Review

Biological Psychiatry

Consequences of Pharmacological BACE Inhibition on Synaptic Structure and Function

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ABSTRACT

Alzheimer's disease is the most prevalent neurodegenerative disorder among elderly persons. Overt accumulation and aggregation of the amyloid β peptide (Aβ) is thought to be the initial causative factor for Alzheimer's disease. Aβ is produced by sequential proteolytic cleavage of the amyloid precursor protein. Beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) is the initial and rate-limiting protease for the generation of Aβ. Therefore, inhibiting BACE1 is considered one of the most promising therapeutic approaches for potential treatment of Alzheimer's disease. Currently, several drugs blocking this enzyme (BACE inhibitors) are being evaluated in clinical trials. However, high-dosage BACE-inhibitor treatment interferes with structural and functional synaptic plasticity in mice. These adverse side effects may mask the therapeutic benefit of lowering the Aβ concentration. In this review, we focus on the consequences of BACE inhibition–mediated synaptic deficits and the potential clinical implications.

Keywords: Alzheimer's disease, BACE inhibitor, BACE1, Dendritic spines, On-target side effects, Synaptic plasticity

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BACE1: A THERAPEUTIC TARGET FOR ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is the most common form of senile dementia. It is a huge burden for patients, relatives, and health care systems worldwide. The two typical neuropathological hallmarks of AD are senile plaques and neurofibrillary tangles, which are composed of aggregated amyloid β peptide (Aβ) and hyperphosphorylated tau protein, respectively (1). Aβ is the product of sequential proteolytic cleavage of the amyloid precursor protein (APP) by the beta-site APP cleaving enzyme 1 (BACE1) and the gamma-secretase complex. BACE1 is the rate-limiting enzyme of the amyloidogenic pathway (2,3) and thus is considered one of the major therapeutic targets for the treatment of AD (4,5).

BACE1 is a transmembrane aspartic protease with a luminal active site that sheds the ectodomain of membrane proteins (6). BACE1 is mainly expressed in the central nervous system. BACE1 has more than 40 membrane protein substrates, including APP, seizure protein 6 (SEZ6), and close homologue of L1 (CHL1) (6–10). Under physiological conditions, BACE1 substrates are processed in acidic compartments, such as the trans-Golgi network and endosomes, where BACE1 displays its maximum proteolytic activity (11,12). Knockout of *Bace1* almost completely abolishes Aβ production in wild-type (WT) and transgenic APP mouse models (13,14). Therefore, BACE1 is considered the principal enzyme for initiating Aβ generation (9). Recently, a rare APP mutation ($App^{Ala673Thr}$) was discovered in elderly members of the Icelandic population, called Icelandic mutation; this mutation protects against AD and age-related cognitive decline. The mutation site is located close to the β-cleavage site of APP. It reduces Aβ generation by 40% in vitro by preventing β cleavage of APP and shifting the BACE1 cleavage to the β′ site (15,16). The Icelandic mutation also affects the aggregation properties of Aβ (15–18). One allele with the $App^{Ala673Thr}$ mutation reduces the production of Aβ by 20% (19).

In past decades, both academia and industry invested substantial resources into developing chemical compounds to inhibit BACE1 function. Most of them inhibit the activity of both BACE1 and BACE2 (20–23). Therefore, they are called "nonselective" BACE inhibitors. Although BACE2 is also expressed in the brain, the protein level of BACE2 is much lower than that of BACE1 (24–26). The neurophysiological functions of BACE2 and its substrates are not yet clear. Several BACE inhibitors are currently being tested in phase 2 and/or 3 trials (Table 1). Although BACE inhibition effectively reduces Aβ levels in a dosage-dependent manner, the recent EPOCH (Efficacy and Safety Trial of Verubecestat [MK-8931] in Mild to Moderate Alzheimer's Disease) and APECS (Efficacy and Safety Trial of Verubecestat [MK-8931] in Participants With Prodromal Alzheimer's Disease) trials failed to rescue cognitive decline in prodromal AD patients.

BACE1 is located in various subcellular compartments within neurons, including the soma and neurites as well as synapses. It mainly localizes in early endosomes or transport vesicles (Figure 1) (27–29). The transportation of BACE1 within neurites occurs via trafficking vesicles. For the anterograde axonal transport, BACE1 is transferred with APP, and this cotransport is regulated by calsyntenin-1 (30). Under physiological conditions, part of the APP protein is cleaved by BACE1 in these vesicles (30,31). The retrograde trafficking of BACE1 is regulated by vacuolar protein sorting-associated protein 35 in

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Table 1. Ongoing BACE-Inhibitor Clinical Trials

