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Chapter 11

Potential Therapeutic Strategies to Prevent the Progression of Alzheimer to Disease States

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Additional information is available at the end of the chapter

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1. Introduction

Alzheimer is an age-dependent neurodegenerative process distinct from normal aging and characterized morphologically by the presence of senile plaques and neurofibrillary tangles, which progress from the brain stem and inner parts of the temporal lobes to most the telencephalon.

Senile plaques are mainly composed of different species of fibrillar β-amyloid (Aβ), a product of the cleavage of the β-amyloid precursor protein (APP), and they are surrounded by dystrophic neurites, reactive astrocytes and microglia. Aβ fibrillar deposits also occur in diffuse plaques, subpial deposits and in the wall of the cerebral and meningeal blood vessels in the form of amyloid angiopathy. A substantial part of β-amyloid is not fibrillar but soluble and forms oligomers of differing complexity which are toxic to nerve cells.

Neurofibrillary tangles are mainly composed of various isoforms of tau protein, which is hyper-phosphorylated and nitrated. It has an altered conformation and is truncated at different sites through the action of a combination of several proteolytic enzymes giving rise to species of low molecular weight which are toxic to nerve cells. Abnormal tau deposition also occurs in the dystrophic neurites of senile plaques and within the small neuronal processes, resulting in the formation of neuropil threads.

The mechanisms of disease progression are not completely understood but Aβ initiates the pathological process in the small percentage of familial cases due to mutations in genes encoding APP, presenilin 1 and presenilin 2, the latter involved in the cleavage of APP, and potentiates tau phosphorylation in sporadic cases that represent the majority of affected individuals (β-amyloid cascade hypothesis). Moreover, Aβ act as a seed of new β-amyloid production and deposition under appropriate settings, and abnormal tau promotes the

production and deposition of hyper-phosphorylated tau. Therefore, Aβ and hyper-phosphorylated tau promote the progression of the process and this may occur in an exponential way once these abnormal proteins are accumulated in the brain.

In addition to these pathological hallmarks, multiple alterations play roles in the degenerative process. Several genetic factors, such as apolipoprotein ε4 (APOE4), and external factors, such as vascular and circulatory alterations and repeated cerebral traumatisms, among others, facilitate disease progression in sporadic forms. Furthermore, metabolic components mainly, but not merely, associated with aging have a cardinal influence, including mitochondrial defects and energy production deficiencies, production of free radicals (oxidative and nitrosative reactive species: ROS and NOS) and oxidative and nitrosative damage, increased reticulum stress damage, altered composition of membranes, inflammatory responses and impaired function of degradation pathways such as autophagy and ubiquitin-proteasome system.

It has been proven that the degenerative process, at least the presence of neurofibrillary tangles, starts in middle age in selected nuclei of the brain stem and entorhinal cortex, and then progresses to other parts of the brain. Instrumental stages of Braak cover stages I and II with involvement of the entorhinal and transentorhinal cortices; stages II and IV also affect the hippocampus and limbic system together with the basal nucleus of Meynert; and stages V and VI involve the whole brain although neurofibrillary tangles are not found in selected regions such as the cerebellar cortex and the dentate gyrus. The distribution of senile plaques is a bit different as they first appear in the orbitofrontal cortex and temporal cortex and then progress to the whole convexity.

A concomitant decline in neuronal organization occurs most often in parallel with senile plaques and neurofibrillary tangles manifested as synaptic dysfunction and synaptic loss, and neuronal death and progressive isolation of remaining neurons.

An important observation is that about 80% of individuals aged 65 years have Alzheimer-related changes, at least at stages I-III, whereas only 5% have cognitive impairment and dementia. About 25% of individuals aged 85 years suffer from cognitive impairment and dementia of Alzheimer type. Stages I-IV are often silent with no clinical symptoms. Cognitive impairment and dementia usually occur at stages V and VI when the neurodegenerative process is very advanced. Importantly, the progression from stage I to stage IV may last decades, whereas the progression to stages V and VI is much more rapid. Therefore, Alzheimer is a well-tolerated degenerative process during a relatively long period of time, but it may have devastating effects once thresholds are crossed. Moreover, clinical symptoms may be complicated by concomitant vascular pathology.

Several attempts have been made to predict the evolution to disease states. Neuroimaging, including high resolution and functional magnetic resonance imaging, positron emission tomography and the use of relative selective markers of β-amyloid and tau deposition in the brain, together with reduced levels of Aβ and increased index of phospho-tau/total tau in the cerebrospinal fluid, are common complementary probes (biomarkers) in addition to the data

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provided by the neuropsychological examination. Unfortunately, these tests, at present, detect relatively advanced stages of the process in pathological terms.

It is very illustrating to visualize under the microscope how a brain at middle stages of the degenerative process has been working without apparent neurological deficits during life. The adaptive capacities of the brain in coping with current functions in spite of the decrepitude of composition and organization resulting from the chronic progression of the degenerative process are impressive.

Taking into consideration this scenario, it is compulsory to increase understanding of the first stages of the degenerative process and to act on selective targets before the appearance of clinical symptoms.

The present review is not a mere list of putative treatments of Alzheimer's disease (AD) but rather an approach to learning about observations made on experimental models and early stages of disease aimed at curbing or retarding disease progression on the basis of definite rationales. It is also our aim to encourage the consideration of Alzheimer as a degenerative process not necessarily leading to dementia [1]. This concept has important clinical implications as it supports early preventive measures in the population at risk (i.e. persons over 50 years) even in the absence of clinical symptoms.

2. Experimental therapeutic strategies to prevent Alzheimer progression to Alzheimer Disease (AD) states

Several reviews have focused on various aspects related to habits and dietary elements which may act as protective factors against AD, including physical and mental exercise, low caloric intake, various diets with low fat content, and vitamin complements [2, 3]. It is worth noting that neuropathological studies in old-aged individuals usually present combined pathologies, and combination of Alzheimer changes and vascular lesions are very common [4]. It is well documented that vascular pathology potentiates primary neurodegenerative pathology and that vascular factors may be causative of cognitive impairment and dementia [5]. Therefore, therapies geared to reduce vascular risk factors are also protective factors against AD clinical manifestations.

2.1. Targeting Aβ

Most of the current drug development for the prevention or treatment of AD is based on the β-amyloid cascade hypothesis and aims at reducing the levels of Aβ in the brain. Overproduction, aggregation and deposition of the Aβ peptide begin before the onset of symptoms and they are considered an essential early event in AD pathogenesis. Thus, targeting these early Aβ alterations is assumed to reduce the progression to disease states. The different strategies developed to achieve this objective include decreasing Aβ production through modulating secretase activity, interfering with Aβ aggregation, and promoting Aβ clearance.

2.1.1. Secretase-targeting therapies

APP is processed in the brain exclusively by three membrane-bound proteases, α-, β- and γ-secretase. Therefore, specifically modifying such enzyme activity should result in a reduction of Aβ production [6].

- *α-secretase activators*: α-secretase initiates the non-amyloidogenic pathway by cleaving APP within the Aβ sequence, thereby preventing the production of Aβ and producing a non-toxic form of APP derivative which is neuroprotective and growth- promoting [7]. Therefore, compounds that stimulate α-secretase activity could become an attractive strategy to reduce Aβ production. In fact, some indirect methods of promoting α-secretase activity, such as the stimulation of the protein kinase C (PKC) or Mitogen-activated protein kinases (MAPK) pathways, the use of α-7-nicotinic acetylcholine (ACh) receptor and 5-hydroxitryptamine (5-HT) receptor 4 agonists, and γ-aminobutyric acid A receptor modulators, result in α-secretase-mediated cleavage of APP and reduced Aβ levels *in vivo* [8]. However, the development of a direct activator of α-secretase as a drug treatment for AD seems premature because of the lack of knowledge about the consequences of chronic up-regulation of α-secretase-mediated cleavage on other substrates [6].
- *β-secretase inhibitors*: the β-secretase enzyme initiates the amyloidogenic pathway, cleaving APP at the amino terminus of the Aβ peptide. Further cleavage of the resulting carboxy-terminal fragment by γ-secretase results in the release of Aβ. β-secretase activity is specifically mediated by the β-site APP cleaving enzyme 1 (BACE1), which is also involved in the processing of numerous substrates in addition to APP. The research of drugs inhibiting BACE1 activity was encouraged by studies revealing that the expression of mutated BACE1 reduces amyloidogenesis and cognitive impairment in APP transgenic mice [9, 10]. The first generation of BACE1 inhibitors was peptide-based mimetics of the APP β-cleavage site. Unfortunately, these compounds exhibited some difficulties because of the large substrate binding site of BACE1 and because of the difficulty in crossing the blood–brain barrier (BBB) and penetrating the plasma and endosomal membranes to gain access to the intracellular compartments where endogenous BACE1 plays its function. Recently, non-peptide small-molecule BACE1 inhibitors have been reported to improve bioavailability and to lower cerebral Aβ levels in animal models of AD [11, 12]. However, the involvement of BACE1 in other important physiological processes raises concerns about minimizing the potential adverse effects derived from generalized BACE1 inhibition.
- *γ-secretase inhibitors (GSIs)*: γ-secretase is a complex composed of presenilin 1 and presenilin 2 (PS1 and PS2) forming the catalytic core and three accessory proteins, anterior pharynx-defective 1 (APH-1), nicastrin and presenilin enhancer protein 2 (PEN2). The γ-secretase complex displays a high degree of subunit heterogeneity and little is known about the physiological roles of the diverse complexes and how they process different trans-membrane substrates in addition to APP. This heterogeneity suggests that selective targeting of one particular subunit might be a more effective treatment strategy than non-selective γ-secretase inhibition [13]. Thus, removal of APH-1B and APH-1C isoforms in a mouse model of AD decreased Aβ plaque formation and improved behavioral deficits [14]. A number of orally bioavailable and brain-penetrating GSIs have been shown to decrease Aβ production

