European Journal of Medicinal Chemistry 132 (2017) 294–309

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Review article

Recent progress in the identification of selective butyrylcholinesterase inhibitors for Alzheimer's disease

Qi Li [a], Hongyu Yang [a], Yao Chen [b], Haopeng Sun [a, *]

[a] Department of Medicinal Chemistry, China Pharmaceutical University, Nanjing, 210009, China
[b] School of Pharmacy, Nanjing University of Chinese Medicine, Nanjing, 210023, China

ARTICLE INFO

Article history:
Received 24 December 2016
Received in revised form
13 March 2017
Accepted 25 March 2017
Available online 27 March 2017

Keywords:
Alzheimer's disease
Selective butyrylcholinesterase inhibitors

ABSTRACT

Alzheimer's disease (AD) is one of the most prevalent neurodegenerative disorders with notable factor of dysfunction in cholinergic system. Low ACh level can be observed in the pathogenesis of AD. Several AChE inhibitors have already been used for clinical treatments. However, other than normal conditions, ACh is mostly hydrolyzed by BuChE in progressed AD. Account for an increased level of BuChE and decreased level of AChE in the late stage of AD, development of selective BuChE inhibitor is of vital importance. Up till now, compounds with various scaffolds have been discovered to selectively inhibit BuChE. Different effective anti-BuChE molecules are concluded in this review.

Contents

1. Introduction

Neurodegenerative disease is a typical type of debilitating and fatal diseases, caused by chronic progressive central nervous system degeneration, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington disease (HD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), *etc*. It is characterized by loss, deterioration and dysfunction of a large number of specific neurons [1]. With the aging of the population, neurodegenerative disease has become a serious medical problem in modern society. Due to its severity and complexity, the treatment meets lots of difficulties. In recent years, as the research of neurodegenerative disease deepening, the therapeutic strategies and drugs targeting different pathogenesis are emerging. However, so far, few drugs have been clinically applied in curing this disease, especially in treatment for AD.

AD is one of the most common neurodegenerative disorders characterized as dementia, memory loss and cognitive impairment

* Corresponding author.
E-mail address: sunhaopeng@163.com (H. Sun).

http://dx.doi.org/10.1016/j.ejmech.2017.03.062
0223-5234/

with aging [2]. As summarized in *World Alzheimer Report 2016*, 47 million people are living with dementia worldwide, and this number is estimated to increase to more than 131 million by 2050 [3]. Thus, enormous material and financial resources are gradually devoted into treatment of AD, but its complex pathology is still not clear. Low level of acetylcholine (ACh) [4], β-amyloid (Aβ) aggregation [5], tau-protein hyperphosphorylation [6] and oxidative stress [7], *etc.* are all responsible for pathogenesis of AD.

The most popular explanation of mechanism of AD development is cholinergic hypothesis, which directly contributes to cognitive decline [8]. Moreover, it has been found that amyloid protein plaques can be caused by both cholinesterases (ChEs), named as acetylcholinesterase (AChE EC 3.1.1.7) and butyrylcholinesterase (BuChE EC 3.1.1.8), and using the inhibitors can decrease those plaques [9]. In fact, abnormalities in cholinergic system are also closely related to other neurodegenerative disorders, such as PD, dementia with Lewy bodies and vascular dementia [10,11]. Normally, ACh can be hydrolyzed by both AChE and BuChE. Histochemically, AChE is mostly of neuronal origin, while BuChE is mostly of glial origin [12]. Under normal conditions, ACh is dominantly decomposed by AChE instead of BuChE, while the physiological role of BuChE is still unclear [13,14]. Although BuChE is considered as a minor role in regulating brain ACh level, it has been reported to correlate with drug metabolism and detoxification. Besides, BuChE is closely associated with lipoprotein metabolism and diseases like obesity, cardiovascular disease and hepatic adiposity, *etc.* [15] There are no physiological defects in BuChE knockout mice [16]. Similarly, BuChE silent people can also live healthily to an old age [17]. However, in progressed AD, level of AChE in brain declines to 55–67% of normal values while BuChE increases to 120% of normal levels, indicating that BuChE plays a critical role for ACh hydrolysis in the late stage of AD [18,19]. Patients with AD have elevated level of BuChE in the neocortex and limbic structures, such as hippocampus and amygdala [20]. Ratio of BuChE: AChE shifting from 0.6 to as high as 1.1 contributes to the formation of cholinergic deficits in these regions, leading to the behavioral and cognitive dysfunction [21]. The potential importance of BuChE has been demonstrated by the AChE knockout mice model, in which BuChE compensates for the lack of AChE, maintaining normal cholinergic pathways in AChE nullizygous animals [12,22]. Moreover, it has also been confirmed by substitution for AChE in the neuromuscular junction of AChE nullizygotes [23]. It has been observed that BuChE can hydrolyze ACh surrogating AChE in the presence of a specific AChE inhibitor in human brain [24]. Nowadays, the application of AChE inhibitors seems to be the most helpful way to restore ACh level [9]. However, patients with "classical" AChE inhibitors may get some side-effects like nausea and vomiting, which are results of an accompanying undesirable inhibition of peripheral ChEs [25].

