Apomorphine: A Novel Efficacy for Alzheimer’s Disease and Its Mechanisms

Yasumasa Ohyagi*
Department of Neurological Therapeutics, Graduate School of Medical Sciences, Kyushu University, Japan

Alzheimer’s disease (AD) is the major cause for dementia in the elderly people. At present, four drugs are generally used for AD patients in the world, i.e., donepezil, galantamine, rivastigmine and memantine. The former three drugs are the acetylcholine esterase inhibitors while memantine is the NMDA receptor antagonist. These drugs are known to be the ‘symptom-modifying’ drugs that partially attenuate the progression of dementia but not cure the AD patients. Thus, many companies and researchers are developing the ‘disease-modifying’ drugs and doing clinical tests for AD patients.

Two major pathological AD hallmarks, senile plaques (SPs) and neurofibrillary tangles (NFTs) are widely known. SPs consist of amyloid-β protein (Aβ), and NFTs consist of hyper-phosphorylated tau protein (p-tau). Since formation of Aβ oligomers pre-cysts p-tau accumulation in neurons, Aβ oligomers are thought to be the major therapeutic target in the early stage of AD (Amyloid cascade hypothesis). However, recent clinical trials of drugs for anti-Aβ aggregation and γ-secretase inhibition, and clinical trials of anti-Aβ antibodies have all failed [1]. Although other following trials of anti-Aβ drugs are still under investigation, some other direction of AD therapeutics is thought to be necessary.

On the other hand, some groups including us have been focusing on the pathogenesis of intraneuronal Aβ42. Although Aβ42 is a minor species of the secreted Aβ, Aβ42 is more aggregative and toxic for neurons compared to Aβ40, the major species of secreted Aβ. Various mechanisms of intraneuronal Aβ42 are suggested such as dysfunction of synapse, mitochondria, protease and endoplasmic reticulum (ER) [2]. Very recently, we have found that Aβ42 with a toxic turn conformation may accumulate in neurons inducing ER stress before appearance of memory impairment in an AD mouse model, 3xTg-AD [3]. Thus, attenuation of intraneuronal Aβ42 accumulation may be a novel strategy for the cure of AD, and we searched for a new drug that promotes degradation of intracellular Aβ. For the first time, we reported that apomorphine (APO), a kind of dopamine receptor agonist for Parkinson’s disease, could enhance degradation of intracellular Aβ via activation of proteasome and insulin-degrading enzyme (IDE) and that subcutaneous injection of APO actually improved memory function in 3xTg-AD mice [4]. Furthermore, since APO was known to be an anti-oxidative stress drug, we analyzed the anti-oxidant mechanisms of APO. We then found that APO treatment induced up-regulation of glutathione peroxidase (GPx) and protected cells from oxidative stress [5]. Since another dopamine agonist did not improve cognitive function of 3xTg-AD mice [4] and dopamine receptor antagonists did not inhibit cell-protective effects of APO [5], anti-Aβ effects of APO may not be mediated by dopamine signaling. Thus, identifying the molecular mechanisms of APO treatment must be a novel way to develop new AD drugs, which might be more clinically effective than the drugs targeting extracellular Aβ oligomers.

Why have the recent anti-Aβ drugs, e.g., anti-Aβ aggregation drugs and anti-Aβ antibody, failed to improve cognitive function in the clinical trials for AD patients? There may be two major reasons. First, if such drugs stop Aβ neurotoxicity completely, treatment should have to start before accumulation of NFTs and cognitive impairment.

In this context, anti-Aβ oligomer drugs may be prophyllactic but not therapeutic agents. Thus, design of clinical trials should be modified using preclinical AD patients. Second, the ‘Amyloid cascade hypothesis’ itself should be reappraised. Many researchers and companies have been developing candidate drugs based on this famous hypothesis. Although Aβ oligomers and fibrils may enhance the pathogenic mechanisms, those may not play the pivotal role in AD. Then, what is the central mechanism of AD pathogenesis? For example, oxidative stress has long been thought to be an important pathogenesis in AD as well as other age-related neurodegenerative diseases [6]. However, the real causes of excessive oxidative stress in AD brain are still unclear.

One of the recent major topics in AD research is the relationship between AD and diabetes mellitus (DM). Elevated insulin resistance and decreased insulin signaling may occur in neurons in AD brain [7]. DM may be a major risk factor for AD pathogenesis [8], and AD is recently called the type-3 diabetes [9]. Thus, it has been reported that some clinical trials of insulin administration for AD and MCI patients may actually improve memory function [10]. It is also reported that Aβ oligomers exacerbate the insulin resistance of neurons [11]. Elevated insulin resistance may lead to increases in Aβ production [12] and GSK-3 activity [13], resulting in Aβ and p-tau accumulation, respectively. Interestingly, we analyzed the molecular effects of APO using DNA microarray and have found that APO treatment may up-regulate insulin-signaling pathway resulting in increased in IDE expression and activity (unpublished data).

In conclusion, the complicated pathogenesis of intraneuronal Aβ, oxidative stress and insulin resistance may be an important target to develop novel eradical medicine potentially including APO.

References