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and deposition in APP mouse models and in humans [15-17]. However, target-based toxicity of GSIs has been a major obstacle to the clinical development of these compounds. In fact, two large Phase III clinical trials of *Semagacestat*, the only GSI extensively studied in AD, were prematurely interrupted because of the observation of detrimental cognitive and functional effects of the drug [18]. Several dozen γ-secretase substrates have been identified, including Notch1 trans-membrane receptor, which plays an important role in a variety of developmental and physiological processes by controlling cell fate decisions. To overcome these toxicity issues, pharmaceutical companies have been trying to develop a second generation of 'Notch-sparing' GSIs, which revealed beneficial effects in *in vitro* and in animal models of AD [19-21]. They are currently under clinical studies. Such 'Notch-sparing' GSIs have higher pharmacological selectivity than the first GSIs probably due to the distinct binding to the substrate docking site on γ-secretase of Notch and APP. Identification of several γ-secretase inhibitors has been reviewed elsewhere [22].

2.1.2. Aβ degrading enzymes

Almost 20 enzymes are currently known to contribute to Aβ degradation in the brain, although the most studied are two zinc metalloproteases, neprilysin (NEP) and insulin-degrading enzyme (IDE). NEP is one of the major Aβ-degrading enzymes in the brain [23] and NEP levels are decreased in the brain of AD and animal models [24, 25]. Lentiviral delivery of the NEP gene to the brain of AD transgenic mice reduced Aβ pathology [26]. A number of subsequent studies with NEP and other related peptidases such as endothelin-converting enzymes 1 and 2 (ECE-1 and ECE-2) further supported this observation [27]. Similarly, over-expression of IDE in neurons significantly reduces brain Aβ levels, prevents Aβ plaque formation and its associated cytopathology, and rescues the premature lethality present in these particular APP transgenic mice [28]. A growing body of evidence has been accumulated supporting the potential therapeutic properties of IDE in AD [29].

Other specific Aβ-cleaving proteases such as angiotensin-converting enzyme (ACE), matrix metalloproteinase-9 (MMP-9) and the serine protease plasmin, which have distinct sub-cellular localizations and differential responses to aging, oxidative stress and pharmacological agents, are also potential candidates to become novel therapeutic strategies for AD prevention and treatment [27].

Targeting the delivery of these compounds to the brain remains a major challenge. The most promising current approaches include peripheral administration of agents that enhance the activity of Aβ-degrading enzymes and direct intra-cerebral release of enzymes by convection-enhanced delivery. Genetic procedures geared at increasing cerebral expression of Aβ-degrading enzymes may offer additional advantages [30].

2.1.3. Decreasing Aβ aggregation

Compounds that suppress the aggregation or reduce the stability of Aβ oligomers may bind monomers in order to attenuate formation of both the oligomeric and senile plaque fibrillar Aβ constituents. One of the amyloid-binding drugs more extensively studied in animal models

and AD patients is tramiprosate (3-amino-1-propanesulfonic acid; Alzhemed). Tramiprosate was effective in reducing Aβ polymerisation *in vitro*, inhibiting the formation of neurotoxic aggregates, and decreasing Aβ plaque formation in animal models [31]. However, recent phase III clinical trials did not produce any significant improvement in cognition in AD patients chronically treated with tramiprosate in spite of the significant reduction in hippocampus volume loss [32]. Similarly, some other compounds known to inhibit Aβ aggregation and fibril formation showed positive effects in animal and *in vitro* models of AD but failed to produce conclusive results in human clinical trials. This is the case with scyllo-inositol and PBT2. Scyllo-inositol inhibited cognitive deficits in TgCRND8 mice and significantly ameliorated disease pathology, even in animals at advanced stages of AD-like pathology, without interfering with endogenous phosphatidylinositol lipid production [33, 34]. Yet a phase II clinical trial failed in supporting or refuting a benefit of scyllo-inositol in mild to moderate AD patients [35]. PBT2 is a copper/zinc ionophore which targets metal-induced aggregation of Aβ. When given orally to two models of Aβ-bearing transgenic mice, PTB2 was able to markedly decrease soluble brain Aβ levels within hours and to improve cognitive performance within days [36]. These results correlated with a rapid cognitive improvement in AD patients in a recent phase IIa clinical trial [37], an observation that argues for large-scale testing of PBT2 for AD.

Another promising recent experimental approach is the use of dendrimers as agents interfering with Aβ fibrilization. Dendrimers are globular branched polymers, typically symmetric around the core with a spherical three-dimensional morphology. Their chemical structure allows dendrimers to couple to active amyloid species through hundreds of possible sites. Dendrimers have been shown to be able to modulate Aβ peptide aggregation by interfering in different ways with the polymerization process, including fibril breaking, inhibition of fibril formation and acceleration of fibril formation [38, 39]. However, some dendrimers assayed in amyloidogenic systems are toxic to cells. The development of non-toxic glycodendrimers, which reduce toxicity by clumping fibrils together [40], opens the possibility of using dendrimers with low intrinsic toxicity in AD. Additional difficulties in dendrimer administration involve the crossing of the BBB so as to reach their targets in the brain.

2.1.4. Facilitating Aβ clearance: Immunotherapy against Aβ

Active and passive immunotherapy against Aβ peptide has been explored as a therapeutic approach to stimulate the clearance of Aβ in the brain at the preclinical and clinical stages of the disease in animal models. Pioneering studies proved that vaccination of young APP transgenic mice using a synthetic aggregated form of $A\beta_{42}$ (AN-1792) effectively prevented Aβ plaque formation, neuritic dystrophy and astrogliosis in adult brains [41]. Subsequent studies further demonstrated improvement of memory loss in those APP transgenic mice vaccinated against Aβ [42, 43]. Different models, methods and ways of administration showed the beneficial effects of active and passive immunization in animal models of AD. Nevertheless, the phase II trial in humans was discontinued because of the occurrence of aseptic meningoencephalitis in a number of cases [44-46]. The cause of the meningoencephalitis was a concomitant T-cell-mediated autoimmune response [45, 46]. Moreover, several studies in APP transgenic mice have reported an increased risk of microhemorrhages at sites of cerebro-

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vascular Aβ deposits [47]. Yet important conclusions were drawn from the studies in humans: immunization reduced the number of Aβ plaques and the number of dystrophic neurites, including tau phosphorylation around plaques, but not Aβ burden in blood vessels; however, immunization increased intracerebral levels of soluble Aβ [48-50].

New vaccines containing immunodominant B-cell epitopes of Aβ [51] and recognizing other Aβ residues [52, 53], and the use of passive immunization with deglycosylated antibodies [54] have demonstrated positive effects in the clearance of Aβ without causing inflammatory response or hemorrhages in animal models of AD [55]. These findings have prompted new clinical trials which are currently evaluating the toxicity and effectiveness of at least ten vaccines in mild-to-moderate AD patients worldwide [56]. While vaccines hold great hope as AD therapies, it is important to stress that immunization at pre-symptomatic stages is essential in order to avoid the irreversible brain damage occurring even at the early symptomatic stages [57].

2.2. Targeting tau

The interest in tau-related therapies is still emerging and very few clinical studies are underway, in part because of the difficulties encountered with anti-Aβ strategies that captured most efforts in the two last decades, but also because of the challenging identification of tractable therapeutic targets related to tau. Current research in the prevention of tau pathology developed in animal models of AD has resulted in some promising results [58]. Main rationales in tau pathology are based on: 1: inhibition of tau aggregation, 2: reduction of tau phosphorylation by inhibition of tau kinases or activation of phosphatases (including PP2a activity), 3: reduction of tau levels by increasing tau degradation or by using active immunization, and 4: stabilization of microtubule [59].

