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Review

Alzheimer's secretases regulate voltage-gated sodium channels

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ABSTRACT

BACE1 and presenilin (PS)/γ-secretase are primary proteolytic enzymes responsible for the generation of pathogenic amyloid β-peptides (Aβ) in Alzheimer's disease. We and others have found that β-subunits of the voltage-gated sodium channel (Na_vβs) also undergo sequential proteolytic cleavages mediated by BACE1 and PS/γ-secretase. In a follow-up study, we reported that elevated BACE1 activity regulates total and surface expression of voltage-gated sodium channels (Na_v1 channels) and thereby modulates sodium currents in neuronal cells and mouse brains. In this review, we focus on the molecular mechanism of how BACE1 and PS/γ-secretase regulate Na_v1 channels in neuronal cells. We will also discuss potential physiological and pathological roles of BACE1- and PS/γ-secretase-mediated processing of Na_vβs in relation to Na_v1 channel function.

Alzheimer's disease (AD) is the most common cause of dementia in the elderly [2]. AD patients lose their ability to acquire new memories and the capacities for reasoning, abstraction, and language skills. In addition, AD patients in late stages frequently show severe personality changes and various neuropsychiatric symptoms, including depression, aggressiveness, agitation, and generalized anxiety [1,70]. Epileptic and myoclonic seizures are common in early-onset AD patients with familial presenilin mutations, but are also frequently found in late-onset forms of the disease [9,17,18,31].

Two major pathological hallmarks of AD are extracellular amyloid deposits (senile plaques) and hyperphosphorylated tau protein in neurofibrillary tangles [54]. Amyloid deposits are composed predominantly of amyloid β peptides (Aβ), central in AD pathogenesis [16,47]. Aβ is generated from sequential cleavage of the amyloid β precursor protein (APP), mediated by β-site APP cleaving enzyme 1 (β-secretase, memapsin 2, BACE1) and presenilin/γ-secretase (PS/γ-secretase).

In neuronal as well as non-neuronal cells, APP undergoes two distinctive cleavage pathways mediated by α-/γ- or β-/γ-secretases (Fig. 1). Cleavage by α-secretase gives rise to a soluble extracellular domain (sAPP-α) and a C-terminal fragment (C83) that is further processed by PS/γ-secretase to generate p3 fragment and an intracellular domain (AICD, Fig. 1A). In β-/γ-secretase pathway, APP is first cleaved by BACE1 to generate sAPPβ and C99 that is then converted to AICD and Aβ by PS/γ-secretase activity (Fig. 1B).

BACE1 is a membrane-bound aspartic protease that is highly expressed in the brain [22,51,56,67]. PS/γ-secretase is a membrane protease complex consisting of Nicastrin, Aph-1, Pen-2, and a catalytic component PS, which is ubiquitously expressed in various tissues [49]. These proteases have been extensively studied to understand their pathological roles in Alzheimer's disease. A number of studies have suggested that altered BACE1 and/or PS/γ-secretase activity play important roles in the pathogenesis of sporadic and familial AD by modulating Aβ generation [3,12,14,49,55,68]. In addition to their pathological roles, mouse knockout studies have also demonstrated that these proteases play important physiological roles in brain function. BACE1-null mice show cognitive and behavioral deficits together with altered electrophysiological properties in neurons [11,30,46,59]. BACE1-null mice even display spontaneous behavioral seizures [21]. Deficits in sodium channel may contribute to these phenotypes since hippocampal neurons from BACE1-null mice display a positive shift in voltage-dependent sodium current inactivation as well as an increase in sodium current densities as compared to control wild-types [11,21]. Adult-specific deletion of PS also induces deficits in synaptic plasticity and presynaptic function and even neurodegeneration in mice [45,50,69,71]. These deficits likely derive from altered cleavages of neuronal substrate proteins of BACE1 and/or PS/γ-secretase.

