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Therapeutics of Alzheimer's Disease

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1. Introduction

Alzheimer's disease (AD) is the most common age-related neurodegenerative disorder, its prevalence is increasing along with population longevity and there is no cure for this disease so far, despite of the amount of information research has provided. This leads us to seek for better treatments able to improve the patient's and caregivers' quality of life. In this chapter we will review some of the main aspects of those proteins playing a key role in the pathological processes of Alzheimer's disease, as well as the therapeutic strategies currently in use and those that have been developing in the last few years for the treatment of this disease.

We will take a look on the processes of formation of the characteristic lesions of the Alzheimer's brain and sum up some of the properties of the main proteins involved in such processes leading to neuronal damage and death and the resulting cognitive decline. We will also have an overview of the current drugs of choice for Alzheimer's treatment and discuss about the latest therapies research has been developing to treat AD in its different stages, such as a therapy of our own proposal for the repair of neuronal membranes prior to initiate a conventional drug treatment and the advantages these strategies would provide combined on patients with a mild to moderate neuronal damage. At last we will focus on the importance of an integral care of Alzheimer's patients.

2. A quick view into the Alzheimer's brain

Two characteristic lesions develop within the brain of an AD patient, namely neuritic plaques and neurofibrillary tangles, both responsible for the symptomatology due to neuronal damage and death. We will take now a short look into these lesions.

2.1 Neuritic plaques

The so called neuritic or amyloid plaques are mainly extracellular aggregates of insoluble filaments of β-amyloid peptides with adjacent microglia, frequently surrounded by astrocytes. The dystrophic neurites are located into and around these amyloid deposits. Plaques are largely found in the limbic and association cortices, where they slowly start to develop over the years preceding the onset of the disease.

2.1.1 β-amyloid formation

β-amyloid peptides (Aβ) are the result of the sequential actions of the secretases over the amyloid precursor protein (APP). When APP is cleaved by the β- and γ-secretases the insoluble amyloid species are released (Figure 1). Some authors suggest a physiological role for Aβ in memory processes and as a regulator of the potassium channels expression and neuronal excitability (Ohno et al., 2004; Plant et al., 2006).

2.1.2 The amyloid precursor protein

APP is a type I membrane protein member of a small family with a large extracellular domain and a short cytoplasmic one, APP presents three main isoforms (695, 751 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-neural 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 (Thinakaran & Koo, 2008; Hung & Selkoe, 1994; Haas et al., 1991). APP undergoes a variety of post-translational modifications and proteolitic cleavages along and after its pass through the secretory pathway, releasing its derivatives into the lumen of secretory vesicles and the extracellular space (Selkoe, 2001). This protein has a poorly understood physiological role, but there have been autocrine and paracrine growth functions as well as trophic functions described, it is involved in neurite growth and synaptogenesis (Hung et al., 1992; Muresan et al., 2009; Chan et al., 2002).

2.1.3 The secretases

The α-, β- and γ-secretases cleave APP in several sites generating soluble peptides and membrane fragments as well as the insoluble Aβ peptides ($A\beta_{40}$ and $A\beta_{42}$) of amyloid plaques, these last as a result of the sequential actions of β-secretase (beta-site APP cleaving enzyme-1, BACE1) and the γ-secretase complex (composed by the presenilines-PS1 or PS2-, APH-1, PEN-2 and nicastrin).

The β-secretase gene is localized in chromosome 11 and it responds to stress conditions. Almost every tissue expresses BACE1, nevertheless its highest levels of expression are found in the brain. This enzyme has a 501 amino acids sequence containing two aspartil protease active sites and is located within cholesterol rich lipid rafts; it is believed BACE1 plays a role in synaptic function and the myelination process (Riddell et al., 2001; Ma et al., 2007; Cole & Vassar, 2007). On the other hand, γ-secretase is an enzymatic complex formed by four essential protein subunits necessary for an active mature complex. Mutations in either of the two preseniline genes (PS1, chromosome 14 and PS2, chromosome 1) have been described in cases of familial AD (Yu et al., 2000; Thinakaran & Koo, 2008). This secretase cleaves APP in several sites within its transmembrane domain perhaps to regulate programmed cell death, there is some evidence supporting a relationship between APP and PS expression levels and apoptotic activity (Vito et al., 1996).

2.2 Neurofibrillary tangles

These lesions are mainly the result of the intracellular aggregation of hyperphosphorylated protein tau in the form of paired helical filaments (PHFs) in the brain regions affected by AD, such as the enthorrinal cortex, hippocampus, parahippocampal gyrus, amygdala and frontal, temporal, parietal and occipital association cortices and subcortical nuclei projecting

to these regions (Brion et al., 1985; Grundke-Iqbal et al., 1986; Kosik et al., 1986; Nukina & Ihara, 1986; Wood et al., 1986).

