European Review for Medical and Pharmacological Sciences 2016; 20: 1903-1910

The news advances on Alzheimer's disease's therapeutics

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Abstract. – Alzheimer's disease (AD) is a multifaceted disorder, characterized by the failure of memory and dementia. AD affects mostly elder above 65 years of age and is confirmed by post-mortem detection in the brain, of extracellular senile plaques of amyloid-beta (Aβ) and intracellular neurofibrillary tangles. These pathological hallmarks appear in the brain when the disease is already installed. The difficulty of earlier diagnosis and possibly, the poor understanding of the disease etiology, limit the benefits afforded by available treatments. Indeed, several putative drugs resulting from thorough investigations in preclinical studies have failed to produce clinical results, suggesting the development of further therapeutic alternatives.

Recently, the regular practice of physical activity has been shown as one of the effective preventive or curative mean against AD. This finding rekindles the debate on the place of the intrinsic vascular component in the AD pathogenesis which is an aspect of the disease often considered as a distinct pathology. A new integrative conception of the disease may offer an advantage to current therapies which may gain in potency if combined in a multi-target manner to yield true improvements. This review will revisit the pathophysiology of AD and discuss the advanced therapeutics currently in use.

Key Words:
Alzheimer's disease, Dementia, Cerebrovascular pathology, Therapeutics, Physical exercise.

Introduction

Alzheimer's disease (AD) is the most common form of dementia and cause of disability in the elderly population over 65 years old worldwide[1]. The illness is sporadic, mostly late-onset, genetically non-obvious, despite the consistent expression of the E4 allele of apolipoprotein E that increased the risk of AD and lower age of the onset of the pathology[2,3]. The rare inherited familial form of AD, an early-onset, affects people carrying mutations of the amyloid precursor protein (APP), and/or presenilin-1 and 2 (PS-1, PS-2) genes[4].

Beside the genetic aspects, the outbreak of AD is insidious, but there is common gradual signs and symptoms noticeable including, memory loss affecting acquired skills, difficulty of performing familiar tasks, problems with language, disorientation in time space, impaired judgement, problem with abstract thinking, misplacing things, change in mood and behaviour, change in personality and loss of initiative. The appearance of the memory deficits becomes clinically detectable[5-7] when the neurodegeneration is already occurred[8], and there is no possibility for early detection. Yet, numerous studies[9-11] that elucidated the major pathological characteristics and molecular mechanisms underlying the pathogenesis of AD have identified Aβ, neurofibrillary tangles, neuroinflammation and neurodegeneration as the main players.

Consequently, the trend of deciphering these molecular mechanisms had conducted to the development of current medications that only provide temporary benefits by improving symptoms or retarding the progression of the pathology. Therefore, the failure to properly face this devastating illness might be explained partly by the lack of earlier detection of the disease and/or possibly the poor understanding of the disease etiology.

Indeed, the traditional paradigm considers the often disregarded aspect of the intrinsic vascular component as a distinct pathology, namely vascular dementia. The vision of AD as only a neuronal pathology becomes no more tenable[12-14] because of the lack of therapy and, mostly, recent data have shown that the majority of demented patients displayed mixed AD and vascular pathology with several cerebrovascular alterations[13,14]. In line with these findings, previous data have shown that at the preclinical stage, AD brains emphasize the reduction of blood supply

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at rest[15] and altered perfusion to activate some central nervous areas[16]. This is in keeping with their manifestation in populations, such as individuals with mild cognitive impairment (MCI), or those expressing the E4 allele of apolipoprotein E[17], or in populations that are prone to develop AD namely, elderly, subjects with chronic cardiovascular disorders (hypertension, hypercholesterolemia and diabetes mellitus), stroke, and head trauma patients, and more so in groups exhibiting several of these factors at once[18]. Moreover, treatments of vascular risk factors have been associated with the reduction of the incidence of AD and the slowdown of cognitive decline in AD patients[13,14]. Accordingly, recent data[19] suggest life style, particularly the regular physical exercise as one of the best way to prevent AD or to slow the decline of physical and cognitive functions in AD patients; indicating strongly that both vascular pathologies and neuronal affections are overlapped in AD[12].