Compound	Company	Trial Phase	NCT Number[a]	Doses (mg)	Aβ Reduction, % (mg)[b]	Patient Population	Expected Completion Year
CNP520	Novartis, Amgen	2/3	NCT02565511 NCT03131453	50 15/50	~60 (10) ~80 (35)	Asymptomatic at-risk persons (APOE4)	2023 2024
AZD3293 (LY3314814)	Eli Lilly, AstraZeneca	2/3	NCT02783573 NCT02972658 NCT02245737 NCT03019549	 20/50 	~60 (20) ~80 (50) 	Early and mild AD	2021 2020 2019 2017
LY3202626	Eli Lilly	2	NCT02791191		~50 (1)	Mild AD	2019
Elenbecestat (E2609)	Eisai, Biogen	2/3	NCT02322021 NCT03036280 NCT02956486	 50	~50 (5) ~80 (50) 	Early AD	2020 2020 2020
JNJ-54861911	Janssen	2/3	NCT02569398 NCT02406027	5/25 5/10/25	~50 (5) ~80 (25)	Asymptomatic at-risk persons and early AD	2023 2022
Verubecestat (MK-8931)	Merck	2/3 3	NCT01739348 NCT01953601	12/40/60 12/40	~50 (12) ~80 (40)	Prodromal AD	2017 2018

Aβ, amyloid β peptide; AD, Alzheimer's disease; BACE, beta-site amyloid precursor protein cleaving enzyme; NCT, National Clinical Trial.
[a]Numbers refer to the study codes in the ClinicalTrials.gov database.
[b]Data from preclinical human studies or phase 1 studies.

both axons and dendrites (32). In addition, Ras-related protein Rab-11b GTPase is involved in regulating the bidirectional transportation of BACE1 in axons (33). Posttranslational modifications (e.g., s-palmitoylation) are also involved in modifying the distribution of BACE1 within neurons (34). A recent report demonstrated that BACE1 is located at both pre- and postsynaptic compartments (29), indicating that it has important synaptic functions. BACE1 accumulates within axonal dystrophies at Aβ plaques in AD mouse models and patients with AD (28,35). This pathological BACE1 accumulation might directly facilitate the local generation of Aβ and thereby further promote the deposition of Aβ (36,37).

BACE1 has many substrates, indicating that it may be involved in various physiological functions (38,39). Knocking out *Bace1* in mice (*Bace1*$^{-/-}$) leads to a number of physiological and behavioral deficits, including increased astrogenesis and impaired maturation and migration of newborn neurons (40,41), impaired axon myelination during development (42,43), axon guidance errors in the olfactory bulb and hippocampus (44,45), impaired remyelination in injured sciatic nerves in adult mice (46), and reduced muscle spindle density resulting in a swaying walking pattern and motor deficits (47), as well as decreased anxiety (48). BACE1 is involved in these physiological functions via its substrates. Several of these substrates are located at the synapse and have a critical role in synaptic function and plasticity (Table 2). In this review, we focus on the functions of BACE1 and its substrates at the synapse.

PHYSIOLOGICAL FUNCTIONS OF BACE1 AT THE SYNAPSE

Role of BACE1 for Synaptic Structure

A synapse is the junction formed between two neurons, which transmits electrical or chemical signals from one to the other cell. The postsynaptic compartment of excitatory synapses, the dendritic spine, is a dynamic structure that can change its shape within minutes, and such a change may persist over weeks to months. The term "structural plasticity" refers to the ability of dendritic spines to change their physical structure (49–51). Increased spine formation and stabilization is associated with learning and memory (51). Synapse loss and impairment of synaptic plasticity are thought to be the most important mechanism for dementia (52).

BACE1 Function in Presynaptic Structures. As mentioned above, BACE1 is located at presynaptic terminals and is especially enriched in mossy fiber terminals (28,45). In *Bace1*$^{-/-}$ mice, mossy fiber terminals have normal ultrastructure (28); however, the infrapyramidal bundle of mossy fibers is significantly shorter, indicating a potential alteration in axonal outgrowth (45,53). Abnormal axonal growth might be due to reduced β cleavage of contactin-2, a cell adhesion molecule that is important for regulating axon guidance and pathfinding (53,54). Furthermore, abnormal axonal growth-cone collapse has also been observed in both *Bace1*$^{-/-}$ and BACE inhibitor–treated mice (44,55,56). It has been suggested that the altered function of the neural cell adhesion molecule CHL1 is involved in this process (57). Cleavage of CHL1 by BACE1 generates an N-terminal fragment (CHL1-NTFβ) (7), which is critical for the function of growth cone in thalamic neurons by its interaction with semaphorin 3A (56).

BACE1 Function in Postsynaptic Structures. BACE1 is also located within dendritic spines (29). The density and plasticity of dendritic spines in *Bace1*$^{-/-}$, *Bace1*$^{+/-}$, and BACE-inhibited WT mice has been studied by various groups (58–62). The total spine density is significantly reduced in the hippocampal CA1 region of *Bace1*$^{-/-}$ mice (63). Moreover, the proportion of mushroom spines is also significantly lower. This finding is concurrent with the reduction of postsynaptic density protein 95 (PSD95) (63). These changes might be the consequences of an altered BACE1 cleavage of the presynaptic protein neuregulin 1 type III (47,64,65). Indeed, neuregulin 1 type III accumulation is known to cause a reduction in the density of dendritic spines by altering the