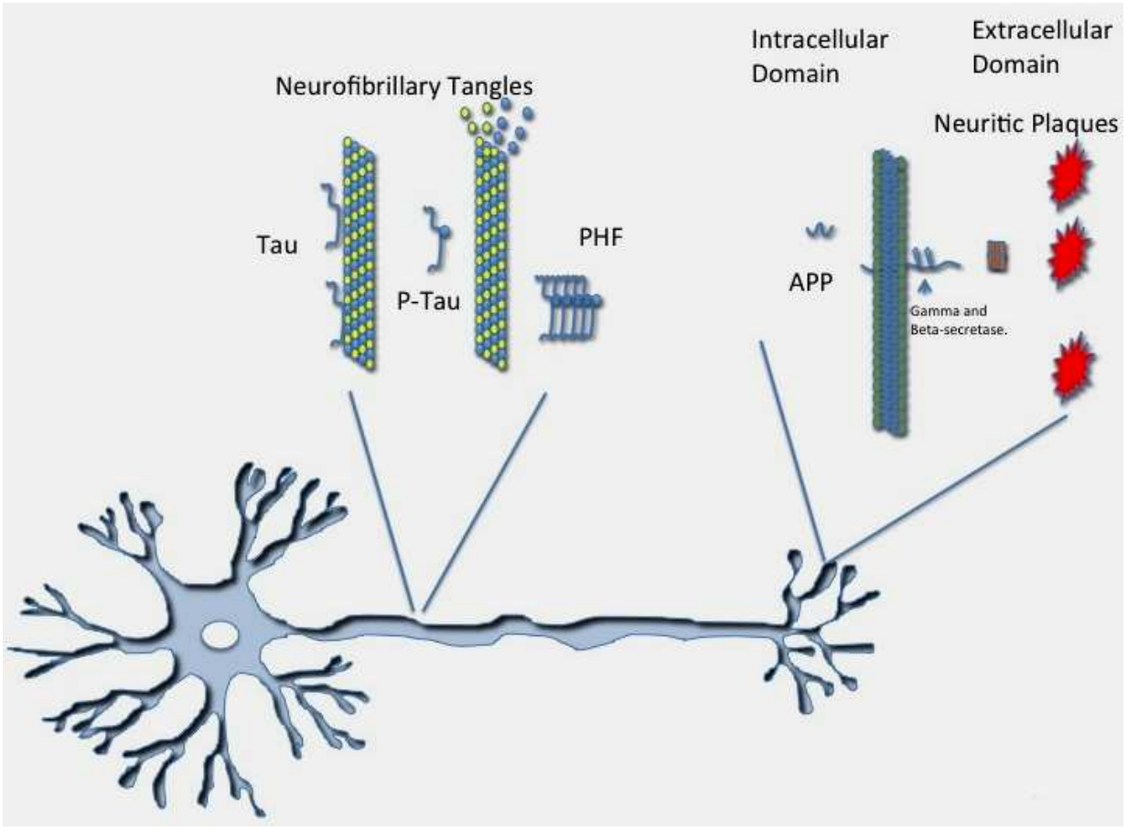

Fig. 1. Processes of formation of neuritic plaques and neurofibrillary tangles

Microtubule-associated protein tau (MAPT) promotes the microtubule assembly and stabilization required for morphogenesis and axonal transport in neurons, but it is also found in other cell lines (Johnson & Hartigan, 1999; Ingelson et al., 1996; Thurston et al., 1996). Tau gene is localized in chromosome 17. This protein controls microtubule stability in two ways: isoforms and phosphorylation. Tau phosphorylation in several sites regulates in a negative manner the protein's ability to bind to microtubules (Pope et al., 1994; Preuss et al., 1995; Preuss & Mandelkow, 1998; Illenberger et al., 1998), being this one the reason why the hyperphosphorylation of tau is a crucial event in the pathophysiology of AD. When tau gets hyperphosphorylated, it dissociates from microtubules and forms the PHFs which aggregate in the perinucleic cytoplasm, leaving a destabilized membrane to deform and lose synaptic activity (Figure 1). While neuritic plaques are thought to develop in a minor amount within the normal aging brain, the hyperphosphorylation of tau is almost an exclusive event of AD and the so called tauophaties.

3. The Alzheimer's therapeutic strategies

As we shall remember there is no cure for AD, however drug treatments are available to help with the symptomatology in several aspects of the disease and researchers keep

making efforts around the world to find better treatments as well as preventive strategies and ultimately a cure for AD.

3.1 Available drug treatments

Now we will review some of the characteristics of those drugs most widely used and approved by the Food and Drug 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 the 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.

3.1.1 Acetylcholinesterase inhibitors

Diminished cholinergic function is a normal feature in aging, in AD and other dementias it becomes of special severity however. The physiological processes underlying AD's pathology cause a decline in acetylcholine levels, exacerbated by the neurotransmitter's degrading enzyme, the acetylcholinesterase. The members of this group support communication between nerve cells by increasing the acetylcholine levels and availability at the synaptic cleft (Figure 2), they suppress acetylcholinesterase to prevent acetylcholine degradation.

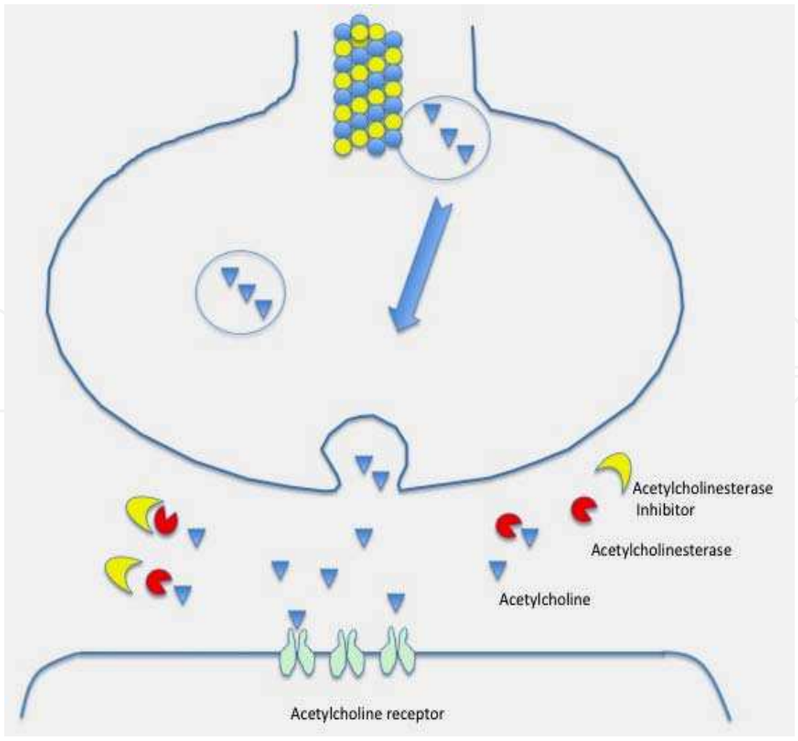

Fig. 2. Action mechanism of acetylcolinesterase inhibitors

There are three types of acetylcholinesterase inhibitors: short-acting, medium-duration and irreversible inhibitors; the difference between each other is the way they interact with the active site of the enzyme (Rang et al., 2001). The general side effects of these drugs may include diarrhea, nausea, dizziness, fatigue, loss of appetite and insomnia; the treatment with any of them should be monitored and start with low initial doses progressively increased until the maximum recommended daily dosage is reached. Precautions must be taken with concomitant (cardiovascular, gastrointestinal, pulmonary, urinary, neurological) diseases (De la Vega-Cotarelo & Zambrano-Toribio, 2011).

A. Tacrine (Cognex)

Derived from acridine, tacrine was one of the first drugs developed to help with the main symptoms of AD such as memory problems, cognitive decline and behavioral changes. Tacrine has been approved for the treatment of mild-to-moderate AD. Besides its acetylcholinesterase inhibiting activity, tacrine may also act as a potassium channel blocker which would increase the release of acetylcholine by functional cholinergic neurons. It should be noticed that tacrine has been associated with increased levels of transaminases (40-50% of patients) although its damage mechanism and efficacy remain controversial. This drug is contraindicated in conditions including cardiovascular disease, asthma, hyperthyroidism, urinary obstruction, prostatic hypertrophy, peptic ulcer and hepatic disease. The treatment with tacrine initiates with 10 mg/6h for at least 6 weeks and progressively increases every 6 weeks until a 30 mg/6h dosage; this treatment must be monitored for drug interactions, liver toxicity, severe side effects and efficacy to identify the need for interruption due to highly adverse conditions induced by tacrine administration.