In this review, we will revisit the vascular and neuronal pathologies which compose the pathophysiology of AD, and further, we will discuss the promising treatments currently used, with a particular consideration of benefits associated with physical exercise for AD.

Pathophysiology of Alzheimer's Disease

Cerebrovascular Pathology

Chronic brain hypoperfusion[15,20] and altered neurovascular coupling[7,16] are prominent features of AD. Many studies showed that chronic hypoperfusion decreased brain clearance of Aβ peptide, oxidative stress, and the shortage of pivotal brain nutrient. These create a threat for brain homeostasis[21,22] which contribute to synaptic failure, neuronal dysfunction and neurodegeneration in AD[23,24]. In addition, soluble Aβ, which possesses choline toxicity properties[25], is also responsible for the cholinergic deafferentation of intracerebral microvessels[26] in AD. This possibly explains the reduced hyperemia, particularly during attention task, known to recruit the basal forebrain. Moreover, aggregated forms of Aβ1-42 and 40 settled within vessel walls of small to medium arteries in circumferential bands consistent with smooth muscle cell synthesis, lead to cerebral amyloid angiopathy (CAA)[27]. As the amyloid makes its way toward capillaries and arterioles, faulty clearance across the blood-brain barrier (BBB) and increased arterial stiffness hindering vessel pulsations that drive Aβ drainage would result in abluminal deposition[28,29]. This abluminal deposition leads to cerebrovascular dysfunction in AD patients, demonstrating, therefore, a decrease of the basal cerebral glucose utilization (CGU), particularly in parietotemporal and posterior cingulated cortex and altered neurometabolic coupling[22]. The resulting insufficient CBF that poses a threat for homeostasis and protein synthesis underlying learning[24] could activate hypoxia-sensitive pathways culminating in the upregulation of deleterious proteins, such as Aβ peptide and the transforming growth factor β1 (TGF-β1), which are both, detrimental for cerebrovascular structure and function[30]. Thus, neural degenerative and vascular pathologies coexist in late life. Each of them adds to the likelihood of developing AD. This suggests that concurrently targeting the vascular and neuronal deficits in AD should bear promise in controlling disease outcome[31].

Neuroinflammatory Pathology

Aβ Deposition

Extracellular deposition of Aβ as senile plaques derived from the sequential cleavage of APP by β and γ-secretases complexes[32]. Mounting of evidence suggests that the soluble oligomeric species of Aβ actually mediates the synaptic dysfunction in AD[33] through the binding of potentials receptors[34] expressed on astrocytes, microglia and neurons to induce synaptic toxicity and also form cerebral amyloid angiopathy (CAA)[27], and contribute to increase the size of plaques. Thus, targeting the Aβ cascade through inhibition and modulation of secretase activities, with the aim of counteracting the formation of Aβ aggregates or removing various Aβ forms, had already constituted a therapeutic strategy. But, several clinical trials in vaccinal attempts were negative at phase 3 with cases of meningitis[35]. Data from amyloid-based immunotherapy also showed that intervention appearing in early stages of Aβ accumulation are more effective, suggesting that this treatment approach in AD patients still in progress[36].

Neurofibrillary Tangles

Neurofibrillary tangles are composed of abnormally hyperphosphorylated and aggregated microtubule associated protein tau (τ). In a normal cell, τ is a neuronal microtubule-associated

protein that stabilizes axonal microtubules[11], and is responsible for intracellular trafficking. The protein τ became dissociated from microtubules when phosphorylated. In AD brain, τ is abnormally hyperphosphorylated by kinases[37] and destabilizes the microtubule network, leading to cytoskeletal collapse, loss of viability, and neuronal death. Drug development that targets kinases responsible for τ hyperphosphorylation or inhibits τ aggregation or stabilizes microtubules, may also constitute an interesting avenue that is currently in investigation[38].