2.2.1. Inhibition of tau aggregation

Some compounds that are known to inhibit tau-tau interactions have been tested as agents aimed at slowing Alzheimer progression to disease states. Among them, phenothiaziazine methylene blue inhibits tau-tau interactions, is neuroprotective and is able to facilitate soluble tau clearance in a mouse model of human tauopathy [60, 61]. Moreover, phenothiaziazine methylene blue has shown beneficial effects in a phase II clinical trial conducted for one year [62]. Another promising inhibitor of tau aggregation is the immunosuppressant FK506, which exerts its beneficial effects in transgenic mice by directly binding tau to the FK506 binding protein 52 and by modulating microglial activation [63, 64].

However, some concerns araise from the use of tau aggregation inhibitors in that at least some tau aggregation inhibitors enhance the formation of potentially toxic tau oligomers [65].

2.2.2. Reduction of tau hyperphosphorylation

Kinases which participate in the phosphorylation of tau and phosphatases which dephosphorylate tau are clear putative therapeutic targets for AD [66]. The most widely studied tau kinases in AD pathogenesis are Glycogen synthase kinase 3 beta (GSK-3β) and Cyclin-

dependent kinase (CDK5) [67, 68]. Several GSK-3β inhibitors, including lithium, aloisines, flavopiridol, hymenialdisine, paullones, and staurosporine, are under active investigation and development [69]. Lithium revealed some promising results when administered in transgenic mice expressing the P301L human 4R0N tau at pre-symptomatic stages; it improved behavior and reduced the levels of phosphorylation, aggregation and insoluble tau in transgenic mice [70]. However, several concerns have arisen in relation of the use of GSK-3β in the treatment of AD; these are based on the fact that lithium lacks specificity over GSK-3β activity and it has a narrow safety margin [71]. Moreover, GSK-3β acts on multiple metabolic pathways that are also impaired with unknown consequences after chronic treatment.

CDK5 inhibitors prevent Aβ-induced tau hyper-phosphorylation and cell death *in vitro* [72, 73]. A recent *in vivo* study further demonstrates that inhibition of CDK5 activates GSK-3β, which plays a more dominant role in overall tau phosphorylation than does CDK5 [74]. Thus, considering that CDK5 inhibitors might be unable to reverse abnormal hyper-phosphorylation of tau and treat neurofibrillary degeneration because of the interplay between CDK5 and GSK-3β, as well as the essential role played by CDK5 in multiple cell signaling pathways [75], the interest of such compounds as a tau-targeting therapy for AD is limited.

Another approach to reverse tau hyper-phosphorylation is up-regulation of tau phosphatases [66]. The major tau phosphatase, PP2A, is down-regulated in AD brain. In consequence, correcting PP2A levels is the primary target to be considered. Among the compounds known to reverse PP2A inhibition, memantine is the most outstanding because of the demonstrated clinical benefit in AD. In an animal model, memantine was able to reverse okadaic acid–induced PP2A inhibition and to prevent tau hyper-phosphorylation, restoring MAP2 expression [76]. Similarly, melatonin has also been shown to restore PP2A activity and reverse tau hyper-phosphorylation, both *in vitro* and in experimental animals [77]. One important concern in considering PP2A as a potential therapeutic target is that all protein phosphatases have much broader substrate specificities than protein kinases. Thus, more undesirable effects might be expected than when using kinase inhibitors [66]. A further intriguing point is that PP2A function and activity depend on multiple subunits and cofactors which are dysregulated in AD [78]. It is not clear how all these elements can be resolved to result in maintained balanced activity.

2.2.3. Reduction of tau levels

A potential alternative to modulate tau phosphorylation is reducing overall tau levels [58]. Experiments carried out in genetically-modified mice expressing reduced tau levels revealed diminished cognitive impairment and Aβ-induced neuronal damage [79-81]. An alternative method to reduce tau levels could is by targeting molecules that regulate the expression or clearance of tau. Tau can be degraded via the ubiquitin-proteasome system and the lysosomal pathways. Reduction of the levels of the tau ubiquitin-ligase CHIP increases the accumulation of tau aggregates in JNPL3 mice, suggesting that increasing the expression of CHIP could result in reduced tau levels [82]. Acetylation of tau inhibits its degradation [83], alters its microtubule binding, and enhances aggregation [84]. Thus, the combination of tau acetylation inhibition and ubiquitination-proteasome enhancement might produce a synergy that lowers the levels of pathogenic tau species.

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Tau degradation can also be enhanced by immunization. Active immunization targeting phosphorylated tau reduces filamentous tau inclusions and neuronal dysfunction in JNPL3 transgenic mice [85, 86]. Moreover, recent studies have raised the possibility of modulating tau pathology by passive immunization revealing reduced behavioral impairment and tau pathology in two transgenic models of taupathies [87].

2.2.4. Microtubule stabilizers

Since microtubule disruption occurs in several models of AD and is associated with tau dysfunction, microtubule stabilizers have been assayed in preclinical and clinical trials for AD [88]. The anti-mitotic drug paclitaxel prevents Aβ-induced toxicity in cell culture [89], as well as axonal transport deficits and behavioral impairments in tau transgenic mice [90]. Unfortunately, paclitaxel is a P-glycoprotein substrate and it has very low capacity to cross the BBB, making it unsuitable for the treatment of human tauopathies. Epothilone D, which has better BBB permeability, improves microtubule density and cognition in tau transgenic mice [91]. Finally, the peptide NAP stabilizes microtubules and reduces tau hyper-phosphorylation [92]. NAP can be administered intra-nasally and has shown promising results in a phase II clinical trial [93].

2.3. Oxidative stress

Several pieces of evidence demonstrate that oxidative stress precedes other hallmarks of the neurodegenerative process in human brains and animal models of AD, including Aβ deposition, NFT formation, and metabolic dysfunction and cognitive decline. It plays a functional role in the pathogenesis of the disease [94-100]. These findings sustain the possibility of using anti-oxidants in the prevention and treatment of Alzheimer [101, 102]. Several studies in AD transgenic mouse models support the potential beneficial effect of antioxidant compounds as preventive drugs.

2.3.1. Naturally-occurring anti-oxidants

Several nutritional antioxidants such as resveratrol, curcumin, epigallocatechin gallate, L-acetyl-carnitine, RRR-α-tocopherol (vitamin E) and ascorbic acid (vitamin C) have been tested to counteract oxidative stress-induced brain damage in AD.

- *Resveratrol* is a polyphenolic compound found in grapes, berries and peanuts with well known anti-oxidant, anti-cancer, anti-inflammatory and estrogenic activities. *In vitro* and animal experiments reveal that resveratrol protects against Aβ toxicity by promoting the non-amyloidogenic cleavage of APP, thus enhancing the clearance of Aβ peptides by promoting their degradation through the ubiquitin-proteasome system, as well as reducing neuronal damage by decreasing the expression of inducible nitric oxide synthase (iNOS) and cyclooxigenase 2 (COX-2), and the pro-apoptotic factors Bax and c-Jun N-terminal kinase (JNK). Moreover, the capacity of resveratrol to induce the over-expression of sirtuins, proteins having a role in cell survival, probably contributes to its neuroprotective effect [103, 104].

- *Curcumin* is a polyphenolic compound present in the rhizome of *Curcuma longa*, commonly used as a spice to color and flavor food, which has anti-inflammatory, anti-carcinogenic and anti-infectious properties. The first evidence of a protective role of curcumin in AD was derived from epidemiological studies based on populations subjected to a curcumin-enriched diet. Additionally, *in vitro* studies have shown that curcumin protects neurons from Aβ toxicity whereas the use of AD transgenic mouse models show that curcumin suppresses inflammation and oxidative damage as well as accelerating the Aβ rate of clearance and inhibiting Aβ aggregation. Curcumin is considered a bi-functional anti-oxidant because it is a direct scavenger of oxidants as well as a long-lasting protector promoting the expression of cytoprotective proteins through the induction of Nrf2-dependent genes [105, 106]. Regrettably, no significant improvement in cognitive function between placebo and curcumin-treated groups has been observed in the only two clinical trials carried out until now [107].

- *Epigallocatechin gallate (EGCG)* is a polyphenolic flavonoid encountered in green tea. Human epidemiological and animal data suggest that tea may decrease the incidence of dementia and AD. EGCG has been demonstrated to exert its neuroprotective activity by reducing Aβ production and inflammation, and increasing mitochondrial stabilization, iron chelation and ROS scavenging [108]. However, to date no clinical trials have been performed to verify whether EGCG neuroprotective/neurorestorative actions can be successfully translated into human beings.