B. Galantamine (Razadyne)

It is a natural compound derived from *Galanthus nivalis*. Galantamine directly stimulates nicotinic receptors to acetylcholine (which are especially important for learning and short-term memory processes) allosterically, avoiding receptor desensitization and down-regulation, although these receptors are damaged in AD. The main characteristics of galantamine are the protective role it has shown in cortical neurons, preventing these cells from the cytotoxicity of the amyloid peptides and from suffering oxidative stress, and the inhibition of Aβ aggregation; besides, galantamine increases acetylcholine release and modulates the levels of other neurotransmitters such as GABA, serotonin and glutamate. Galantamine is approved for mild-to-moderate stages of the disease. Its administration depends on the pharmaceutical presentation but usually dose does not exceed 24 mg/day with a regular evaluation of side effects and clinical benefit.

C. Donepezil (Aricept)

This drug is a piperidine derivative, being a reversible acetylcholinesterase inhibitor with good specificity it shows few side effects, there is no risk for hepatotoxicity with this drug. Donepezil has been approved for moderate-to-severe AD with a maximum administration of 10 mg/day every night before going to bed.

D. Rivastigmine (Exelon)

It is a carbamate compound which, compared to donepezil, shows better tolerance by patients and fewer side effects; however, its effectiveness is more limited than that of donepezil and the main concern about its use is the possibility of severe gastric damage and hepatotoxicity after its prolonged consumption. Rivastigmine has been approved for mild-

to-moderate AD in a low dosage (depending on the route of administration, until 12 mg/day). This drug is also used to treat dementia linked to Parkinson's disease.

3.1.2 Memantine

This non-competitive, voltage-dependent and of moderate affinity N-methyl-D-aspartate (NMDA) receptor antagonist regulates glutamate activity and prevents neuronal cells of an excessive income of calcium ions (Figure 3). Memantine (Namenda) is the only drug of its kind that has been approved by the FDA for the treatment of moderate-to-severe AD; its side effects may include hallucinations, confusion, dizziness, headaches and debilitation. Some authors have reported a decreasing activity for memantine of the amyloid peptide aggregation and prevention of synaptic dysfunction as well. Besides, it has been suggested by studies in transgenic mice inhibiting and reversing activities of the abnormal hyperphosphorylation of tau by a mechanism involving protein phosphatase-2A (Aronov et al., 2001).

The treatment of AD with memantine, as with acetylcholinesterase inhibitors, requires low initial dosages (5 mg/day) which will be progressively increased depending on the patient's tolerance until the maximum recommended is reached (20 mg/day), with constant monitoring of drug interaction, toxicity, efficacy and adverse side effects (Table 1). Memantine is contraindicated in cases of renal insufficiency, epilepsy, concomitant administration of amantadine, ketamine and dextromethorphan and conditions leading to an increase in urinary pH.

3.1.3 Auxiliary drugs

Symptoms of AD are often divided into cognitive, behavioral and psychiatric and thus exists a wide variety of symptoms accompanying the disease. Cognitive symptomatology affects memory, judgment, language, attention, planning and thinking processes while behavioral and psychiatric symptomatology affects the way a patient acts and feels and amongst these last are included anxiety, restlessness, hallucinations and delirium; besides there are other physical problems AD patients are prone to present and the side effects of primary drug treatments and drug interactions. For this reason it becomes of importance to attend the whole range of symptoms accompanying the disease.

For psychiatric symptoms should always be tried first a non-pharmacologic therapy followed, if necessary, by a pharmacologic treatment. Treatable conditions include, as we mentioned before, side effects of the primary drugs and interactions between drugs, symptoms of some common diseases and vision and hearing problems. Medication must target specific symptoms to contribute to the control of behavioral changes due to anxiety and restlessness originated by the accompanying symptomatology of AD (Table 2).

3.2 Developing therapies

A wide variety of research groups around the globe focus their investigations on the discovery of new biomarkers that serve as tools for an early diagnosis of AD in order to make treatments more effective when applied at the very first stages of the disease, where neuronal loss is not that significant for patients to present marked cognitive decline and it could be still possible to delay the neurodegenerative process. Along with that, many research groups are making efforts to develop new therapies for the treatment of AD using pharmacologic and non-pharmacologic strategies. Our group is currently investigating both

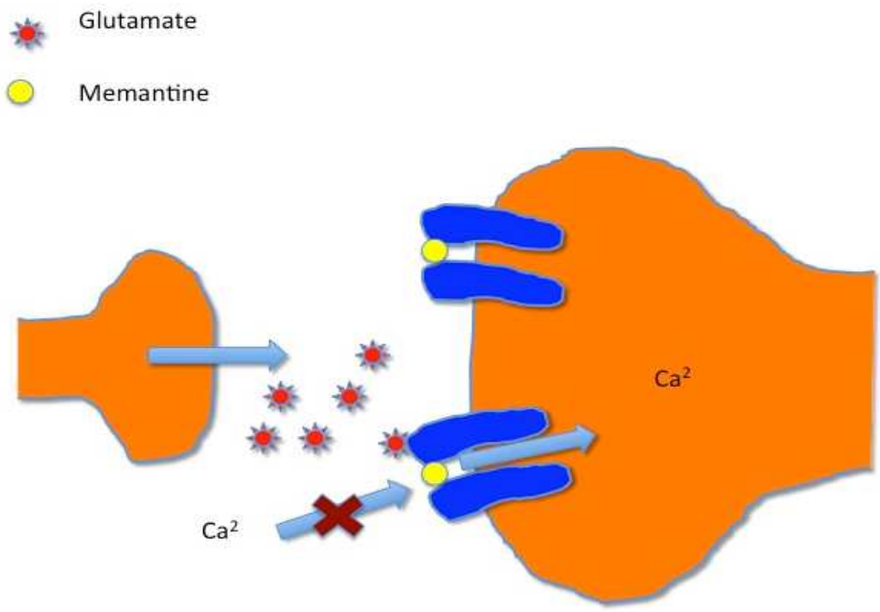

Fig. 3. Action mechanism of memantine

Group	Drug	AD stage	Beneficial effect	Risk	Dosage
Acetilcholinesterase inhibitor	Tacrine	Mild-to-moderate	Improves cognition and behavior	Hepatotoxicity	Initial: 10 mg/6h Maintenance: 30 mg/6h
	Galantamine	Mild-to-moderate	Improves learning and memory, cor-tical protection, in-hibition of Aβ aggregation	Nausea, vomi-ting, weight loss	Solution- Initial: 4 mg/12h Maintenance: 8 mg/12h Capsules-Initial: 8mg/day Maintenance: 16 mg/day Maximum: 24 mg/day
	Donepezil	Moderate-to-severe	Improves cognition Good tolerance	Muscle weakness	Initial: 5 mg/day Maintenance: 10 mg/day
	Rivastigmine	Mild-to-moderate	Improves cognition Good tolerance	Gastric damage Hepatotoxicity	Oral-Initial: 1,5 mg/12h Maintenance: 3-6 mg/12h Transdermic-Initial: 4,6 mg/day Maintenance: 9,5 mg/day
NMDA receptor antagonist	Memantine	Moderate-to-severe	Decreases Aβ aggregation, pre-vents synaptic dys-function, inhibits tau hyperphospho-rylation	Hallucinations Confusion Debilitation	Initial: 5 mg/day Maintenance: 20 mg/day

