



Concepts for Alzheimer's Disease Drug Development

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INTRODUCTION

Alzheimer's disease (AD) was a neuronal disease with no completely cure drug [1,2]. Patient with AD suffer from symptoms which required closely attention [2-5]. The important limitations of management include lacking of good and practical diagnostic methods and insufficient choice in medications. The crucial barriers to the discovery or synthesis of effective drug for treatments of AD including AD are caused by integration and simultaneous occurrence of several complex pathologies in the patient's brain treating at a single pathology is inadequate to

effectively stop or even slow down the disease progression. [6,7]. However, it is not easy to discover or synthesis the drug which combines the appropriate characteristics that enables to act in multi modes of pathogenic sites, exhibits excellent efficacy and safety characteristics in the unique molecule and displays the properties of oral absorption drug and appropriate characteristics of CNS drug in the unique molecule (Table 1). These obstacles have raised the inspiration that if there is a new drug candidate that demonstrates features of multi-targeting action and good safety, it could be an alternative choice for Alzheimer's treatment.

Table 1: Properties for oral absorption drug and appropriate characteristics of CNS drug

Lipinski Rules of Five [8]	Appropriate CNS Drug Characteristics [9]
1. Its molecular weight is less than 500.	1. Molecular weight ≤ 400
2. The compound's lipophilicity, expressed as a quantity known as $\log P$ (the logarithm of the partition coefficient between water and 1-octanol), is less than 5.	2. $\log P \leq 5$
3. The number of groups in the molecule that can donate hydrogen atoms to hydrogen bonds (usually the sum of hydroxyl and amine groups in a drug molecule) is less than 5.	3. Hydrogen bond donor ≤ 3
4. The number of groups that can accept hydrogen atoms to form hydrogen bonds (estimated by the sum of oxygen and nitrogen	4. Hydrogen bond acceptor ≤ 7

atoms) is less than 10.	
5. Number of rotatable bonds ≤ 10	

Cholinesterase inhibitors (donepezil, galantamine and rivastigmine) and NMDA receptor antagonists (memantine) have been approved for treatment AD for more than three decades [10]. They have been limited to being single pathogenic mechanism drugs, for symptomatic use, being insufficient for use in the severe disease stages and cannot directly achieve results at the disease's origins [2,3]. Cholinergic hypothesis still has been accepted as the well-known pathogenic mechanism which has been supported by

numerous of significance studies and it was involved from the beginning of the disease through the late stage (Figure 1). Although, this hypothesis was considered as a long-standing theory, recent studies [11-15] has shown some connections suggesting that the notions of cholinergic theory could be improved and should be adapted in further Alzheimer's drug developments (Table 2). Consistent with this current informatio, the cholinergic postulation is still an important target of AD development (Table 3).

