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Review

Alzheimer's disease, enzyme targets and drug discovery struggles: From natural products to drug prototypes

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ABSTRACT

Alzheimer's disease (AD) is an incapacitating neurodegenerative disease that slowly destroys brain cells. This disease progressively compromises both memory and cognition, culminating in a state of full dependence and dementia. Currently, AD is the main cause of dementia in the elderly and its prevalence in the developed world is increasing rapidly. Classic drugs, such as acetylcholinesterase inhibitors (AChEIs), fail to decline disease progression and display several side effects that reduce patient's adhesion to pharmacotherapy. The past decade has witnessed an increasing focus on the search for novel AChEIs and new putative enzymatic targets for AD, like β- and γ-secretases, sirtuins, caspase proteins and glycogen synthase kinase-3 (GSK-3). In addition, new mechanistic rationales for drug discovery in AD that include autophagy and synaptogenesis have been discovered. Herein, we describe the state-of-the-art of the development of recent enzymatic inhibitors and enhancers with therapeutic potential on the treatment of AD.

Contents

Abbreviations: 2AADPR, 2′-*O*-acetylADP-ribose; 3AADPR, 3′-*O*-acetylADP-ribose; 6-BIO, 6-bromo-3′-oxime; Å, Ångström; ACh, acetylcholine; AChE, acetylcholinesterase; AChEIs, acetylcholinesterase inhibitors; AD, Alzheimer's disease; ADAM, a desintegrin and metalloprotease; ADME, absorption, distribution, metabolism and excretion; APH-1, anterior pharynx-defective phenotype-1; APOE4, ε4 allele of the apolipoprotein E gene; APP, amyloid precursor protein; APP^{sw}-Tau^{vlw} mice, transgenic mice expressing human APP and Tau; ATP, adenosine triphosphate; Aβ, β-amyloid protein; BACE1, β-site APP cleaving enzyme-1; BACEIs, β-site APP cleaving enzyme-1 inhibitors; BBB, blood–brain barrier; BChE, butyrylcholinesterase; BDNF, brain derived neurotrophic factors; cAMP, cyclic adenosine monophosphate; CAS, catalytic anionic site; CAT, choline acetyltransferase; CDK, cyclin dependant kinases; Chol, choline; CK1, casein kinase 1; CMGC, cyclin-dependant kinases, mitogen-activated protein kinases, glycogen synthases kinases and cyclin-dependant kinase-like kinases; CNS, central nervous system; CSF, cerebrospinal fluid; CYP, cytochrome P450; DARP-32, dopamine and cAMP regulated phosphoprotein, Mr. 32 kDa; EC_{50}, half maximal effective concentration; EeAChE, *Electrophorus electricus* acetylcholinesterase; EOAD, early-onset alzheimer's disease; EqBChE, equine butyrylcholinesterase; ES, esteratic site; FDA, Food and Drug Administration; GS, glycogen synthase; GSK-3, glycogen synthase kinase-3; H_2O_2, hydrogen peroxyde; hAChE, human acetylcholinesterase; hBChE, human butyrylcholinesterase; HDAC, histone deacetylase; hSIRT1, human sirtuin-1; hSIRT2, human sirtuin-2; HupA, huperzine A; IC_{50}, half maximal inhibitory concentration; IP_3, inositol triphosphate; kDa, Kylo Dalton; LOAD, late-onset alzheimer's disease; mAChR, muscarinic receptors; MEF, mouse embryonic fibroblasts; mESCs, mouse embryonic stem cells; MPP(+), 1-methyl-4-phenylpyridinium; mTOR, mammalian target of rapamycin; nAChR, nicotinic receptors; NAD^+, nicotinamide adenine dinucleotide; NAM, nicotinamide; $NaNO_2$, sodium nitrite; NFT, neurofibrilary tangles; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLGs, neuroligins; NMDA, n-methyl-D-aspartate; nNOS, neuronal nitric oxide synthase; NPC, human neural progenitor cells; NRXs, neurexins; OKA, okadaic acid; PAF, platelet activating factor; PAS, peripheral anionic site; PD, Parkinson's disease; PEN-2, presenilin enhancer-2; PIK, phosphoinositide kinase; PKA, protein kinase A; PKC, protein kinase C; PKPD, pharmacokinetic and pharmacodynamics; PPARγ, peroxisome proliferator-activated receptor γ; PrP, prion peptide; PSEN-1, presenilin-1; PSEN-2, presenilin-2; PSP, progressive supranuclear palsy; QSAR, quantitative structure–activity relationship; rAChE, rat acetylcholinesterase; RARα, retinoic acid receptor α; rSIRT1, rat sirtuin-1; rSIRT2, rat sirtuin-2; sAPPα, soluble APPα peptide; sAPPβ, soluble APPβ peptide; SIRT, sirtuins; SMERs, small molecule enhancers of rapamycin; SNP, senile neuritic plaques; SOD, superoxide dismutase; Tau, tau protein; tau-P, hyperphosphorylated tau protein; TcAChE, *Torpedo californica* acetylcholinesterase; TSP, thrombospondin.