Table 1. Drugs approved for the AD treatment

the identification of gene expression-based peripheral biomarkers and the effectiveness of a neuronal rehabilitating therapy based mostly on natural products.

Conditions to control	Drugs	Examples
Humor, Irritability	Antidepressants	Citalopram, Fluoxetine, Paroxetine, Sertraline, Trazodone
Anxiety, Verbal problems, Resistance, Restlessness	Anxiolytics	Loracepam, Oxacepam
Hallucinations, Delirium, Aggression, Agitation, Hostility, Lack of cooperation	Antipsychotics	Aripiprazole, Clozapine, Haloperidol, Olanzapine, Ketiapine, Risperidone, Ziprasidone

Table 2. Auxiliary drugs in the treatment of AD's symptomatology

There has been studied the possibility of using anti-inflammatory drugs in the treatment of AD due to the evidence on the importance of inflammatory processes in the pathophysiology of AD. We shall notice two aspects in this subject: the presence of immune response in the AD brain and the immune response originated peripherally in these patients. Neuro-inflammation is a silent process occurring with morphological changes in activated microglia, the generation of reactive oxygen species (ROS) and other toxic materials, complement activation and cytokine release (Rogers et al., 1996; P.L. McGeer & E.G. McGeer, 1999, 2002); it is suggested that this inflammatory process might be due to the amyloid aggregation and damage to the blood brain barrier (BBB) (Hickey, 2001). The stress-induced production of pro-inflammatory cytokines and stress hormones by lymphocytes associates with several age-related diseases. In the AD, these peripheral processes may enhance the amyloid-induced inflammation in the brain. Because all of these, non-steroidal anti-inflammatory drugs (NSAIDs) (Anthony et al., 2000) and berberine (Zhu et al., 2006) have been investigated with therapeutic purposes for AD.

Immunotherapeutic approaches seek for the induction of an immune response against amyloid deposits. Three modalities are distinguished: passive immunization, active immunization and genetic vaccination; the last meaning the transfection of genes which produce the antigen. Immunization has proven efficient in animal models of AD, with several epitopes presenting different immunological properties being tested, as well as the mechanisms by which they exert an effect on Aβ clearance (Menéndez-González et al., 2005). Although clinical trials have failed so far, they rendered some relevant observations for the improvement of these strategies.

Other therapeutic strategies in development involve several methods to restore lipid homeostasis, promote synaptogenesis and regeneration and reduce Aβ production in the AD brain based on ApoE manipulation (Cedazo-Mínguez et al., 2007). Also, an increase in insulin stimuli in the brain could help improve memory in AD patients (Benedict et al., 2007). Nerve growth factor (NGF) and insulin-like growth factor-1 have shown a reduction of cognitive impairment and improvement of neurological functions in models of AD (Alzheimer's Research Center, 2008). Antioxidants, ginkgo biloba, estrogens and omega-3 fatty acids, among some other natural products, have also been investigated for therapeutic effects on AD. Despite the promising results of several of these studies, there still is a long way to go until some of these strategies could be available for the general population; nevertheless, each and every day we could be a step closer to develop a really effective treatment for such a complex disease as AD.

3.2.1 Neuro-rehabilitation in Mild-to-Moderate AD stages

AD treatment with both acetylcholinesterase inhibitors and Memantine has a quite reduced period of about six months of true effectiveness and noticeable results in patients, probably because of two reasons. Neither of these drugs is designed to stop the pathophysiological processes occurring within the AD brain, thus in one hand neurons keep degenerating and lesions growing in a slowly but progressive manner and synaptic connections are interrupted; on the other hand, the plasma membrane of neural cells is suffering a loss in stability and shape what we believe leads to the misplacement of receptors at the cell surface, leaving them unreachable for the neurotransmitter binding or even that both the neurotransmitter cannot be released and its receptor might not be properly carried to the cell surface because of the resulting damaged anterograde and retrograde transports. Thus despite of the neurotransmitter's maintained availability at the synaptic cleft, it is not able to reach the postsynaptic neuron and bind to its receptor or even the amount of neurotransmitter released from the presynaptic neuron is not enough to generate an adequate action in the postsynaptic neuron (Figure 4).