- *Acetyl-L-Carnitine (ALC)* is a natural compound found in red meat whose biological role is to facilitate the transport of fatty acids to the mitochondria. Thus, the main mechanism of action of ALC is the improvement of mitochondrial respiration, which allows the neurons to produce the necessary ATP to maintain normal membrane potential. Yet ALC is neuro-protective through a variety of additional effects, including an increase in protein kinase C activity and modulation of synaptic plasticity by counteracting the loss of NMDA receptors in the neuronal membrane and by increasing the production of neurotrophins [105]. Moreover, ALC reduces Aβ toxicity in primary cortical neuronal cultures by increasing both heme-oxygenase 1 (HO-1) and heat-shock protein 70 (Hsp70) expression, probably through transcription factor Nrf2. In two clinical studies, ALC administered for one year significantly reduced cognitive decline in early-onset AD patients [109, 110] thus sustaining the potential use of ALC in AD prevention and treatment at early stages.

- *RRR-a-tocopherol (Vitamin E)* is probably the most important lipid-soluble natural antioxi-dant in mammalian cells. Most vegetable oils, nuts and some fruits are important dietary sources of vitamin E. The interest in evaluating its potential beneficial properties in AD is also sustained by its known ability to cross the BBB and to accumulate in the central nervous system. Deficiency in the α-tocopherol transfer protein mediating vitamin E activity induces an increase in brain lipid peroxidation, earlier and more severe cognitive dysfunction, and increased Aβ deposits in the brain of Tg2576 mice; this phenotype was ameliorated with vitamin E supplementation [111]. However, although epidemiological studies have demonstrated that increasing the intake of fruit and vegetables rich in vitamins prevents or retards the onset of AD, clinical trials for vitamin E treatment have revealed paradoxical

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results: whereas vitamin E supplementation partially prevents the memory loss associated with the progression of the disease in some cases, the same treatment was detrimental in others [112].

- *Ascorbic acid (Vitamin C)* is an essential nutrient since it acts as a cofactor in elemental enzymatic reactions, but in contrast to most of organisms, humans are not able to synthesize ascorbic acid. The main dietary source of vitamin C is fresh fruit and vegetables. The main interest in vitamin C for the treatment of neurodegenerative processes is related to its potent anti-oxidant properties. Some studies have revealed that vitamin C supplementation reduces oxidative stress, and mitigates Aβ oligomer formation and behavioral decline, but it did not decrease plaque deposition in AD mouse models [113, 114]. Despite epidemiological studies reporting reduced prevalence and incidence of AD in consumers of vitamin supplements [115], meta-analyses revealed the risks of chronic consumption of high doses of vitamin C thus discouraging its routine use in AD. [116]

- *Egb76* is a standardized *Ginkgo biloba* extract already approved in some countries as symptomatic treatment for dementia although the evidence for its effectiveness remains inconclusive [117]. However, Egb761 has anti-oxidant properties, inhibits Aβ oligomerization *in vitro*, reduces impaired memory and learning capacities and enhances hippocampal neurogenesis in AD transgenic mice [118]. For these reasons, *Ginkgo biloba* extract is currently under evaluation as a preventive drug in AD.

In spite of the experimental evidence of beneficial effects of natural anti-oxidants in cultured cells and transgenic models, clinical studies have demonstrated only minimal effect in humans probably due to the bioavailability and pharmacokinetics of these substances [102, 105]. What's more, a slight acceleration in cognitive decline has been observed in patients treated for 16 weeks with a cocktail of natural antioxidants [119].

2.3.2. Mitochondrial antioxidants

In contrast to other antioxidants, those designed to target the free radical damage to mitochondria provide greater therapeutic potential.

- *Lipoic acid (LA)* is a naturally-occurring precursor of an essential cofactor of many mitochondrial enzymes, including pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase, which is found in almost all foods. LA has been shown to present a variety of properties that can interfere with pathogenic processes of AD. LA increases ACh production, stimulates glucose uptake, protects against Aβ toxicity, chelates redox-active transition metals, scavenges reactive oxygen species (ROS) and induces anti-oxidant protective enzymes probably through the activation of the transcription factor Nrf2. Via the same mechanisms, down-regulation of redox-sensitive inflammatory processes is also achieved [120]. Data from cell culture and animal models suggest that LA can be combined with other dietary anti-oxidants to synergistically decrease oxidative stress, inflammation, Aβ levels, and thus provide a combined benefit in the treatment of AD. However, clinical benefits after LA administration were quite small in patients with mild or moderate dementia [121].

- *N-acetyl-cysteine (NAC)* is a precursor of glutathione (GSH), the most abundant endogenous anti-oxidant. NAC acts itself as an anti-oxidant by directly interacting with free radicals, as well as by increasing GSH levels. NAC protects against Aβ-induced cognitive deficits by decreasing the associated oxidative stress and related neuroinflammation, but also by activating anti-apoptotic signaling pathways in neuronal cultures [122]. Late-stage AD patients supplemented with NAC over a period of six months showed significantly improved performance in some cognitive tasks, although levels of oxidative stress in peripheral blood did not differ significantly from untreated patients [123].
- *Coenzyme Q_{10}(CoQ_{10})* is a small electron-carrier of the respiratory chain with anti-oxidant properties due to its role in carrying high-energy electrons from complex I to complex II during oxidative phosphorylation. CoQ_{10} and its analogues, idebenone and mitoquinone (or MitoQ), have been widely used for the treatment of mitochondrial disorders, as well as for the treatment of Friedreich's ataxia, and they are also being tested in other neurodegenerative disorders such as amyotrophic lateral sclerosis, and Huntington's, Parkinson's and Alzheimer's diseases [124]. CoQ_{10} reduces oxidative stress damage and Aβ plaque burden, and ameliorates behavioral performance in mouse models of AD [125, 126]. However, CoQ_{10} presents two major weaknesses. First, the function of the enzyme is entirely dependent on the electron transport chain (ETC) which is usually damaged in AD mitochondria. Second, CoQ_{10} does not efficiently cross the BBB when administered systemically, being unable to directly protect neurons from damage. Consequently, CoQ_{10} derivatives such as MitoQ, which is a more soluble compound able to penetrate the BBB and that does not depend on ETC, are seen to offer more promising results [127].

2.4. Inflammation

There is a general consensus that neuroinflammation is a prominent feature in AD with activated microglia being one of the main manifestations. Neuroinflammation is a complex process that has both beneficial effects, in terms of maintaining brain homeostasis after various kinds of insults, and detrimental effects when sustained chronically [128]. This latter situation is what occurs in AD, in which neuroinflammation is driven by different mechanisms including Aβ production and plaque formation, tau pathology, oxidative stress, and autocrine and paracrine release of cytokines and other inflammatory molecules which contribute to a feed-forward spiral favoring the self-propagation of neuroinflammation.

Early epidemiological studies suggesting that long-term use of antiinflammatories might reduce the risk for developing AD [129] prompted several studies designed to evaluate the preventive properties of non-steroid anti-inflammatory drugs (NSAIDs). The main NSAID mechanism of action is to inhibit the activity of cyclooxigenase-1 and -2 (COX-1 and COX-2) which are the enzymes responsible of the production of prostaglandins and other inflammatory agents [130]. The administration of the NSAID ibuprofen at early stages of the pathological process resulted in the reduction of the Aβ burden, dystrophic neurites and activated microglia in at least three different AD transgenic models [131-134]. Another study indicated that ibuprofen was effective even in older mice once lesions are well established [135]. Other NSAIDs such as indomethacin and nimuselide exhibit milder effects compared to ibuprofen

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in the Tg2576 mice [136, 137]. In contrast, the selective COX-2 inhibitor celecoxib failed to reduce the inflammatory burden and, even worse, increased the $A\beta_{42}$ levels when administered to young Tg2576 mice [138].

In spite of the promising results in animal models and the data from retrospective human epidemiological studies identifying long-term use of NSAIDs as being protective against AD, prospective clinical trials have not confirmed the efficiency of this group of drugs in the amelioration of symptoms and in the progression of AD [139].

Other anti-inflammatory agents such as trifusal have been shown to be beneficial in certain AD transgenic mice models [140].

2.5. Energetic failure: Metabolic deficiency and mitochondrial impairment

Several findings indicate that brain glucose hypometabolism, deficient bioenergetics and mitochondrial dysfunction precede clinical symptoms in AD [1, 141-143]. The energetic failure observed even in the prodromal phase of the Alzheimer process is thought to be produced by the combination of mitochondria dysfunction, alteration of energy metabolism at pore-mitochondrial level, and increase in energetic demands of altered nerve cells. Thus, strategies to improve brain energy supply and to preserve mitochondrial functions becomes relevant in the prevention of progression to disease states [1, 144-146].

2.5.1. Metabolic deficiency

The primary fuel for the brain under normal conditions is glucose, whereas the energetic contribution made by fatty acids is minor. Therefore, facilitation of energy metabolism and energy availability has been assayed in animal models and AD by facilitating glucose metabolism and shifting towards the use of alternative fuels.