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1. Alzheimer's disease: an overview

Alzheimer's disease (AD), a multifactorial neurodegenerative disease, is single-handedly the main factor behind dysfunction among persons over age 85, and the major cause of dementia in old age (Larson et al., 1992). According to epidemiological surveys, an estimated 7–10% of individuals over 65 and 50–60% over 85 suffer from AD (Evans et al., 1989; McKhann et al., 1984), reaching approximately 35 million people worldwide. In Europe, 7.3 millions of citizens suffer from dementia. Owing to the increased life expectancy this number will increase dramatically in the future, escalating up to 114 million cases by 2050 (Ferri et al., 2005; Brodaty et al., 2011; Berr et al., 2005; Minati et al., 2009).

AD patients develop a gradual and insidious cognitive deficit that becomes incapacitating in the advanced stages of the disease. These devastating symptoms significantly compromise the patients' quality of life, leading to absolute dependence, hospitalization and, unavoidably, death (Hughes et al., 1982). The most common form of Alzheimer's is the late-onset AD (LOAD) form, which accounts for approximately 95% of AD cases (Monczor, 2005). Although the specific cause of AD is unknown, analyzing the risk factors, age and family history in a first-degree are arguably the most important for developing dementia (Aliev et al., 2008). However, the mentioned risk factors alone cannot be responsible for all documented cases of Alzheimer disease. Some detected cases, particularly with early onset (EOAD), are familial and inherited as autosomal dominant disorder. Familial AD risk is markedly genetic and, so far, four genes have been associated with AD pathology: the APP (amyloid protein precursor), preselinin 1 (PSEN-1), preselinin 2 (PSEN-2) and the ε4 allele of the apolipoprotein E gene (APOE4) (Wollmer, 2010; Frank and Gupta, 2005).

Classic features found in the brains of AD patients include neuronal loss in regions associated with memory and cognition, particularly of cholinergic neurons, neurotransmitter depletion (mainly acetylcholine, ACh) and synaptic dysfunction (Monczor, 2005; St George-Hyslop, 2000). Microscopically, the most common findings are abnormal protein deposits, including senile neuritic plaques (SNP) and neurofibrillary tangles (NFT) (Goedert and Spillantini, 2006). Senile plaques are the result of the extracellular accumulation of insoluble aggregates of β-amyloid protein (Aβ) while NFT occur intracellularly and are composed of paired helical filaments of hyperphosphorylated tau protein (tau-P). These abnormalities lead to the activation of neurotoxic cascades and to cytoskeletal changes that eventually cause synaptic dysfunction and neuronal death (Goedert and Spillantini, 2006). Protein misfolding and abnormal aggregation both play a critical role in AD pathology, leading to the formation of insoluble pathological conformers that cause neuronal degeneration and cellular death (Sadqi et al., 2002). The main feature of AD etiology is the multiplicity of pathological stimuli associated with increased risk, disease development and progression, commonly referred to as hypothesis. Indeed, several of these hypotheses have been proposed to date, including the amyloid hypothesis (Goedert and Spillantini, 2006), cholinergic hypothesis (Craig et al., 2011), glutamatergic hypothesis (Bezprozvanny and Mattson, 2008), oxidative stress hypothesis (Pratico, 2008), metal hypothesis (Bonda et al., 2011) and the inflammatory hypothesis (Trepanier and Milgram, 2010).

Current therapies with acetylcholinesterase inhibitors (AChEIs) and *N*-methyl-D-aspartate (NMDA) receptor antagonists are based on the cholinergic and glutamatergic hypothesis, respectively (Schmidt et al., 2008). Though active at ameliorating AD symptoms, none of the current drugs are able to modify disease progression, a fact that has provided the driving force behind the ongoing research for new and potent anti-Alzheimer compounds (Schmitt et al., 2004; Schmidt et al., 2008). Hence, the wide range of pathologic features in AD is continuously broadened and gives rise to a growing set of promising therapeutic targets. Mainly, these non-classic macromolecular targets are enzymes involved in key physiological and pathological processes that have been connected with neurotoxicity and neurodegeneration, such as secretases, sirtuins, and caspases.

In this review, we provide a thorough insight on the state-of-the-art of the development of enzymatic inhibitors and enhancers of classic and non-classic targets with therapeutic potential for AD. These new approaches drive the drug discovery in neurodegeneration toward the development of novel potent disease-modifying agents that aim at improving the quality of life of AD patients and paving the way to solving the complex and yet unresolved puzzle of AD.

2. Classic enzymatic targets

2.1. Acetylcholinesterase

Cholinergic transmission has a vital role in cerebral cortical development and activity, cerebral blood flow, sleep-wake cycle, learning, memory and cognition (Rees and Brimijoin, 2003; Brimijoin, 1983). Acetylcholine is responsible for stimulating contractions of smooth muscle in the gastrointestinal tract, urinary tract and eye, as well as decreasing heart rate and relaxing the smooth muscle of blood vessels, causing vasodilation. The biological response to cholinergic stimuli is dependent on the type of