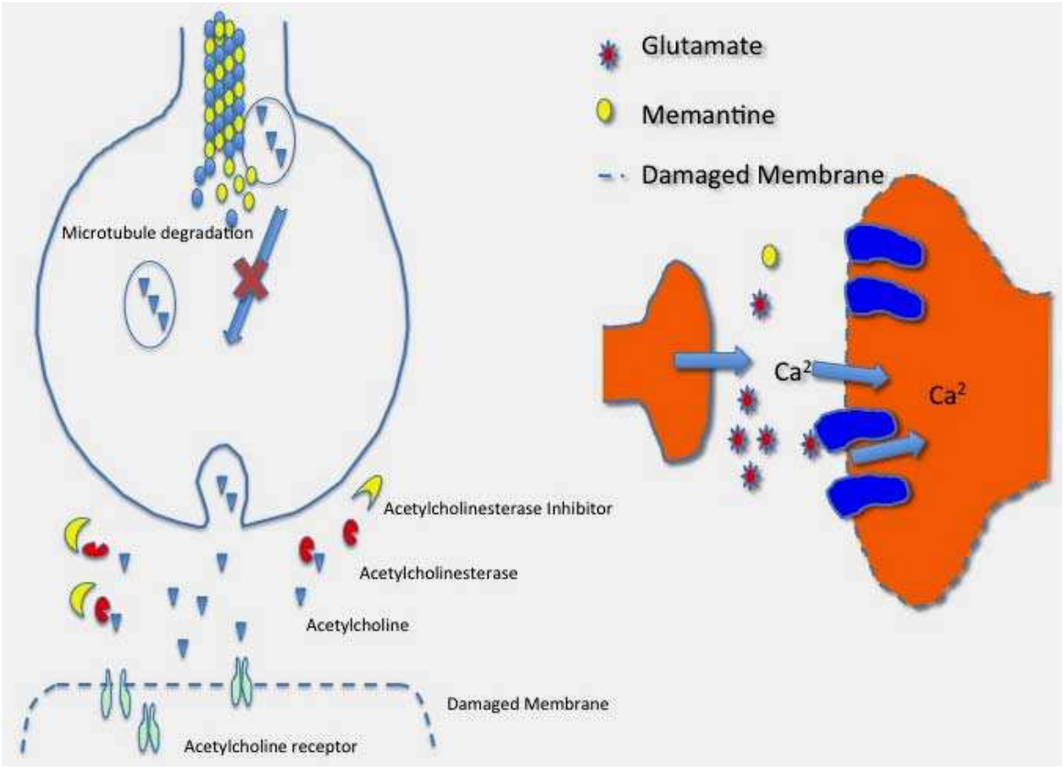

Fig. 4. Drugs do not function because of the damaged membrane

Because of all the above, our group proposed an alternative therapy for AD focused on neuronal membrane repair what would restore its functionality, including the transport of molecules such as neurotransmitters and their receptors, the availability of receptors binding domains and the correct placing of membrane molecules (receptors, enzymes and carriers). This therapy is based on a daily consumption of natural products including omega-3 and folic acids, ginkgo biloba and resveratrol which cause no side effects and have shown to provide good advantages for neuronal functionality, in addition of their easy

accessibility. We also include Nimesulide for the inflammatory component of AD, and Fluoxetine or Escitalopram to promote neuronal reconnection. We suggest that a rehabilitation of neuronal membranes followed by or combined with the conventional drug treatments (Table 3) would enhance and prolong the beneficial effects of the treatment in AD patients. This therapy has shown good results so far (Aranda-Abreu et al., 2011) and there are currently more subjects initiating the protocol to test this therapy including normally aged individuals, AD patients and patients suffering from neurological disorders and dementias different from AD.

Day	Omega-3	600 – 1000 mg	(Membrane repair)
	Resveratrol	60 mg	(Antioxidant)
	Ginkgo biloba	60 mg	(Memory processes)
	Escitalopram	10 mg	(Neuronal reconnection)
Night	Folic acid	1 mg	(Neuronal integrity maintenance)
	Nimesulide	100 mg	(Anti-inflammatory – If necessary)
Alzheimer's drug treatment as medical doctor indicated			

Table 3. The Neuro-rehabilitation therapy recipe*

The neuro-rehabilitation therapy involves four aspects:

A. Neuronal membrane restoration.
B. Maintenance of neuronal integrity.
C. Neuronal reconnection.
D. Activation of memory processes.

A. Neuronal membrane restoration

Omega-3 fatty acids, such as docosahexaenoic acid (DHA), are involved in neurite development, the remodeling of membrane lipid rafts and neurogenesis, and they have shown a reduction in the hyperphosphorilation of tau and amyloid aggregation in AD. Cholesterol rich lipid rafts associate with the stabilization and proper clustering of membrane receptors. Because of this, we use omega-3 fatty acids to repair the damaged neuronal membranes in order to restore the correct positioning and trafficking of membrane molecules, such as neurotransmitters and their receptors; this would help to stabilize the synaptic activity (Figure 5) and thus improve cognitive functioning.

B. Maintenance of neuronal integrity

The integrity of neuronal membranes should be maintained in both the remaining healthy neurons and those already restored. This is important because we shall remember here that we are not making the damaging processes to stop and thus membranes would tend to degenerate if we do not help to delay these processes. With this purpose we included folic acid in the neuro-rehabilitation therapy as it plays an important role in neuroplasticity and the maintenance of neuronal integrity by a mechanism involving one-carbon metabolism, which associates with neurological and psychiatric pathologies when deranged.

* From Aranda-Abreu et al., 2011, Dovepress.

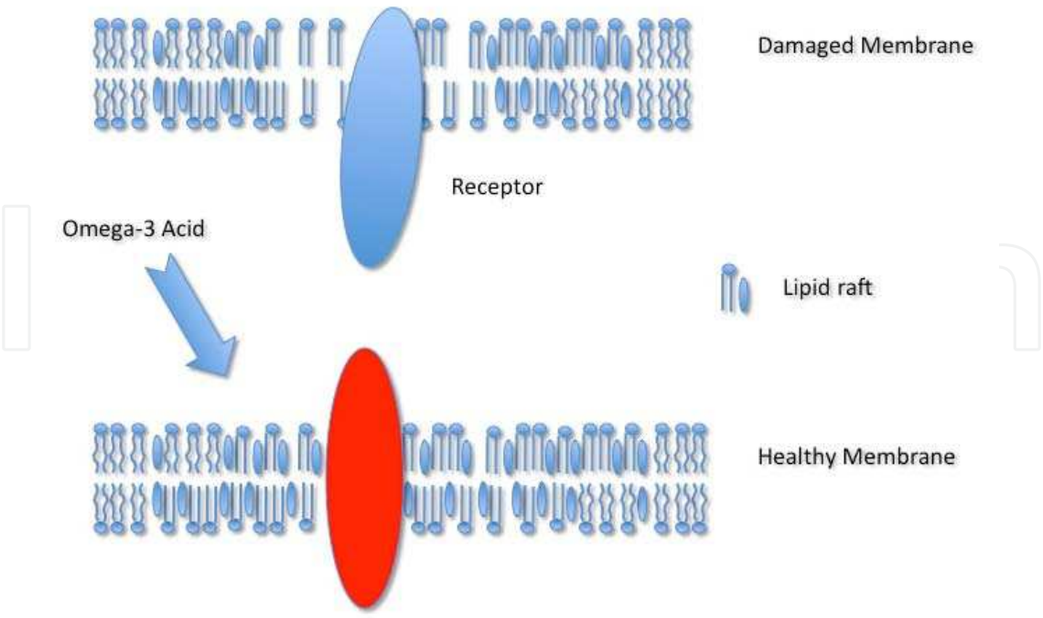

Fig. 5. Membrane restoration by the remodeling of lipid rafts

Resveratrol is also included in this therapy with the purpose of maintaining neuronal integrity. Resveratrol belongs to a group of molecules known as phytophenols, which act as free radical scavengers. Resveratrol is found in grape extracts and its use as antioxidant has become very popular nowadays because it protects against ROS toxicity and provides beneficial effects on inflammatory and neoplastic processes. In addition, resveratrol has shown a protective effect against Aβ toxicity in neuronal cell lines. The protection resveratrol provides to neuronal cells makes it a good agent to guard the integrity of these cells.