- *Targeting reduced glucose metabolism*: Reduction in the utilization of glucose in AD [147] can be due to several causes including deficient insulin signaling, impairment in glucose transport mechanisms and dysfunction in glucolysis. Preclinical studies in animal models of AD have revealed some beneficial effects of anti-diabetic treatments. Thus, the use of the insulin sensitizer rosiglitazone, an activator of peroxisome-proliferator-activated receptor gamma (PPARγ) receptor, resulted in the rescue of behavioral deficits and insulin responsiveness in Tg2576 mice [148, 149]. Similarly, exendin-4, an antidiabetic agent that stimulates the insulin signaling pathway through activation of glucagon-like peptide -1 (GLP1) receptors, shows beneficial effects in AD, and reduces brain soluble Aβ levels, amyloid plaque burden, and cognitive impairment in treated APP/PS1 transgenic mice [150, 151]. Therefore, it seems that the positive effects of targeting insulin signaling in AD are related to the role played by insulin receptor in memory formation, inflammation and Aβ neuroprotective effects rather than to the facilitation of glucose transport into the brain [149, 150]. This hypothesis seems also to be supported by a recent study revealing that insulin did not ameliorate the disruption of energetic homeostasis induced by Aβ oligomers in cultured neurons [152]. In the end, clinical trials designed to test whether PPARγ agonists could be beneficial in AD patients provided negative results [153].

- *Shift to alternative energy source*: Under metabolically challenging conditions neurons can utilize acetyl-CoA generated from ketone body metabolism, produced distally in the liver or locally in the brain by glial cells. In this way, ketone bodies can bypass defects in glucose metabolism and enter the tricarboxylic acid cycle in the mitochondria of neurons as a source of ATP. The use of ketogenic diets reduces Aβ40 and Aβ42 levels in young AD transgenic mice [154] and enhances mitochondrial bioenergetic capacity, reducing Aβ generation and increasing mechanisms of Aβ clearance in a mouse model of AD [155]. The ketogenic compound AC-1202 administered in patients with AD has shown a significant improvement in some cognitive parameters more notable in individuals APOE4(-) [156]. Another possible alternative source of ATP is creatine. Preliminary studies have shown that creatine has protective effects against Aβ *in vitro* [157] and against injury *in vivo* by maintaining ATP levels and mitochondrial function [158], suggesting a potential therapeutic effect of creatine supplementation in AD.

2.5.2. Mitochondrial dysfunction

In addition to the already discussed antioxidant compounds, other potential drugs targeting mitochondrial dysfunction in AD are available. Several findings point towards a role for Aβ toxicity in the mitochondrial dysfunction found in AD.

The progressive Aβ accumulation in mitochondria is associated with diminished enzymatic activity of respiratory chain complexes (III and IV) and reduction in the rate of oxygen consumption, contributing to cellular dysfunction in AD [159]. Aβ in mitochondria binds to Aβ-binding alcohol dehydrogenase (ABAD) to block ABAD activity, increasing the production of ROS, reducing the mitochondrial membrane potential and the activity of the respiratory chain complex IV, and ultimately leading to a decrease in ATP levels [160]. In fact, double transgenic mice over-expressing mutated APP and ABAD exhibit exaggerated oxidative stress and memory impairment [160]. Therefore, compounds designed to block Aβ-ABAD interactions are considered putative therapeutic agents in AD. In line with this hypothesis, a recent study has shown that AG18051, a novel small ABAD-specific compound inhibitor, partially blocked the Aβ-ABAD interaction, prevented the Aβ42-induced down-regulation of ABAD activity and protected cultured neurons against Aβ42 toxicity by reducing Aβ42-induced impairment of mitochondrial function and oxidative stress [161]. Furthermore, the introduction of an ABAD-decoy peptide into transgenic APP mice reduces Aβ-ABAD interaction and protects against Aβ-mediated mitochondrial toxicity [162].

Another line of research suggests that drugs that activate ATP-sensitive potassium (K_{ATP}) channels present in the mitochondrial inner membrane exhibit therapeutic potential in the treatment of AD, as K_{ATP} channels are activated when cellular ATP levels fall below a critical value thereby reducing excitability so as to maintain ion homeostasis and preserve ATP levels [163]. Long-term administration of diazoxide improves neuronal bioenergetics, suppresses Aβ and tau pathologies, and ameliorates memory deficits in the 3xTgAD mouse model of AD [164].

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Finally, another potential drug in the treatment of AD that acts on mitochondrial pathways is latrepirdine, also known as Dimebon™ [165]. Latrepirdine reduces Aβ-induced mitochondrial impairment and increases the threshold of inductors to mitochondrial pore transition, making mitochondria more resistant to lipid peroxidation and increasing neuronal survival *in vitro* [166-168]. The interest in developing latrepirdine as a drug against AD is also supported by its multiple potential mechanism of action apart from mitochondrial effects, including anti-excitotoxic agent, inhibitor of AChE, channel-regulatior and neurotrophic stimulator [165]. A preliminary clinical trial revealed that latrepirdine was safe and well tolerated, and significantly improved the clinical course of the disease in patients with mild-to-moderate AD [169]. Current phase III clinical trials are already being conducted [165].

2.6. Neurotransmitter dysfunction

The alteration of several transmitter systems is assumed to trigger both cognitive and neuropsychiatric symptoms in AD. A number of *post-mortem* studies indicate that neurotransmitter systems are not uniformly affected in AD. Thus, while cholinergic, serotonergic and glutamatergic deficits are present at relatively early stages of AD, dopaminergic and GABAergic systems appear to be affected later [170].

2.6.1. Cholinergic system

A large body of evidence has shown that basal forebrain cholinergic neurons are vulnerable to AD leading to a progressive cholinergic denervation of the cerebral neocortex [171, 172]. Taking into account the involvement of this system in the cognitive processing of memory and attention, the current attempts in cholinergic therapy in AD are justified [172, 173]. The various cholinergic strategies include the use of ACh precursors, inhibitors of cholinesterases, muscarinic and nicotinic agonists, and ACh releasers, in addition to the rescue of cholinergic function by nerve growth factor (NGF) which is reviewed in section 2.8.

- *ACh precursor.* Animal studies report that choline and lecithin increased the production of brain ACh which argues for their use in the treatment of cholinergic deficits in AD. However, evidence from randomized trials did not sustain this hypothesis [174].
- *Cholinesterase inhibitors (ChEIs).* Physostigmine, tacrine and derivatives donepezil, galantamine and rivastigmine have been tested in AD patients during the last three decades. Their therapeutic properties have been profusely reviewed [172, 175-177] and for this reason a detailed revision of ChEIs is beyond the scope of this chapter. Nevertheless, it is worth briefly indicating additional mechanisms of action of these compounds beyond inhibition of cholinesterases, including increase of nicotinc ACh receptor expression, facilitation of APP processing and attenuation of Aβ-induced toxicity [173, 178]. In spite of the fact that their efficacy has been proved in several clinical trials, only approximately 50% of patients respond positively. This limited effect of ChEIs on cognitive decline, together with the occurrence of undesirable side-effects such as diarrhea, nausea, insomnia, fatigue and loss of appetite, reduces the therapeutic capacities of ChEIs.

- *Muscarinic receptor 1 agonist.* The cholinergic deficiency in AD appears to be mainly pre-synaptic. Thus, the pharmacological stimulation of the post-synaptic M1 muscarinic receptors, which are preserved until late stages of AD, may balance the degeneration of pre-synaptic cholinergic terminals unable to properly synthesize and release ACh [173]. In fact, the selective M1 agonist AF267B reduces memory impairment, Aβ42 levels, and tau hyper-phosphorylation in AD triple transgenic mice [179], corroborating some early studies *in vitro* [180, 181]. This selective agonist is currently under clinical evaluation for safety and tolerability and a number of other M1 agonists are being investigated [173].
- *Nicotinic agonists.* Preclinical studies in animal models and some pilot studies in AD have shown that the activation of pre-synaptic nicotinic ACh receptors may reduce cognitive impairment by increasing ACh release and may have beneficial effects on Aβ metabolism [182, 183]. Thus, chronic nicotine treatment results in a significant reduction in plaque burden and in cortical Aβ concentrations in Tg2575/PS1-A246E mice [184]. However, nicotine exacerbates tau pathology in 3xTg-AD mice [185]. These apparently contradictory results may be due to the presence of several subtypes of nicotinic receptors, the activation of which may have disparate effects in AD. Therefore, more specific nicotine agonists are needed to act exclusively on determinate subtypes of nicotinic receptor [186]. In this line, α7 nAChR gene delivery into mouse hippocampal neurons leads to functional receptor expression and improves spatial memory-related performance and hyperphosphorylation of tau [187]. Regarding α4β2 nicotinic receptor, the selective agonist cytisine inhibits Aβ cytotoxicity in cortical neurons [188].
- *ACh releasers.* Facilitation of ACh release can be achieved with depolarizing agents of the cholinergic neurons acting via potassium-channel blockade as happens with linopirdine and analogues [189] or by the blockade of the pre-synaptic inhibitory M2 muscarinic receptor via specific antagonists [190, 191]. However, clinical trials using linopirdine did not demonstrate effectiveness in improving cognitive function [192]. On the other hand, certain selective M2 antagonists, such as SCH-57790 and SC-72788, restore memory impairments in animal models that mimic to some extent the cholinergic failure in AD [193]. It must be kept in mind that the potential benefit of M2 antagonists is limited because of the progressive pre-synaptic cholinergic degeneration in AD and because of the possible side-effects derived from the blockade of peripheral M2 receptors including cardiac M2 receptors.