Chronic Neuroinflammation

Cytokines [Interleukin-1β, interferon-γ, tumor necrosis alpha (TNF-α), interleukin-6], chemokines and free radicals emanating from activated glial cells recruited at the site of Aβ plaques promote inflammatory cycle in astroglial cells and oxidative stress[39] which damage surrounding neurons. These damaged or dying neurons release in turn, subsequent immune mediators and/or modulators that exacerbate the inflammatory neurotoxicity and worsen the situation in an unresolved brain inflammation. In addition, oxidative stress and proinflammatory cytokines can stimulate γ-secretase activity and enhance the expression of amyloidogenic APP processing[40]. Therefore, the use of anti-inflammatory approaches has been considered for the prevention and treatment of AD[40]. But, clinical studies showed mitigating data, allowing considering anti-inflammatory, particularly the non-steroidal (NSAID), as delaying the onset of AD in some patients, with any significant preventive effect against dementia development.

Neuronal Death

In AD brains, trophic factors, neurotransmitters, and their respective receptors are likewise reduced, as is the neuronal glucose transporter-3[41], disturbances in axonal transport linked with neurofibrillary tangles and microtubules disarrangement[42], as well as presynaptic and postsynaptic markers decreased. These suggest that neurodegeneration and neuronal death are the consequence of upstream manifestation. Indeed, particular substantial neurodegeneration of cholinergic neurotransmission occurs in the basal forebrain, parietal, prefrontal and entorhinal cortices as well as in hippocampus[8] and appears when memory deficits become clinically detectable. In addition, this degeneration of cholinergic system in the basal forebrain[43] is accompanied with that of noradrenaline-containing neurons of the locus coeruleus[44], and the decreases in the levels of dopaminergic, serotoninergic, and somatostatin markers in various brain areas[45]. The glutamatergic system is also affected in the vicinity of degenerating regions, surging in extracellular glutamate that leads to excitotoxic death, primarily mediated by NMDA receptor, with excessive activation of glutamate receptors. This results in neuronal Ca2+ overload and possibly, excitotoxic death[46]. Hence, therapeutics against excitotoxicity may be acceptable strategies in addition to also targeting all the individual mechanism underlying the pathogenesis of AD occurring before neuronal death.

Current Promises Therapeutics in Use

Peroxisome Proliferator-Activated Receptor γ Agonists

Agonists of Peroxisome Proliferator-Activated Receptor γ (PPAR γ) were used to treat type-2 diabetes. Rosiglitazone (Avandia, Glaxo-SmithKline), removed from the North American market, and Pioglitazone (Actos, Takeda Pharmaceutical, North America, Inc) were the two prescribed members. They act by enhancing insulin activity and offer benefits on AD, being associated with their ability as nuclear receptor ligands to regulate transcription of a wide variety of oxidative, inflammatory, fibrotic and neuronal survival genes, although transcription-independent effects may also be involved. This suggests the ability to improve neuronal, glial, and cerebrovascular networks in AD, and consequently to rescue brain hemodynamics[47]. In AD patients, pioglitazone has ameliorated cerebral perfusion and increased regional cerebral blood flow (CBF) in the parietal lobe, concomitantly with an improvement in cognition[48], but failed to rescue memory deficits. As well, the magnitude of improvement in clinical trials with pioglitazone[48] was not superior to that offered by cholinesterase inhibitors, indicating that thiazolidinediones may make advantageous for subpopulations such as diabetic AD patients, who could avoid cholinesterase inhibitor.