In addition to APP, dozens of additional BACE1 substrates and PS/γ-secretase substrates have been reported to date. This supports the proposed multifunctional roles of BACE1 and PS/γ-secretase

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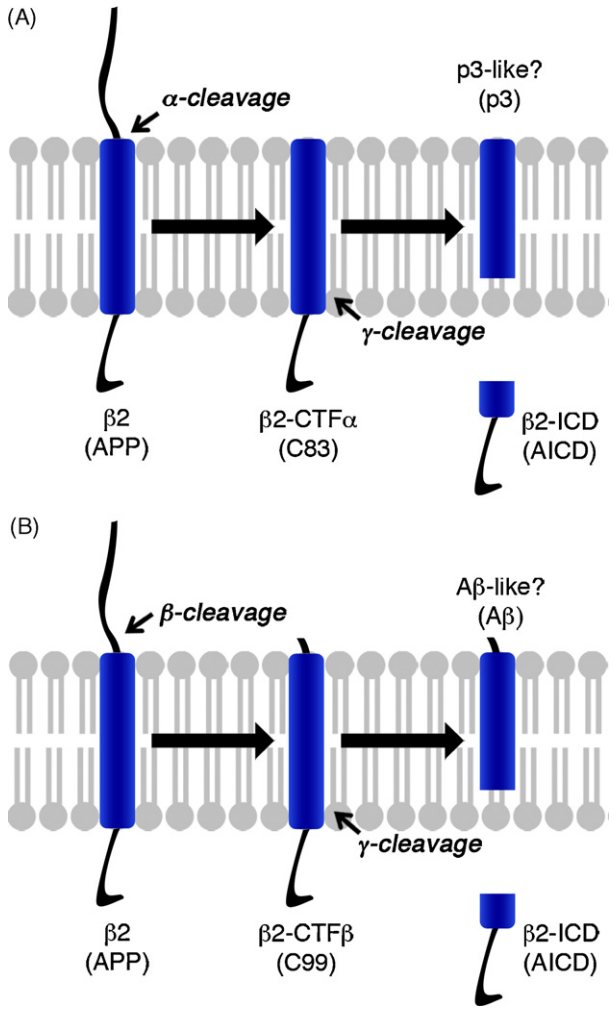

Fig. 1. APP and $Na_v\beta_2$ are processed via similar cleavage pathways. (A) In the non-amyloidogenic pathway, APP/β2 undergo extracellular domain shedding by α-secretase and is subsequently cleaved by PS/γ-secretase to produce β2/APP intracellular domain (AICD/β2-ICD). (B) In the amyloidogenic pathway, APP/β2 first undergo an extracellular domain shedding by BACE1. A membrane-tethered C-terminal fragment, C99/β2-CTFβ, is then cleaved by PS/γ-secretase to produce AICD/β2-ICD and the amyloid β peptide (Aβ).

[35,49,57]. While most PS/γ-secretase substrates undergo a sequential cleavage pathway regulated by α-/γ-secretase, only a few PS/γ-secretase substrate proteins also undergo an alternative β-/γ-secretase cleavage pathway similar to APP. In brains, Neuregulins 1, 3 (NRG-1, 3) and β-subunits of the voltage-gated sodium channel ($Na_v\beta$s) are reported as cleaved by both BACE1 and PS/γ-secretase under physiological conditions [19,20,28,29,64,65].

Similar to APP, $Na_v\beta_2$ is processed by two distinctive cleavage cascades mediated by α-/γ-secretase or β-/γ-secretase (Fig. 1). Cleavage by α-secretase (ADAM10) gives rise to a C-terminal fragment (β2-CTFα) that is further processed by PS/γ-secretase activity to generate an intracellular domain (β2-ICD, Fig. 1A). In the β-/γ-pathway, $Na_v\beta_2$ is first cleaved by BACE1 to generate β2-CTFβ and then converted to β2-ICD by PS/γ-secretase activity (Fig. 1B). It is not clear yet whether PS/γ-secretase -meditated processing of β2-CTFs also generates Aβ-like peptides.