2.6.2. Glutamatergic system

Low concentrations of Aβ oligomers are able to activate certain glutamate receptors including NMDA receptors. The activation of NMDA receptors may increase glutamate activity, raise intracellular Ca2+ concentration and promote excitotoxicity and neuronal damage [194, 195]. Another process contributing to the excessive glutamate activity in AD is the impairment of glial cells to remove glutamate form the synaptic cleft possibly due to the action of free radicals on the glutamate transporter 1 (GLT-1) [196]. Glutamatergic activation, in turn, may disrupt synaptic plasticity promoting long term depression (LTD) and inhibiting long term potentiation (LTP) of 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl)propanoic acid (AMPA) receptor-mediated synaptic transmission [197]. The associated persistent reduction in the number of

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functional synaptic AMPA receptors reduces fast excitatory transmission and eventually triggers spine retraction and synaptic loss [198]. Moreover, glutamate receptors are not only involved in the process of Aβ-mediated synaptic dysfunction but also play important roles in Aβ production [199, 200].

Based on these observations, several studies have been designed in an attempt to correct glutamatergic dysfunction in AD, including the modulation of both AMPA and NMDA receptors [201]. First attempts were carried out with AMPAKines [202], which are drugs that prolong the action of glutamate on AMPA receptors by increasing their sensitivity. Interestingly, AMPAKines proved effective in restoring cognitive deficits in aging rats [203, 204]. These compounds were tested in AD patients [205]. The modulation of the NMDA receptor was assessed via the glycine co-agonist site in rats with disrupted glutamatergic temporal systems resulting in improved learning and memory [206]. Preliminary clinical studies suggested some promising effects in AD [207] but full-scale trials have not yet been initiated.

The most relevant glutamatergic strategy against AD is the non-competitive NMDA antagonist memantine [201, 208], which has succeeded in clinical trials in moderate and severe AD as reviewed in detail elsewhere [209, 210]. Several studies performed in animal models of AD corroborate the beneficial properties of memantine as a symptomatological and neuroprotective treatment in AD [211-215]. Nevertheless, memantine has no benefits in cases with mild AD [216] suggesting that this drug is not a good choice for preventing the progression to disease states.

2.6.3. Serotonergic system

Loss of serotonergic nerve terminals in AD was described several years ago [217, 218]. Although the suggested serotonergic dysfunction was initially related almost exclusively with the neuropsychiatric symptoms of AD, including anxiety, irritability, fear and depression, recent studies have demonstrated that serotonin signaling also plays an important role in cognition and in the development of Aβ and tau pathologies [219].

Antidepressant compounds, acting through serotonin signaling, result in cognitive improvements and reduce the levels of Aβ and tau pathology in animal models of AD [220, 221]. Similar compounds reduce amyloid burden in humans [221]. Additional serotonergic compounds that are currently being investigated in AD are 5-hydroxytryptamine (5-HT or serotonin) receptors: 5-HT_1 and 5-HT_6 antagonists, and 5-HT_4 agonists. The 5-HT_{1A} antagonist lecozotan (SRA-333) enhances cognition in primates and is now being tested in AD [222-224]. The pro-cognitive effects of 5-HT_{1A} antagonists are probably due to the facilitation of glutamategic and cholinergic transmission after reduction of the inhibitory effects of serotonin. Similarly, 5-HT_6 antagonists improve cognitive performance in animal models and human beings by modulating multiple neurotransmitter systems [225]. These properties mark 5-HT_6 antagonists as potential symptomatic drugs in AD. In addition, 5-HT_4 receptor agonists are neuroprotective, modulating the production of Aβ, and have the property of ameliorating cognitive deficits [226, 227].

2.7. Synaptic dysfunction

Synaptic dysfunction and failure are processes that occur early in the Alzheimer process and progress during the course of the disease from an initially reversible functionally-responsive stage of down-regulated synaptic function to stages irreversibly associated with degeneration.

These alterations are manifested early as impaired metabotropic glutamate receptor/phospholipase C signaling pathway [230] and up-regulation of adenosine receptors in the frontal cortex in AD [231].

The initial reversible stages are important targets for protective treatments to slow progression and preserve cognitive and functional abilities [232, 233]. *In vivo* and *in vitro* studies have demonstrated that high levels of Aβ impair structural and functional plasticity of synapses by affecting the balance between excitation and inhibition and contributing to the destabilization of neuronal networks, eventually causing synaptic loss [234]. Two main designs have been proposed to antagonize synaptic plasticity-disrupting actions of Aβ oligomers in preclinical AD: maintenance of the structure and fluidity of the lipid membranes forming the synaptic buttons, and stimulation of synaptic plasticity by neurotrophic factors.

Minor changes in the fluidity of phospholipidic membranes might have an important impact on the function of synapses by influencing neurotransmitter receptor activity. In fact, AD brains exhibit altered lipid composition of lipid rafts, key membrane microdomains that facilitate the transfer of substrates and protein-protein and lipid-protein interactions, as a result of the abnormally low levels of n-3 long-chain polyunsaturated fatty acids, mainly docosahexaenoic acid (DHA), increasing viscosity and energy consumption and contributing to synaptic dysfunction [142, 235]. Abnormal lipid raft composition may also modify the activity of key enzymes that modulate the cleavage of APP to form toxic Aβ. Thus, the preservation of adequate membrane composition has become an alternative way to prevent the deleterious effect of Aβ at the synapses. DHA is a major lipid constituent of synaptic end-sites and its delivery is a prerequisite for the conversion of nerve growth cones to mature synapses [236]. Numerous epidemiological studies have highlighted the beneficial influence of DHA on the preservation of synaptic function and memory capacity in aged individuals or after Aβ exposure, whereas DHA deficiency is presented as a risk factor for AD [237]. Moreover, a number of studies have reported the beneficial effects of dietary DHA supplementation on cognition and synaptic integrity in various AD models [238]. According to thes evidence, DHA, which can be synthesized or obtained directly from fish oil, appear to be one of the most valuable diet ingredients whose neuroprotective properties contribute to preventing AD.

Cytidine 5'-diphosphocholine, CDP-choline, or citicoline is an essential intermediate in the biosynthetic pathway of structural phospholipids in cell membranes, particularly phosphatidylcholine. Chronic administration has been beneficial in patients with mild cognitive impairment [239].

Another emerging potential line to preserve synaptic function is the targeting of scaffolding proteins that modulate neurotransmitter receptor activity at the synapses. Scaffolding proteins stabilize post-synaptic receptors at the spines in close proximity to their intracellular signaling

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proteins, phosphatases and kinases, thereby facilitating signal-transduction cascades. Evidence from *in vitro* cell and animal models of AD indicates that reductions in the post-synaptic density membrane-associated guanylate kinase (PSD-MAGUK) proteins are linked to synaptic dysfunction that might trigger plastic changes at early stages of the Alzheimer process [240]. However, specific molecules that affect interactions between scaffolding proteins and neurotransmitter receptors are still in development and further research is necessary to evaluate their potential benefit in AD.

2.8. Neurotrophic factors

Neurotrophins represent a family of proteins that play a pivotal role in the mechanisms underlying neuronal survival, differentiation, modulation of dendritic branching and dendritic spine morphology as well as synaptic plasticity and apoptosis [241]. All the members of the neurotrophin family, including NGF, brain-derived neurotrophic factor (BDNF) and neurotrophins 3 to 7, transduce their biological effects by interacting with two types of cell surface receptors, the tyrosine kinase receptor (Trk) and the p75 pan-neurotrophin receptor ($p75^{NTR}$) [241]. Other growth factor families also related to synaptic plasticity include the cytokine family of growth factors, the transforming growth factor-β (TGFβ) family, the fibroblast growth factor family and the insulin-like growth factor family. Evidence accumulated during recent years suggests that targeting neurotrophic factor signaling can retard nerve cell degeneration and to some extent preserve synaptic function. The most studied neurotrophic factors in AD are NGF, BDNF and TGFβ1.