Renin-Angiotensin Blockers and Statins

A meta-analysis study on the renin-angiotensin system (RAS) inhibition with antihypertensive drugs had shown that RAS-targeting antihypertensive drugs attenuated the incidence of AD in hypertensive patients, and slowed down cognitive

decline in patients with AD[49]. In California, autopsy evaluation of participants exposed to RAS blockers with or without AD had demonstrated less amyloid deposition markers, and neurofibrillary tangles compared to untreated hypertensives[50]. Yet, well-controlled randomized clinical trials are awaited to clarify the exact therapeutic value of RAS blockers in AD patients or in subsets of AD[51]. Another class of compounds used against risk factors of AD are statins, a class of pleiotropic drugs acting through inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in the synthesis of cholesterol[52]. The well-studied member of this class is simvastatin which penetrates the BBB. Statins are involved in the improvement of endothelial cell function. They possess antioxidant and anti-inflammatory properties, as well as central nervous system effects[52]. Particularly, statins had reduced the prevalence of AD in prescribed populations[53,54]. They also lower cognitive decline in mild-to-moderate patients[55].

Cholinesterase Inhibitors

Cholinesterase inhibitors are the standard FDA approved symptomatic therapy or mild-moderate cases of AD. These compounds were developed to prolong the synaptic life of acetylcholine that is partly responsible for attention deficits and cognitive decline in AD, being affected by the cholinergic-specific denervation. Four compounds were available including tarcine (Cognex, Parke-Davis Pharmaceuticals), donepezil (Aricept, Pfizer Inc.), rivastigmine (Exelon, Novartis Pharmaceuticals Corporation) and galantamine (Reminyl, Janssen Inc.), but tarcine is no longer used after demonstrating liver-toxicity side effects. However, many properties have been discovered for galantamine, that actually, provides mainly dual action mechanism on the cholinergic system including the inhibition of Acetylcholinesterase and the modulation of n-acetycholine receptor activity[56]. Other important properties founded integrated the inhibition of Aβ aggregation and cytotoxicity[57] and the scavenging of reactive oxygen species with protection against oxidative damage. As well, regarding the AD circulation, cholinesterase inhibitors were found to preserve or improve perfusion in AD patients undergoing therapy[16].

NMDA Receptors Blockers

The second class of FDA-approved medications acts by blocking N-methyl-D-aspartate (NMDA) receptor. This is in keeping with the excess of glutamate release from damaged cells induce a massive influx of Ca2+ into neurons via NMDA receptor activation, resulting in excitotoxicity and ultimately to neuronal death in AD. Memantine (Namenda™), a neuroprotective agent that block NMDA receptors, was approved for treatment of moderate to severe AD in 2003[58].

Plant Alkaloids

This group includes candidates such as galantamine (approved by the FDA) or huperzine A (approved by China pharmaceutical community), and caffeine, rhynchophylline and isorhynchophylline, indometacin, capsaicin, morphine, nicotine, harmine.

Coffee

Drinking three to five coffees daily at midlife has been associated with a 65% lower risk of dementia[59], though epidemiological studies have produced mixed results. Some studies suggest a protective association while others report no benefits, suggesting additional investigations.

Rhynchophylline and Isorhynchophylline

Rhynchophylline and isorhynchophylline that act as calcium channel antagonists, anticoagulants and vascular smooth muscle cell proliferation inhibitors on cardiovascular disease including hypertension, bradycardia, and arrhythmia had demonstrated beneficial effects on central nervous system diseases such as dementia, ischemia, amnesia and epilepsy[60] and protect τ protein against hyperphosphorylation.

Morphine

Several studies had demonstrated that morphine protects neurons against microglia-mediated neuroinflammation and oxidative stress[61], as well as against intracellular amyloid toxicity by inducing estradiol release and upregulation of heat shock protein-70. However, the use of morphine for AD is compromised by its highly addictive properties and it severely limited and restricted used.

Nicotine

Nicotine and its main metabolite cotinine can also represent good candidate as they have demonstrated capacities to bind Aβ and block its aggregation, thus, protecting n-acetylcholine receptors, known to have high affinity with Aβ.

However, clinical studies investigating the efficacy of nicotine against AD pathology have not demonstrated significant improvements in memory, although they demonstrated a clear positive effect on attention in AD patients[62].