$Na_v\beta$s assemble with channel-forming α-subunits and regulate cell surface expression and inactivation channel kinetics of the voltage-gated sodium channels (Na_v1 channels) [6,7,24,25]. In addition, $Na_v\beta$s interact with neuronal adhesion molecules and therefore play a role in neuronal adhesion and migration [4,5,25,34]. While all the β-subunits ($Na_v\beta$1–4) are cleaved by

Table 1
Summary of Na_v1 channel changes by elevated BACE1 activity.

	Neuroblastoma cells with BACE1 overexpression	BACE1-transgenic mouse brains
Full-length $Na_v\beta2$	↓[a]	↓[a]
$Na_v\beta^2$-CTF	↑	↑
β2-ICD	↑	N/D[b]
scn1a ($Na_v1.1$) mRNA	↑	↑
$Na_v1.1$ total protein	↑	↑
$Na_v1.1$ surface protein	↓	↓[c]
Na^+ current density	↓	↓[c]

[a] Moderate or slight decrease.
[b] Not detected.
[c] Na_v1 channel surface levels and sodium current density are analyzed in hippocampal neurons acutely dissociated from BACE1-transgenic mice.

BACE1 and PS/γ-secretase *in vitro*, only $Na_v\beta_2$ and $Na_v\beta_4$ have been shown as physiological BACE1 substrates in mouse brains [65]. Our laboratory focused on $Na_v\beta_2$ because of its neuron-specific expression and primary role in regulating sodium channel α-subunits in hippocampus and cortex [8,26].

One of the well-known PS/γ-secretase functions is to modulate signaling cascades via "regulated intramembrane proteolysis" or RIP of specific proteins [35,48]. For example, PS/γ-secretase-mediated cleavage of the Notch receptor releases a membrane-bound intracellular domain (NICD) that localizes to the nucleus and regulates target gene transcription [48]. Since PS/γ-secretase-mediated cleavage of $Na_v\beta_2$ also releases β2-ICD, we investigated whether PS/γ-secretase can initiate RIP by cleaving $Na_v\beta_2$. To directly address a potential nuclear function of β2-ICD, we generated a recombinant β2-ICD fragment and expressed it in rat and human neuroblastoma cells. We found that this recombinant β2-ICD fragment localized to the nucleus and specifically increased both protein and mRNA levels of a sodium channel α-subunit, $Na_v1.1$ [28]. Elevated BACE1 activity increased β2-ICD levels and thereby $Na_v1.1$ levels while the inhibition of BACE1 or PS/γ-secretase activity significantly decreased $Na_v1.1$ levels in neuroblastoma cells and cultured primary neurons [28,29]. We also found that levels of $Na_v\beta_2$ cleavage products and $Na_v1.1$ α-subunits were increased in brains of BACE1-trangenic mice as compared to wild type controls [28], summarized in Table 1. Although further studies are required to see whether β2-ICD interacts with other transcriptional machinery to regulate gene transcription under physiological conditions, our data suggest a novel mechanism of Na_v1 channel regulation through RIP of $Na_v\beta_2$.

When we checked whether elevated total $Na_v1.1$ levels increased voltage-dependent sodium currents, paradoxically we found that BACE1 elevation dramatically decreased sodium current density and surface levels of Na_v1 α-subunits in neuroblastoma cells and hippocampal neurons [28], see Fig. 2. These results strongly suggest that $Na_v1.1$ α-subunits resulting from $Na_v\beta_2$ cleavage followed by increased $Na_v1.1$ α-subunit mRNA, are not translocated into the plasma membrane (Fig. 2). One possibility is that the intracellular accumulation of $Na_v1.1$ precursors may directly or indirectly interfere with Na_v1 channel trafficking. In the same publication, we have shown that elevated BACE1 activity induces $Na_v1.1$ accumulation in an unusual HSP70-positive intracellular compartment [28]. It is interesting to note that elevated BACE1 activity induces impaired trafficking of APP along axons, similar to the impaired trafficking of Na_v1 α-subunits to the cell surface [32]. It is also possible that highly elevated BACE1 depletes $Na_v\beta$s, and in particular $Na_v\beta_2$, that is required for surface expression of Na_v1 α-subunits. However, we were still able to detect significant amount of intact $Na_v\beta_2$ in brains of BACE1-transgenic mice [8,28].