- *NGF*: Mature basal forebrain cholinergic neurons are highly dependent on the availability of NGF for the maintenance of their biochemical and morphological phenotype, and for survival after lesions or variegated insults [242, 243]. For this reason, exploitation of NGF activity on cholinergic neurons may provide an attractive therapeutic option for preventing cholinergic cell degeneration in AD. Levels of proNGF, the precursor form of NGF, are highly elevated in AD brains and animal models, a feature that may be associated with a reduced conversion to NGF and augmented degradation of mature NGF. These combined effects have been interpreted as causative of cholinergic atrophy in AD [244]. A role for Aβ peptide in the induction of such NGF altered metabolism has been described [245]. Minocycline, a second-generation tetracycline antibiotic known to potentiate NGF activity, is able to normalize proNGF levels and to reverse the increased activity of the NGF-degrading enzyme matrix metalloproteinase 9, as well as to increase the expression of iNOS and microglial activation, leading to improved cognitive behavior in a transgenic mouse model of AD [245]. Yet a disturbing finding is the demonstration of AD proNGF when compared to proNGF of control individuals [246-248]. Whether this abnormal form of AD-related proNGF has any impact on the pathogenesis of AD needs further investigation. Another putative therapy is the use NGF, but NGF does not readily cross the BBB and requires intra-cerebroventricular infusion to reach targeted brain areas. Pilot clinical trials were discontinued because of the side-effects of NGF infusions [249]. Therefore, the development of NGF therapy is constrained by the need to achieve adequate concentrations in the relevant brain areas with susceptible target neurons while preventing unwanted

adverse effects in non-target regions or cells. Alternative strategies that are currently under development include gene therapy and nasal delivery of recombinant forms of NGF, the use of small molecules with NGF agonist activity, NGF synthesis inducers, NGF processing modulators, and proNGF antagonists [250].

- *BDNF*: This neurotrophin is normally produced in the cerebral cortex with high levels in the entorhinal cortex and hippocampus in adulthood [241]. BDNF levels are reduced in the cerebral cortex and hippocampus in AD [251-254]. Several studies have shown beneficial effects of BDNF in animal models of AD [255]. For instance, sustained BDNF gene delivery using viral vectors after disease onset resulted in elevated BDNF levels in the entorhinal cortex and hippocampus which were associated with improvement in learning and memory, and with restoration of most genes altered as a result of mutant APP expression in that specific transgenic mice model [256]. Similar results were obtained in a different mouse model of AD, and in aged rats and primates by using distinct BDNF delivery systems [256, 257]. It is worth pointing out that BDNF did not change β-amyloid plaque density in any case suggesting that the therapeutic effects of BDNF occur independently of direct action on APP processing. However, the multiple variegated effects of BDNF on neuronal function also raise the hypothetical possibility that unintended adverse effects of BDNF may limit its clinical efficacy in AD [256]. An additional point must be considered; BDNF signaling pathway is also altered in AD as TrkB expression is reduced and truncated TrkB is highly expressed in astrocytes at least in advanced stages of the disease [251]. Therefore, regarding BDNF function in AD, there is not only an alteration in the expression of BDNF but also an impaired downstream pathway that may corrupt the signal of the trophic factor acting on inappropriate receptors. Preliminary clinical trials are currently in progress to evaluate the safety and efficacy of BDNF.

- *TGFβ1*: Astrocytes and microglia are the major sources of TGF-β1 in the injured brain [258, 259]. Impaired TGF-β1 signaling has been demonstrated in AD brain, particularly at the early phase of the disease; this is associated with Aβ pathology and neurofibrillary tangle formation in animal models [260]. Reduced TGF-β1 seems to induce microglial activation [259] and ectopic cell-cycle re-activation in neurons [261]. Several drugs may induce TGF-β1 release by glial cells, including estrogens [262], mGlu2/3 agonists [263], lithium [264], the antidepressant venlafaxine [265] and glatiramer, which is a synthetic amino acid co-polymer currently approved for the treatment of multiple sclerosis [266]. All of them have neuroprotective effects in different *in vitro* and *in vivo* models of AD pathology [260]. Additionally, small molecules with specific TGF-β1-like activity are being developed as neuroprotectors [267].

A final point must be considered. A generalized sprouting is produced around β-amyloid deposits in senile plaques in both humans and in animal models [268-270]. The reasons for such sprouting are not well defined but amyloid species may play a trigger role. In any case, trophic factors might increase aberrant sprouting at the senile plaques through receptors expressed at these localizations.

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2.9. Autophagy

Autophagy is a catabolic process occurring in all cell types in which the machinery of the lysosome degrades cellular components such as long-lived or damaged proteins and organelles. Thus, a failure of autophagy in neurons results in the accumulation of aggregate-prone proteins that might exacerbate neurodegenerative process [271, 272]. Autophagy is also implicated in the accumulation of altered mitochondria and polymorphous inclusions in the dystrophic neurites around amyloid plaques [273-278].

Indeed, autophagic dysfunction is implicated in the progression of Alzheimer from the earliest stage, when a defective lysosomal clearance of autophagic substrates and impaired autophagy initiation occurs and leads to massive buildup of incompletely digested substrates within dystrophic axons and dendrites [279]. The pharmacological induction of 'preserved' autophagy might enhance the clearance of intracytoplasmic aggregate-prone proteins and therefore ameliorate pathology [272]. Attempts to restore more normal lysosomal proteolysis and autophagy efficiency in mouse models of AD pathology have revealed promising therapeutic effects on neuronal function and cognitive performance, demonstrating the relevance of the failure of autophagy in the pathogenesis of AD, and the potential of autophagy modulation as a therapeutic strategy. Autophagy induction with the mTOR-inhibiting drug rapamycin in young mice resulted in a reduction in Aβ plaques, NFT and cognitive deficits in the adulthood in two different models of AD [280-283]. Interestingly, rapamycin did not alter any of those parameters when administered in old animals once the pathology was established, highlighting the importance of early treatmenting in the disease progression [282]. However, the kinase mTOR plays an important role in multiple signaling pathways apart from negatively regulating autophagy [284]. Therefore, rapamycin treatment is also a putative inducer of undesirable side-effects. Other drugs including lithium, sodium valproate and carbamazepine acting have ben proved to induce autophagy through the inhibition of of inositol monophosphatase in an mTOR-independent pathway [285]. These compunds reveal positive effects by reducing the accumulation and toxic effects of aggregation-prone proteins in cell models as well as by protecting against neurodegeneration in *in vivo* models of Huntington's disease [286]. Further research is needed to learn whether they can also be useful tools in the treatment of AD.

2.10. Multi-target treatments

Considering the multifactorial etiology of AD, and the numerous and complex pathological mechanisms involved in the progression of the disease, it is quite reasonable that treatments targeting a single causal or modifying factor may have limited benefits. Therefore, growing interest is focused on therapeutic agents with pleiotropic activity, which will be able to target, in parallel, several processes affected in AD [287, 288]. Several compounds already mentioned in the previous sections fulfill these properties, such as DHA which presents anti-inflammatory, anti-oxidant, neuroprotective and anti-tau phosphorylation properties apart from the modulation of synaptic membrane composition [289], and curcumin, which in addition to anti-oxidant properties also exhibits anti-inflammatory and Aβ- and tau-binding properties [106]. Similarly, rosiglitazone and dimebon are known to produce beneficial effects through insulin receptor signaling mod-

ulation and mitochondrial protection [153, 165]. Other multi-target potential treatments currently under development for AD are based on the use of the following compounds:

- *Caffeine*: This is one of the most consumed psychoactive drugs which mainly acts blocking adenosine receptors 1 and 2 [290, 291]. In addition, caffeine reduces amyloid burden in animal models of AD [292, 293]. Epidemiological studies in humans have also shown protection against cognitive decline [294-296].
- *Estrogen*: This steroid hormone is known to play an important role in neuronal survival, mitochondrial function, neuroinflammation and cognition, with important neuroprotective effects [297-299]. Some of the neuroprotective actions mediated by estrogens are related to the insulin-like growth factor-1 (IGF-1) signaling pathway [300]. Several studies in animal models of AD have revealed therapeutic properties of estrogen against the progression of the disease. For instance, the treatment of ovariectomized 3xTg-AD mice with estrogen resulted in prevention of the increased Aβ accumulation and worsening memory performance induced by the depletion of sex steroid hormones [301]. Clinical and epidemiological studies in AD support the beneficial effets of estrogens [302]. However, a critical factor for success in estrogen therapy for AD is the age at the initiation of the treatment; the efficacy of estrogens is greatest in younger women and in women who initiated the estrogen therapy at the time of menopause [303].
- *Cannabinoids*: The natural compounds derived from *Cannabis sativa* or synthetic compounds acting on endogenous cannabinoid system have emerged as potential agents against several neurodegenerative processes [305]. Cannabinoids offer a multi-faceted approach for the treatment of AD as the stimulation of the widely brain-expressed cannabinoid receptors provides neuroprotection against Aβ [305, 306] and reduces neuroinflammation [306-308] and tau phosphorylation [306, 309] in AD-like transgenic mice. In addition, cannabinoids support brain repair mechanisms by augmenting neurotrophin expression and enhancing neurogenesis [310]. Moreover, cannabinoids are able to reduce Aβ-dependent oxidative stress [311] and Aβ-mediated lysosomal destabilization related to apoptosis [312]. In addition, some cannabinoids are able to inhibit acetylcholinesterase activity [313]. It is worth stressing that molecular achievements of cannabinoids are accompanied by cognitive improvement and reduction of several degenerative markers in two different animal models of AD [306, 308]. Examination of the potential beneficial effects of chronic administration of low doses of cannabinoids with little psychotropic effect at early stages of the degenerative process in humans seems very promising.
- *Erythropoietin (EPO) and derivatives*: EPO is effective in neuroprotection against ischemia and traumatic brain injury [314]. In addition, animal studies reveal that EPO both reduces tau phosphorylation through modulation of PI3K/Akt-GSK-3beta pathway [315] and protects against Aβ-induced cell death through anti-oxidant mechanisms [316]. An additional characteristic of EPO that confers potential utility in AD is the specific effect on cognition: EPO enhances hippocampal LTP and memory by modulating plasticity, synaptic connectivity and activity of memory-related neuronal networks [317]. In spite of these benefits, chronic administration of EPO is problematic because of the concomitant excessive erythropoiesis. In this sense, some new derivatives of EPO that do not bind to the classical EPO