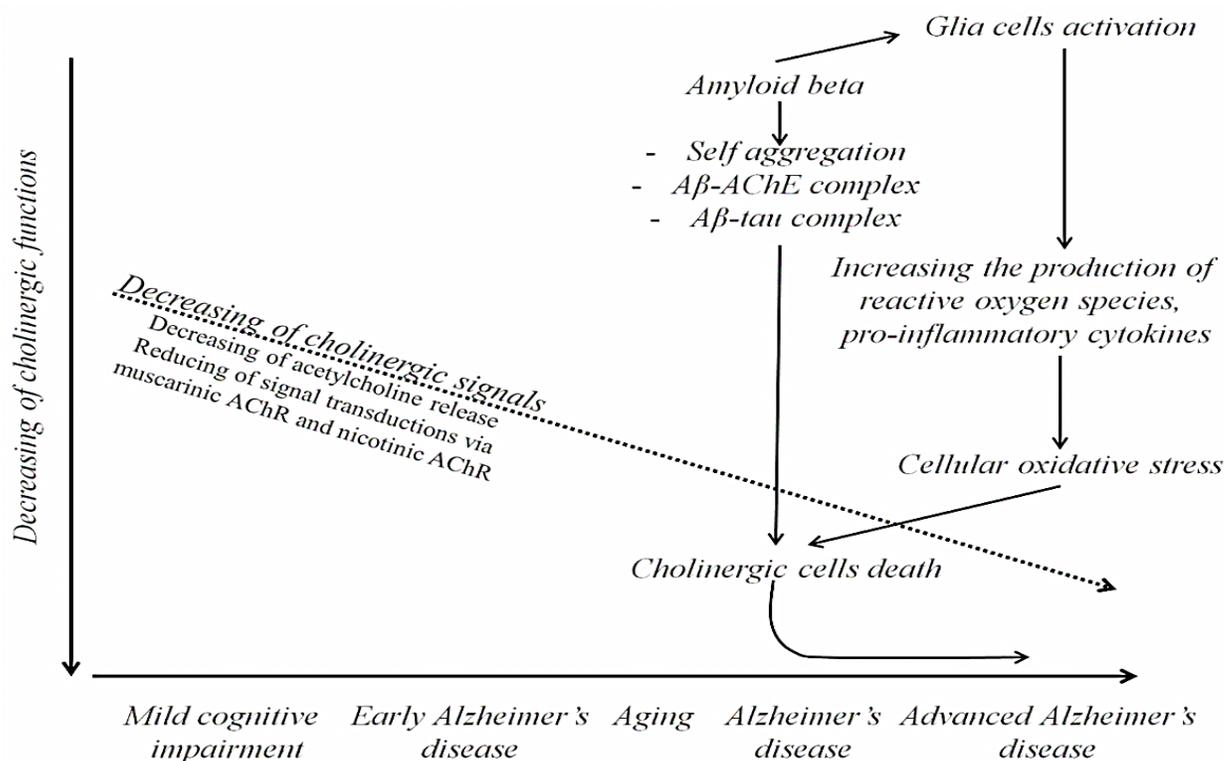


Figure 1: Changes of cholinergic functions with aging and Alzheimer's disease

Note: Decline of cholinergic signals involve with aging and AD at the onset through the late stage of disease. Intracellular oxidative stress and neuro inflammation cause cholinergic cells death and lead AD patient undergo the severe disease stage.

Table 2: The traditional versus more recent concepts of cholinergic hypothesis and the expected characteristic of the novel Alzheimer's drug replacement

The Traditional Concept	More Recent Concepts	Expected Characteristic of the Novel Alzheimer's Drug Candidate
Alzheimer's symptoms caused by the reduction of acetylcholine levels in patient's brain [16]. Acetylcholine is destroyed by AChE which is the target of existing drugs [14].	Many studies [17-19] have raised the impression that if a large number of AChE were used to hydrolyze acetylcholine, it would be the reason for BuChE increasing, therefore the entire cause was still not completely terminated. In addition, in studies [12-14] of Alzheimer's patients it has been observed that there is a decrease of AChE and increase of BuChE levels.	Non-selective AChE and BuChE inhibitor
	The studies [20-22] proposed that AChE also demonstrates a non-cholinergic function which attaches to A β at the PAS of the AChE and forms to be the AChE-A β complex. This complex is shaped together in the brain and is described as a neurotoxic agent. Latest pharmacological data expressed that the AChE-A β complex displayed more neurotoxicity than A β alone [23,24]. Additionally, the AChE in the complex is still function [22].	Inhibit the AChE-A β complex formation by inhibit the activity of AChE at PAS

Table 3: The traditional versus more recent concepts of cholinergic hypothesis and the expected characteristic of the novel Alzheimer's drug replacement (Cont.)

The Traditional Concept	More Recent Concepts	Expected Characteristic of the Novel Alzheimer's Drug Candidate
	The inhibition of AChE and BuChE can reduce oxidative stress through the cholinergic anti-inflammatory pathway [25,26]. The mechanism of this pathway is the increasing of acetylcholine neurotransmitters and maintains the viability of healthy neurons, which indirectly preserve neuronal cells from oxidative stress destruction [26].	Protect the neuronal cells from oxidative stress and neuro-inflammation

In summary, the cholinergic theory is clearly indicated to be a main target of Alzheimer's treatment, and the recent additional knowledge of AChE-A β complex formation can be applied to the design a candidate for treatment of AD. The

challenge question is raised that is it better if we have a drug candidate which acts as a multi targeting agent and safes to use in human?

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