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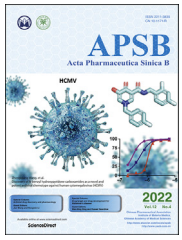

Editorial of special column on Drug targets and drug development for Alzheimer's disease

Alzheimer's disease (AD) is the most common form of progressive dementia in people aged 65 years and over. The major pathological features of AD are the accumulation of extracellular β-amyloid plaques and intracellular neurofibrillary tangles composed of aggregated, hyperphosphorylated tau. In addition to an accumulation of protein aggregates, mitochondrial dysfunction, altered lipid metabolism and increased neuroinflammation also play critical roles in the pathogenesis of AD and its associated dementia. Decades of research have worked to develop drugs that treat AD by targeting amyloid β-peptide (Aβ), which have shown no to minimal efficacy. Therefore, there is a need to identify novel therapeutic targets and approaches that can meaningfully treat this devastating neurodegenerative disease.

We are pleased to present a special issue on "Drug targets and drug development for Alzheimer's disease". This thematic column contains both review and original research articles that cover a diverse range of topics on whole body and lipid metabolism, mitochondrial dysfunction, autophagy-lysosomal degradation, and the high-throughput screening of small molecules that target Aβ. Metabolic disorders have been linked to AD both in the whole body and at the cellular level in the brain. In a review article by Dr. Zhang's group[1], the current understanding of whole-body metabolism, sex differences, microbiome, circadian regulation, as well as mitochondrial bioenergetics, mitochondrial quality control, and mitochondrial-linked inflammatory responses was comprehensively summarized in the context of potential AD therapeutics. Additional perspectives[2,3] related to metabolism in the pathogenesis of AD, including ATP binding cassette protein A1 (ABCA1) in cholesterol mobilization and genetic variation in apolipoprotein E (*APOE*), were also summarized and highlight genetic and non-genetic factors that affect lipid metabolism. These entities could be considered when targeting lipid metabolism against AD. Mitochondrial dysfunction in neurons has been considered as an important contributor to AD pathogenesis. Interestingly, partial inhibition of mitochondrial complex I has shown benefits in AD mouse models. The development of safe complex I inhibitors for potential treatment of AD was elegantly summarized by Dr. Trushina[4]. Moreover, Aβ and tau-containing neurofibrillary tangles are generally cleared by the autophagy−lysosome pathway, the function of which declines with advancing age. A current mechanistic understanding of how autophagy is impaired in aging and AD were beautifully summarized in two review articles[5,6]. In addition, two original research articles[7,8] describe promising novel small molecules that either directly target Aβ or activate a transcriptional program that boosts autophagy−lysosomal degradation of Aβ and tau aggregates. Overall, we believe that this timely special issue will advance our understanding AD and provide mechanistic insights into its pathogenesis, as well as novel drug development efforts.

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Conflicts of interest

The authors have no conflicts of interest.

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