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receptor (carbamylated EPO) or that have such a brief half-life in the circulation that they do not stimulate erythropoiesis (asialo EPO and neuro EPO) have demonstrated neuroprotective activities without the potential adverse effects on circulation associated with EPO [318]. Therefore, these new compounds are considered as potential treatments in AD.

- *Statins*: Evidence has accumulated that a high cholesterol level may increase the risk of developing AD and that the use of statins to treat hyper-cholesterolemia is useful in treating and preventing AD [319]. Statins reduce the production of cholesterol and isoprenoid intermediates. These isoprenoids modulate the turnover of small GTPase molecules that are essential in numerous cell-signaling pathways, including vesicular trafficking and inflammation [320]. Thus, statins reduce the production of Aβ by disrupting secretase enzyme function and by curbing neuroinflammation in experimental models of AD [321, 322].
- *Ladostigil* is a dual acetylcholine-butyrylcholineesterase and brain selective monoamine oxidase (MAO)-A and -B inhibitor *in vivo*. Interest in this compound in AD treatment research is sustained by the potential increase in brain cholinergic activity properties but also by the capacity of ladostigil to prevent gliosis and oxidative-nitrosative stress damage. Moreover, ladostigil has been demonstrated to possess potent anti-apoptotic and neuroprotective properties *in vitro* and in various neurodegenerative animal models including AD transgenic mice [323]. These neuroprotective activities involve regulation of APP processing, activation of protein kinase C and mitogen-activated protein kinase signaling pathways, inhibition of neuronal death markers, prevention of the fall in mitochondrial membrane potential, up-regulation of neurotrophic factors, and anti-oxidative activity.
- *Huperzine A* is an extract of the Chinese plant *Huperzia serrata*. Huperzine A is a selective potent inhibitor of AChE [324]. In addition, some studies have shown that huperzine A may shift APP metabolism towards the non-amyloidogenic α-secretase pathway [325]. In addition, huperzine A reduces glutamate-induced cytotoxicity by antagonizing cerebral NMDA receptors [326]. Finally, huperzine A reverses or attenuates cognitive deficits in some animal models of AD [325]. Large-scale, randomized, placebo-controlled trials are necessary to establish the role of huperzine A in the treatment of AD [327].
- *Phytochemicals* as curcumin, catechins and resveratrol beyond their antioxidant activity are also involved in antiamyloidogenic, anti-inflammatory mechanisms and inhibitors of NFkappaB [328-330].
- *Celastrol* is another compound whicha appears to have multiple functions as anti-inflammatory, anti-oxidant and reductor of amyloouid via BACE 1 [331, 332].

3. Concluding remarks

Main targets of therapeutic intervention at early stages of Alzheimer are summarized in Figure 1. Based on the presently available data several conclusions can be drawn. Combination therapies with drugs targeting different pathological factors or the use of multi-target compounds appear to be the most effective strategy in the treatment of the neurodegenerative

process in Alzheimer. Most potential experimental therapies exhibit the highest efficiency when applied during the pre-symptomatic phase of the disease. Therefore, it is essential to develop diagnostic tools to detect Alzheimer at early stages. Moreover, considering that Alzheimer, as a degenerative process not necessarily leading to dementia, affects a large percentage of individuals in the sixth decade of life, it would be wise to introduce habits and low-cost, safe treatments to prevent the progression of Alzheimer early in life, as occurs in artheriosclerosis, to transform AD into a chronic, incomplete and non-devastating disease thereby allowing for normal life in the elderly.

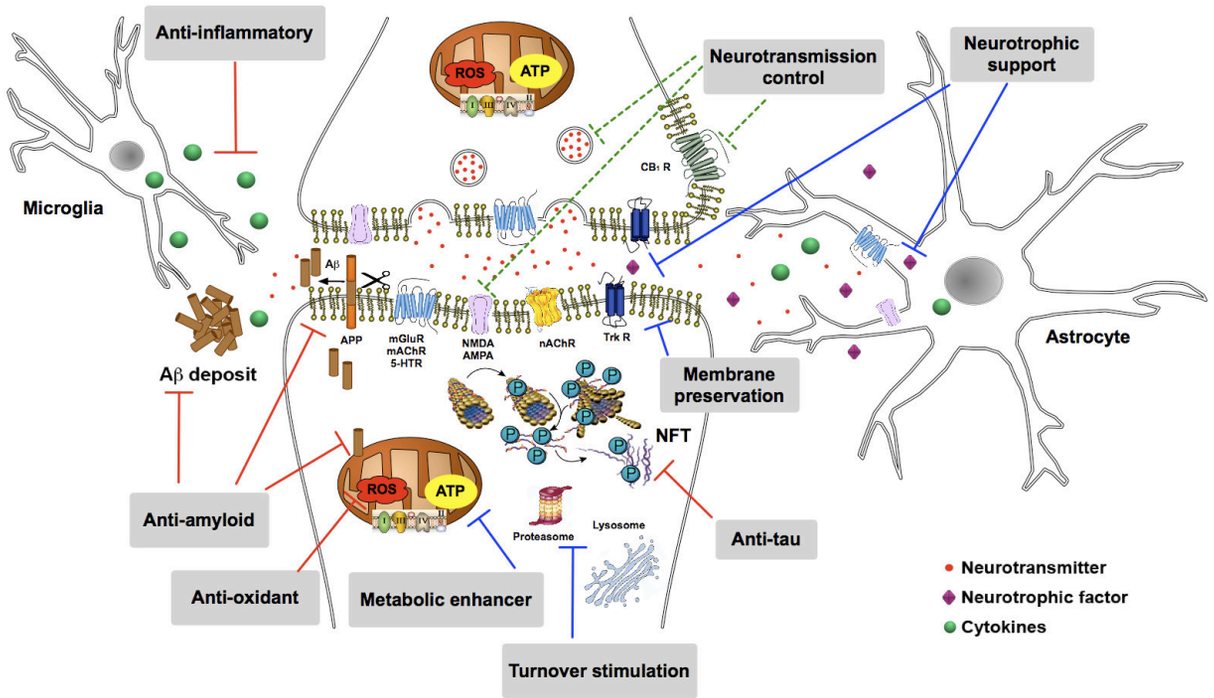

Figure 1. Schematic representation of the main cellular targets that are currently under development to prevent or retard the progression of Alzheimer to disease states. Most of the experimental approaches are designed to block or mitigate (red lines) pathological events occurring at the earliest stages, including abnormal Aβ and tau aggregation, chronic inflammatory responses, and oxidative stress damage. Other strategies (blue lines) aim at stimulating the metabolism to reduce Alzheimer's energetic failure as well as to promote intrinsic mechanisms that protect or repair cellular damage, including synaptic plasticity, preservation of the lipid membrane composition, and the promotion of damaged protein and organelle turnover. Therapeutic approaches based on the modulation of neurotransmission (green dashed lines) are designed to bypass deficient cholinergic neurotransmission whereas other compounds aim to block glutamatergic excitotoxicity. Considering the complex scenario of the Alzheimer neurodegenerative process, multi-target therapies applied at early stages of the disease appear to be the most effective strategy.

In addition to these general conclusions, several points deserve a particular comment. Recognition of the genotypic background, clinical and neuropathological subtypes and different pace of clinical manifestations is important to refine personalized treatments [333-335]. This includes modifications of the treatment as Alzheimer is not a mere accumulation of defects but rather a combination of deficiencies and plastic changes that imply shifts in molecular pathways with disease progression. Drugs and treatments

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beneficious at first stages of the degenerative process may be harmful at advanced stages. Special effort must be put into practice to learn about the combination of drugs at which determinate time for every particular individual.

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