2. Structure details of BuChE

The overall structures of two cholinesterases are very similar. Both of them contain a catalytic active site (CAS), a deep gorge and a peripheral anionic site (PAS). There are almost 65% homologic amino acid sequences in AChE and BuChE [26]. Catalytic triads of human AChE (*h*AChE) and human BuChE (*h*BuChE) consist of conserved amino acids: Ser203, His447, Glu334 in *h*AChE and Ser198, His438, Glu325 in *h*BuChE [27]. However, the presence and extent of residues within the gorge are different, especially showed by acyl-binding pocket, which contains an acyl moiety to catalyze the substrate [28]. Crystal structures of two ChEs are shown in Fig. 1A (AChE, PDB id: 4ey4) and Fig. 1B (BuChE, PDB id: 1p0i). Residues of *h*AChE in acyl-binding site are Phe295 and Phe297, while those of *h*BuChE are Leu286 and Val288. Two aromatic residues of *h*AChE protruding into the gorge partly occupy the space, while replacement by smaller residues in *h*BuChE provides a wider space and allows larger substrates to bind to and be hydrolyzed [28]. Different structural features of the two enzymes contribute to their substrate specificity: AChE has higher selectivity for small molecules like ACh, while BuChE has more affinity for various neuroactive peptides [29]. Hence, it provides a reasonable thought to design selective BuChE inhibitors.

3. Biological functions of BuChE and medical application

BuChE is an α-glycoprotein found in the central and peripheral nervous systems, with a 12-day half-life [30,31]. It is a nonspecific or pseudocholinesterase or serum cholinesterase, hydrolyzing both choline and aliphatic esters. Besides AD progression, an increased activity of this enzyme has been demonstrated in uremia, hyperthyroidism, obesity, diabetes, and in hyperlipidemic subjects [32–34].

BuChE is synthesized in the liver; plasma level declines in acute or chronic liver damage, cirrhosis and liver metastases [35]. In addition, its activity as well has an association with serum concentrations of cholesterol and triglycerides [36,37]. Because of the knowledge above, BuChE plays a pivotal role in many diseases.

3.1. Protein-energy malnutrition (PEM) and inflammation

It has been reported that inflammation is the key factor in the pathophysiology of PEM, by influencing appetite and gastrointestinal motility [34]. For its short half-life, serum BuChE usually acts as a nutritional and prognostic marker for clinical conditions and nutritional status [30]. Level of BuChE falls in patients with PEM, probably for inadequate availability of substrates for synthesis.

BuChE level significantly declines in hospitalized patients diagnosed with protein-energy visceral undernutrition, which is a condition strictly linked with low values of albumin, transferrin, total lymphocyte count and other visceral proteins [38]. In malnourished children with marasmus or kwashiorkor, it has been found that serum BuChE is lower than that in normal children, but increases after three weeks of nutritional rehabilitation [31]. Similarly, in a 200 malnourished infants study, the degree of edema has an inverse relationship with BuChE levels [39]. Thus, BuChE activity seems to be a reliable indicator of patient conditions in the case of malnutrition and inflammation.

Terminal cancer is a condition probably induced by inflammation, with decreased plasma BuChE level. One possible mechanism may be secondary anorexia accompanying with malignancy [40]. In an experiment, 126 hospitalized cancer patients with low serum BuChE level (below 1900 IU/L) underwent a nutritional assessment

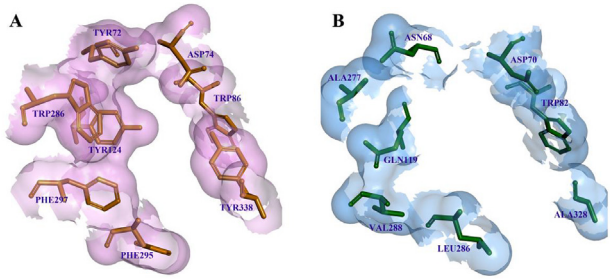

Fig. 1. Differences of crystal structures and acyl-binding pockets of *h*AChE (A, PDB id: 4ey4) and *h*BuChE (B, PDB id: 1p0i). Atoms are represented in orange for *h*AChE and in green for *h*BuChE. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)