Indometacin

Indometacin is a NSAID that belongs to the pyrrolizidine class, prescribed to reduce fever, relieve moderate to severe pain, tenderness, swelling as well as stiffness caused by osteoarthritis, rheumatoid arthritis and acute gouty arthritis. Indomethacin inhibits cyclooxygenase in the production of prostaglandins, and its effects in AD has been found promising in cell cultures[63] and animal model[64]. Preliminary preclinical studies had shown cognitive decline slowing in AD.

Capsaicin

Capsaicin, the primary capsaicinoid found in chili peppers, responsible for spiciness, acts as a hypolipidemic, antioxidant, and anti-inflammatory agent. Capsaicin ameliorates synaptic damage and τ hyperphosphorylation in stressed mouse models[65], despite the capacity to increase the level of membrane-bound APP in rat brains.

Harmine

Harmine reduces τ protein hypophosphorylation and inhibits the dual-specificity tyrosine phosphorylation regulated kinase 1A (DYRK1A)-catalyzed direct phosphorylation of τ. Harmine has thus promising therapeutic benefits in the treatment of AD[66].

Physical Exercises and Wellness

Physical activity with an equilibrated diet increased cerebral blood flow in the dentate girus of the hippocampus which may improve neurogenesis[67]. Consensus guidelines, based on indirect data from epidemiological and prospective studies state a dose-response relationship existing between physical exercise and health benefits along with cognitive outcomes; Greater cognitive performance being related to lower dementia risk in individuals who have greater levels of physical activities. In line with these data, an increase of 2% of the volume of the hippocampus as well as elevation in the plasma concentration of brain-derived neurotrophic factor (BDNF) have been found in older healthy subjects after 1 year of moderately intense aerobic exercise (3 days/week, 40 min/session). Moreover, the increase of BDNF was significantly correlated with the level of physical exercise practiced among people with AD[68]. Consistently, an aerobic program of three weekly 1-hour sessions for 6 months increased the volumes of both gray and white matters in certain prefrontal and temporal cortical regions for elder between 60 and 79 years old[68]. The release of neurotrophic factors by physical activity promotes angiogenesis, thereby facilitating neurogenesis and synaptogenesis, which in turn improve memory and cognitive functions. The neuroprotective mechanisms induced by physical activities are linked to an increase production of superoxide dismutase, endothelial nitric oxide synthase, brain-derived neurotrophic factor, nerve growth factor, insulin-like factor, and vascular endothelial growth factor, and a reduction in the production of free radicals in the brain areas such as hippocampus[69]. Physical exercises also limit the alteration of dopaminergic neurons, substantia nigra and contribute to the optimal functioning of the basal ganglia involved in motor commands and control by adaptive mechanisms involving dopamine and glutamate neurotransmission[70].

Thus, physical activity becomes a powerful instrument for lowering vascular risk factor[71], improving postural and motor functions[19], slowing the decline in physical and cognitive function in AD patients[72], reducing depressive symptoms and even mortality in dementia patients.

Conclusions

AD must be considered as a multifaceted multifactorial disease which interconnects both cerebrovascular and neuronal pathologies. The integration of vascular disease as a part of AD is an asset for the understanding of its complex etiology. As well, the development of biochemical protocols to incorporate biomarkers in the clinical support of diagnosis that could allow the early identification of preclinical or clinical AD, such as AD-specific biomarkers which specifically distinguish AD dementia from another type of dementia disorders, for example, is still one of the main challenges for medical investigators. In line with this option, targeting vascular markers could also offer interesting avenues.

Among recently developed drugs, those aimed at reducing Aβ load and τ phosphorylation seem to gain more importance as a part of pharmacological intervention. But they will gain in poten-

cy if combined in a multi-target manner to yield true improvements. Indeed, new treatments should encompass a combination of pharmacological strategies that support multi target-directed ligand, and a social intervention which may allow the maintenance of quality of life for a maximum period of time. The promotion of physical exercise among healthy, AD patients and people at risk of developing AD is an advantage to prevent or reinforce therapeutics.

Acknowledgements

This reasch was supported by grants from Department of Sience and Technology of Shandong Province (Grant No. BS2011YY063), and Department of Health of Shandong Province (Grant No. 2011QZ030).

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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