C. Neuronal reconnection

Neurons should be capable of making new connections between each other to re-establish cognitive processes. Some drugs such as Fluoxetine (Wang et al., 2008) and Escitalopram (Alboni et al., (2010) could help in this task by the induction of serotonin reuptake. Serotonin regulates neuronal morphology and its recapture is involved in the formation of new synapses, which would reconnect newly restored neurons (Figure 6). With their membranes repaired neurons regain the ability to receive and transmit impulses, thus once they make new inter-neuronal connections, the damaged AD brain would improve its functionality and cognitive impairment might be diminished.

D. Activation of memory processes

Ginkgo biloba is known for its beneficial effects on memory processes as well as its antioxidant activity. Among the pharmacological effects of ginkgo biloba are its antagonism to the platelet activation factor and the increase in GABA levels, glutamic decarboxylase and muscarinic receptors. Although consumption of ginkgo biloba with a therapeutic purpose for AD patients has brought inconclusive results, numerous authors report an improvement of the cognitive impairment in AD patients by the treatment with ginkgo biloba and we have observed good results in these patients after a follow up of one year from initiation of our neuro-rehabilitation therapy, which includes ginkgo.

Despite of the effects of ginkgo biloba on memory, we shall bear in mind that brain stimulation helps to keep it healthy. In AD, as in other neurodegenerative disorders, cognitive stimulation becomes of great importance for the rehabilitation process, improving memory and cognitive impairment. We will point out later the importance of stimulating the brain, along with other aspects, in order to assure the best possible outcome with this or any other AD treatment chosen.

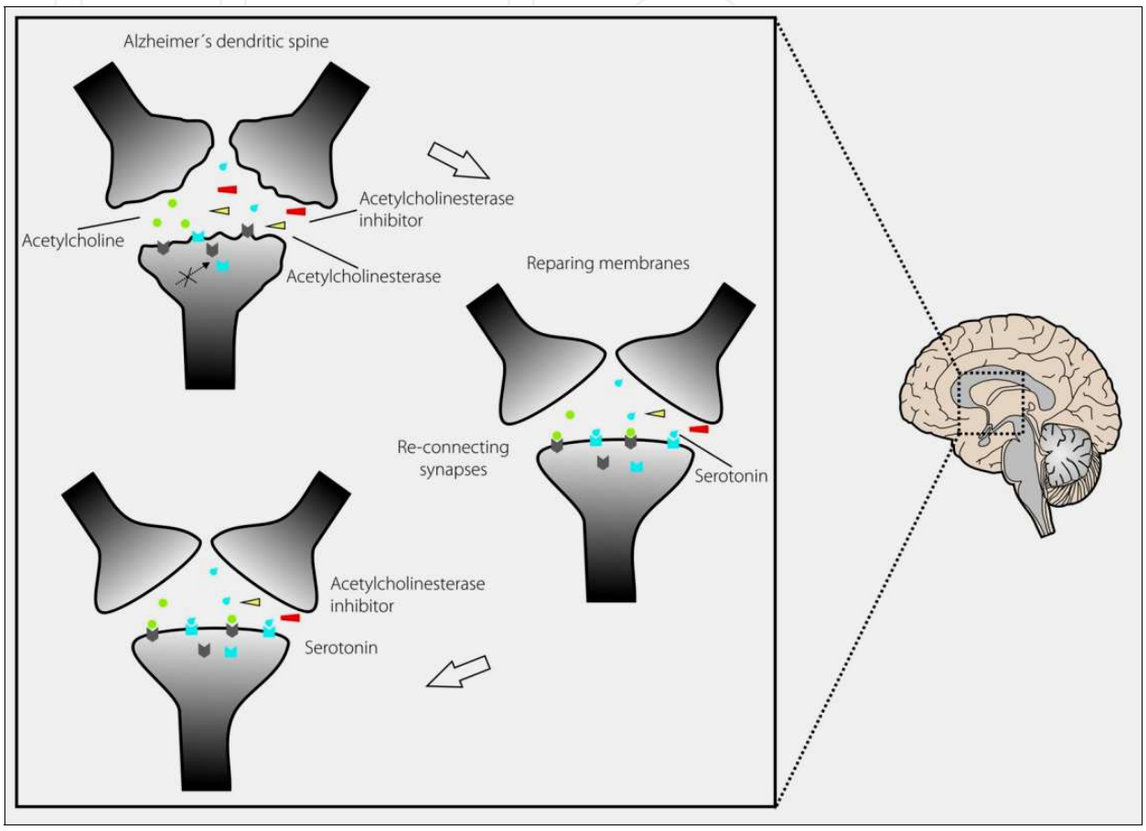

Fig. 6. Neuronal reconnections by serotonin recapture

3.2.2 Stem cells and advanced AD

Nowadays we have all heard about new therapies for all kinds of pathologies based on stem cells and AD is not the exception. In fact, the therapeutic strategy most widely investigated and, probably, promising for the severe cases of AD involves the growingly popular stem cells.

As we know, in AD there is a progressive loss of neuronal cells and thus in advanced stages of the disease the loss in brain mass is very significant, reason why no other pharmacological treatment or non-pharmacological therapy could promise much of an improvement. At this point, the alternative would be to replace the already lost neurons with new ones of the same type, the last being the main problem encountered by researchers in this area. As some groups have been able to successfully proliferate and differentiate stem cells from different sources into neurons of several types in culture, they found this to be difficult to reproduce into the brain. The conditions required *in vivo* for stem cells to differentiate into specific lineages are yet to be unraveled and only then effective and

reproducible protocols could be developed to produce healthy and functional stem/progenitor cell-derived neurons (Wicklund et al., 2010). But even if we are to accomplish this task effectively another concern shall rise: would these cells be also affected by the disease in time? And, if so, how long would they provide an actual improvement on cognition before facing the pathophysiological processes of AD?

In AD, a stem cell-based approach should be able to replace several types of neuronal cells in different brain regions (Figure 7) and show a significant rescue of cognitive functions, some studies in animal models have suggested an improvement of cognition by means of a variety of mechanisms different to the direct alteration of either tau or Aβ pathologies (Blurton-Jones et al., 2009).

Another path to be taken would consist of protocols developed for endogenous stem cells stimulation. The main issue on this matter is the prevalent controversy about discrepant results on the effects of Aβ over stem cells and neurogenesis, as some studies suggest a neurogenic effect while others show neurotoxicity on stem/progenitor cells. Hence, modulation of the microenvironment within the AD brain would be crucial for the feasibility of this and other related approaches (Wicklund et al., 2010).

