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REVIEW ARTICLE

Therapeutic Potential of Multifunctional Tacrine Analogues

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Abstract: Tacrine is a potent inhibitor of cholinesterases (acetylcholinesterase and butyrylcholinesterase) that shows limiting clinical application by liver toxicity. In spite of this, analogues of tacrine are considered as a model inhibitor of cholinesterases in the therapy of Alzheimer's disease. The interest in these compounds is mainly related to a high variety of their structure and biological properties. In the present review, we have described the role of cholinergic transmission and treatment strategies in Alzheimer's disease as well as the synthesis and biological activity of several recently developed classes of multifunctional tacrine analogues and hybrids, which consist of a new paradigm to treat Alzheimer's disease. We have also reported potential of these analogues in the treatment of Alzheimer's diseases in various experimental systems.

Keywords: Multifunctional tacrine analogues, tacrine hybrids, Alzheimer's disease, cholinergic transmission, neuroprotective activity, hepatoprotection.

1. INTRODUCTION

Alzheimer disease (AD) is irreversible and progressive neurodegenerative disorder, including mainly the elderly people. The most important risk factor for AD is age. It is estimated that the number of patients around the world will have tripled in the middle of this century [1]. AD is becoming an increasing challenge for both the health care system and society because the number of elderly people is still growing. Therefore, it is an urgent need for the development of new more effective drugs to be used in the treatment of AD. Although the knowledge on etiology, genetics and pathophysiological mechanism of AD has been extended, we still have not found effective treatment [2]. At the initial stages of the AD, there is growing deterioration of cognitive functions including memory, reasoning, speech, computational skills, praxis and information processing as well as executive function such as ability to plan, self-control, sequencing and monitoring of complex behaviours [3]. The current pharmacological therapy for AD based on the cholinergic hypothesis. With the exception of memantine, a partial antagonist of *N*-methyl-D-aspartate (NMDA) receptor, all drugs that are used today based on increasing the cholinergic transmission by inhibiting cholinesterases. Donepezil **1** (1996 year) [4] and galantamine **2** (2001 year) [5] are selective inhibitors of acetylcholinesterase (AChE), while rivastigmine **3** (2000 year) also inhibits butyrylcholinesterase (BChE) [6] (Fig. **1**). Unfortunately, inhibitors of cholinesterases are not able to stop the development of AD and can only improve cognitive function. Accordingly, it is highly desirable to develop new effective therapeutic strategies to stop or slow progression of AD [7]. Because of AD complexity, the cure paradigm is now shifted to the designing of a single chemical compounds having multiple biological activities and termed as "multifunctional drugs" [8]. The "multifunctionality" is the result of the interaction of chemical substances with various molecular targets. In case of traditional drugs, coformulation of two or more drugs in a single dosage, due to varied metabolism among the patients, can produce highly complex pharmacokinetics as well as pharmacodynamic relationships [9]. Moreover, drug-drug interactions could lead to severe side effects [10]. The advantages of multifunctional compounds including additive or synergistic therapeutic responses, prolonged duration of effectiveness, improved drugable characteristics and more predictable pharmacokinetics and pharmacodynamics relationships [11].

The present review describes the role of cholinergic transmission in Alzheimer's disease and current therapeutic strategies as well as sums up the synthesis of multifunctional tacrine derivatives, which despite inhibitory activity on AChE and BChE, showing additional function according to the current therapeutic approaches.

2. CHOLINERGIC TRANSMISSION AND ALZHEIMER'S DISEASE

The cholinergic system is one of the most important neurotransmitter systems in the brain. The major cholinergic innervation including the limbic system, which is associated with emotions, learning and memory as well as vegetative and survival behaviours [12-14]. Limbic system is anatomi-

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