]. Cyclooxygenase-2 (COX-2) is involved in the inflammatory component of ischemic cascade, playing an important role in the delayed progression of brain damage. In another study, the neuroprotective effect of nimesulide was still evident 30 days after an ischemic episode, providing evidence that COX-2 inhibitors confer a long-lasting neuroprotection. Oral administration of nimesulide was also able to significantly reduce brain damage, suggesting its protective effects are independent of the route of administration [81].

Induction of the endogenous neurogenesis is very important to help any neurological patient to improve therapeutic results, thus we believe a neuronal rehabilitation therapy for AD must also include activities pursuing this objective such as physical exercise and therapy, and mental games to exercise the brain while we rehabilitate neurons and their connections.

Conclusion

Memantine, tacrine, donepezil, rivastigmine and galantamine are the FDA approved drugs for the treatment of AD; nevertheless, the purpose for which they were designed is hard to achieve in the context of an ongoing neurodegenerative process, making it very difficult for current drug treatments to maintain a prolonged beneficial effect on AD patients.

We believe one has to be in the understanding that the only way these drugs might show better treatment outcomes is to look for a neuronal rehabilitation in AD patients [56] while new and better drugs able to target β-secretase activity, dissolution of amyloid plaques, and the restoration of axonal transport and neuronal polarity, are being developed. To cure AD with a single drug might be a hard task to
accomplish; therefore, the treatment should be multidisciplinary and targeted to the care of these patients from the cellular level to the physical and psychosocial aspects, making use not only of drug treatments but also of neurogenesis induction, neuronal membrane rehabilitation and neuroprotection all of which could be importantly influenced by diet, sleep, and physical and mental exercise.

References