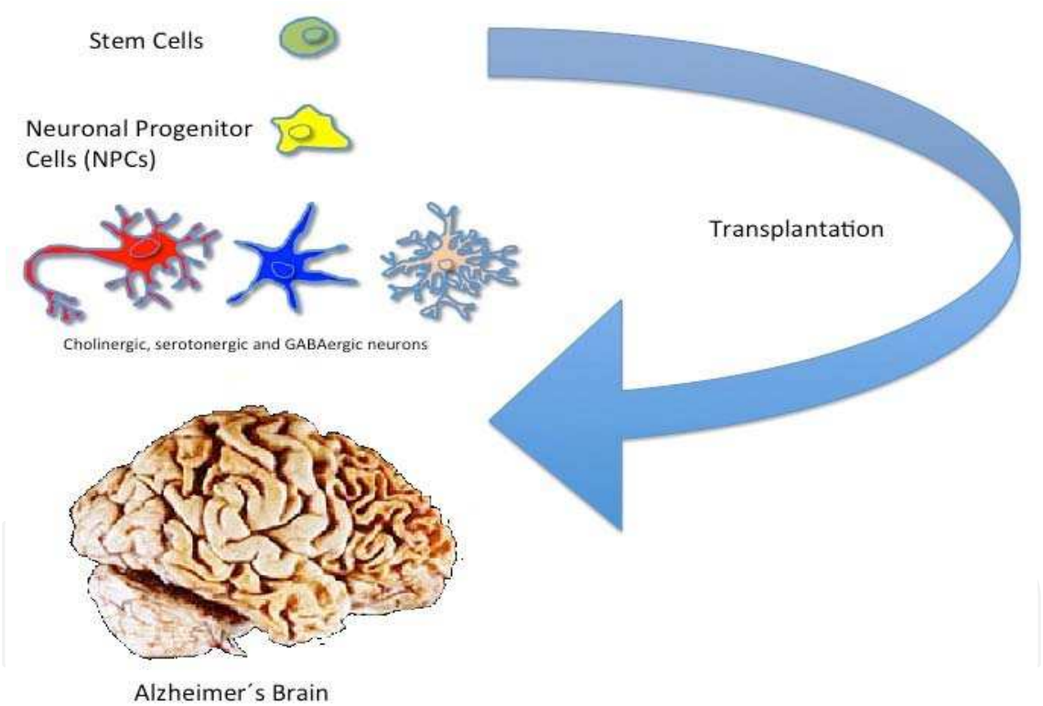

Fig. 7. Stem cell transplantation into the AD brain

4. Integral care of AD patients

There are many aspects we should keep an eye on once an individual is diagnosed with AD, for such a complex disease must be attacked in all possible directions; as there is no magic treatment for AD one could use all the help one can possibly get (Table 4). In our present study we are instructing the caregivers of our patients on the best way to assure an integral care able to render the best outcome for the therapy as it is not enough to repair the

damaged neuronal membranes, to seek for neurogenesis, cognitive stimulation and the maintenance of neuronal functionality actually is the best way to enhance and prolong the positive effects of any AD therapy.

	Characteristics	Recommendations
Nutrition	Required for brain metabolism and synaptic function.	HAD, EPA, vitamins (E, K, C, B6, B12), minerals (iron, iodine, manganese, copper, zinc), unsaturated fatty acids, fish, 5 small meals.
Sleep	Helps neurogenesis, neuronal plasticity, learning and memory	No daytime naps, full 8 hr nighttime sleep, watch for sleep apnea, same bedtime every day.
Physical exercise	Good for metabolism, inflammation, memory, learning, information processing, neurogenesis, neuronal plasticity, neurotransmission	Exercise for 30 minutes, 3 times a week, at least.
Cognitive stimulation	Improvement of learning, memory and praxis, and socialization and mood	Reading, puzzles, crosswords, figure-recognition and problem-solving games, chess, Pictionary, drawing, bingo, etc.
Enriched environment	Regulates stress, mood, behavior, sleep-wake cycle and sensory stimulation	Comfortable, clean and ordered space, social and cultural activities, music, lightning, no loud noises, company, affection
Neuro-rehabilitation	Repairs neuronal membranes, synaptogenesis, improves memory and learning	Daily consumption, monitoring of patients.
Treatment	Helps neurotransmission.	Continue drug treatment as indicated by medical doctor. Monitor for potentially risky side effects.
General health	Improves restlessness, humor, vision and hearing, sleep, etc.	Often checkups, treatment of concomitant diseases, correction of vision and hearing problems.

Table 4. Integral care of the AD patient

4.1 Nutrition

The structure and function of the brain is affected by the nutrients in our diet as up to 50% of carbohydrates are consumed by the brain, lipids constitute neuronal membranes and amino acids, vitamins and some minerals are required for neurotransmitter synthesis and the maintenance of cognitive functions (Lanyau-Domínguez, 2009). Therefore, a healthy diet becomes important not only for preventing neuronal deterioration in non-demented

individuals, but for the maintenance of the remaining healthy neurons in demented patients. For example, glucose intake in the brain requires vitamin B_1, and vitamin B_{12} is necessary for myelination, this last together with vitamin B_6 are involved in neurotransmitter synthesis, vitamin E protects neuronal membranes; iron and iodine are required for cellular metabolism and manganese, copper and zinc are cofactors in the protection against free radicals and ROS; a high consumption of mono- and polyunsaturated fatty acids, DHA and EPA, together with a low consumption of saturated and trans-saturated ones, has been associated with a better cognitive functionality.
AD patients have demonstrated to be prone to develop nutrient deficiency due to loss of independence, disorientation and altered eating behavior which could lead not only to an exacerbation of cognitive decline but to recurrent infectious diseases, anemia and an increase in morbidity and mortality (Finley, 1997; Morley, 1996; Franzoni et al., 1996; Riviére et al., 1999).
We recommend caregivers to implement with the therapy the following diet:

A. Fish or tuna fish at least twice a week.
B. Legumes one to three times per week.
C. Highly energetic meals including bread, pasta, rice and potatoes.
D. Two portions of dairy products.
E. Two portions of meat, chicken and eggs, one portion when fish is included.
F. Five portions of fruits and vegetables.
G. Vegetable oils.
H. Distribute in 5 small meals per day.

4.2 Sleep

In AD, as in other neurological disorders, age-related sleep disorders are exacerbated by several factors including homeostatic alterations in the circadian rhythms, medication side effects, environmental factors and medical illness. The different sleep stages have a role in learning and memory processes as well as in neurogenesis and neuronal plasticity. Furthermore, it is suggested that sleep disturbances could exacerbate Aβ aggregation and that the optimization of sleep time may slow the progression of AD (Kang et al., 2009). Fluoxetine or Escitalopram in our therapy could help to modulate sleep disorders, although we also suggest caregivers to pay attention to the patient's sleep-wake cycle to try to avoid naps during the daytime and wakefulness during the night to promote a better nighttime sleep.

4.3 Physical exercise

Exercise helps keeping our bodies healthy and that includes our brains, it increases cerebral blood flow by the improvement of vascular function, improves metabolism, reduces inflammation and regulates several brain chemicals, but it does not stop here. It has been suggested that exercise may also improve memory and learning, delay age-related memory loss, speed information processing, aid neurogenesis and synaptic plasticity, enhance the glutamatergic system, increase brain derived neurotrophic factor and dendritic spines and reduce cell death (van Praag, 2009; Cotman et al., 2007, as cited in Wollen, 2010). Therefore we ask the participants in our therapy program to include at least 30 minutes of exercise 3

times a week, this would help improve the mood of patients and facilitate cognitive functions.

4.4 Cognitive stimulation

It is crucial to stimulate the brain while following the neuro-rehabilitation therapy as we shall remember our ultimate purpose is to reconnect neuronal networks in order to improve cognition. A higher degree of education and regular reading have proven to decrease the risk to develop AD, thus stimulating the brain helps to keep it healthy ("use it or lose it"). As our therapy is designed to be accessible to our patients' family members or professional caregivers, this aspect is covered with activities that are both stimulating and recreational. Board games and other challenging activities could help activate memory, learning, sensory, motor and language processes and, when performed as a group, they may also contribute to socialization and mood. Therefore we ask our participants to ensure that at least one hour per every day will be destined to activities such as reading, solving crosswords, making puzzles, playing picture-recognition games, pictionary, bingo, chess, etc., and that they will be performed in group at least 3-4 times per week.

4.5 Environment

Studies have shown a significant improvement of cognition by environmental enrichment in models of AD (Jankowsky et al., 2005). Environmental enrichment here seeks for stress reduction, mood improvement, behavioral management, sleep-wake cycle regulation and sensory stimulation. In this aspect it is important to enrich the environment where our patients live within not only by social and recreating activities as we mentioned before, but by making them feel comfortable physically and emotionally. We ask our participants to create a harmonious, quiet and familial environment with an adequate lighting, music, order and affection. Social and cultural activities are also suggested.

4.6 Rehabilitation

The neuro-rehabilitation therapy should be followed as indicated. For it could take some time to show an improvement, maintenance and patience are needed. As we previously reported (Aranda-Abreu et al., 2011), we observed good outcomes with patients followed up to one year after the incorporation of our therapy to their AD treatment and thus we ask for our patients' family members to be patient and follow the instructions to ensure the best possible response to the therapy. We also promote preventive precautions between patients' family members, caregivers and between people above 50 years old because we believe prevention is currently the best weapon we could use to fight the increasing prevalence of AD and other age-related diseases.

4.7 Treatment

For all our participants that have already been diagnosed with AD by the time of initiation of the therapy, we recommend their relatives not to discard the drug treatment previously prescribed by the physician; the neuro-rehabilitation therapy should help these drugs to work more properly when combined. It is important to understand that these drugs do work and provide some benefits for AD patients, but their effect decreases as neurodegeneration continues; when neuronal membranes are repaired and synapses re-established these drugs should exacerbate the positive effects of the neuro-rehabilitation therapy.

4.8 General health care

Our recommendation to provide the best health care is to visit the physician with certain frequency to make sure concomitant diseases, drug side effects and possible limiting organic conditions are attended adequately. Comorbidity could speed up the rate of cognitive decline and discomfort due to physical or psychological illness might exacerbate behavioral and mood changes. Health care must be multidisciplinary in order to attend the whole range of the patients' needs.

5. Conclusion

Alzheimer's is a complex disease due to the presence of diverse pathological processes, it does not only involve plaque and tangle formation but inflammation, immune response, mitochondrial dysfunction, altered membrane traffic and positioning of molecules and a whole series of mechanisms leading to neuronal degeneration and death. Because of this diversity of events drug treatments remain scarcely effective which highlights the need for therapeutic strategies seeking for an integral care of every aspect of the patient's life. In attendance to this need, our group has proposed a neuro-rehabilitation therapy based mostly on natural products for the repair of neuronal membranes and the formation of new synapses in order to re-establish communication and cognitive processes. This therapy involves a change in the patient's lifestyle that would enhance the positive effects and provide a better quality of life for both patients and their families.

Our overall purpose is to identify a fingerprint of the disease detectable in an accessible sample and test its ability to proportion a suitable tool for an early diagnosis of AD, as we offer a choice for the prevention and treatment of the disease. Our work is not quite done yet and our efforts to improve the quality of life for people suffering from AD will continue. There is still a long way to go until the day research finds a cure for AD; meanwhile, alternative diagnostic and therapeutic approaches are being developed by a number of groups around the globe to offer actual and long lasting improvements in patients' cognition. Results have been promising so far and we hope in a future not so far the general population could find access to these approaches, though preventive strategies should be promoted especially for those individuals with a presumed higher risk to develop AD.

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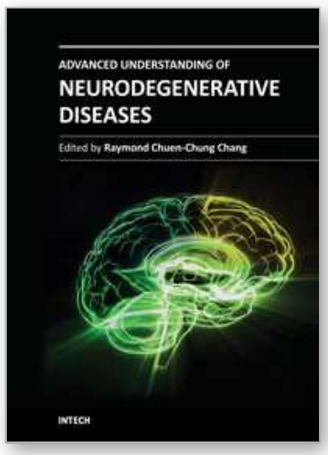

Advanced Understanding of Neurodegenerative Diseases

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Advanced Understanding of Neurodegenerative Diseases focuses on different types of diseases, including Alzheimer's disease, frontotemporal dementia, different tauopathies, Parkinson's disease, prion disease, motor neuron diseases such as multiple sclerosis and spinal muscular atrophy. This book provides a clear explanation of different neurodegenerative diseases with new concepts of understand the etiology, pathological mechanisms, drug screening methodology and new therapeutic interventions. Other chapters discuss how hormones and health food supplements affect disease progression of neurodegenerative diseases. From a more technical point of view, some chapters deal with the aggregation of prion proteins in prion diseases. An additional chapter to discuss application of stem cells. This book is suitable for different readers: college students can use it as a textbook; researchers in academic institutions and pharmaceutical companies can take it as updated research information; health care professionals can take it as a reference book, even patients' families, relatives and friends can take it as a good basis to understand neurodegenerative diseases.

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