BACE1 may also alter sodium currents by modulating additional α-subunits in addition to $Na_v1.1$. Hu et al. have recently

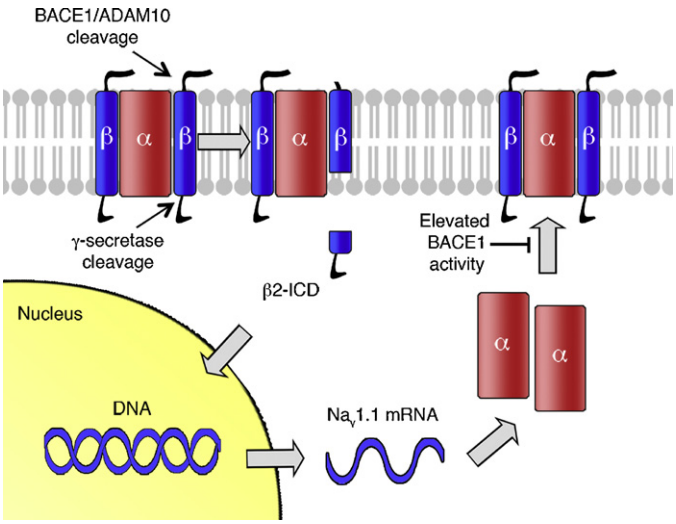

Fig. 2. Schematic representation of Na_v1 channel regulation by BACE1/ADAM10 and γ-secretase. $Na_v\beta_2$ undergoes ectodomain shedding by either α- (ADAM10) or β-secretase (BACE1). The resulting membrane-tethered C-terminal fragments are further cleaved by PS/γ-secretase to release β2-ICD, which then localizes to the nucleus. β2-ICD increases mRNA and protein levels of $Na_v1.1$ α-subunit levels. However, elevated BACE1 activity also interferes with the trafficking of Na_v1 α-subunits to cell surface.

shown that axonal and surface levels of $Na_v1.2$ are significantly increased in hippocampal neurons from BACE1-null mice [21]. Similarly, elevated BACE1 activity may decrease surface levels of $Na_v1.2$, contributing to the dramatic decrease of sodium currents that we have observed in BACE1-transgenic mice [28]. In addition, Huth et al. reported that overexpressed BACE1 can induce a hyperpolarizing shift of $Na_v1.2$ current activation in cultured cell lines [23]. However, this finding does not explain the observed BACE1-mediated decrease of sodium current density in adult hippocampal neurons [28]. Further studies are required to clarify the molecular mechanism underlying BACE1-mediated regulation of Na_v1 channel trafficking. These data suggest the interesting possibility that elevated BACE1 activity specifically modulates the surface expression of membrane proteins essential for neuronal function, such as sodium channels and APP.

$Na_v\beta$s interacts with various neuronal proteins including contactin, tenascin, neurofascin, NrCAM, receptor protein tyrosine phosphatase β (RPTPβ), and ankyrinG [4,5,10,25,27,34,36,37,66]. These interactions are reported to modulate axonal localization of Na_v channels, surface expression, and even neuronal cell adhesion and migration [5,10,27,34,36]. BACE1 and/or PS/γ-secretase mediated cleavage of $Na_v\beta$s may affect these interactions and potentially modulate these functions. Interestingly, we found that blockage of $Na_v\beta_2$ cleavage by PS/γ-secretase inhibitors interferes with cell-cell adhesion and migration in cultured cells [29]. In addition, BACE1-mediated processing of $Na_v\beta_4$ increases neurite extention in Neuro2a cells [38]. These data suggest an additional molecular mechanism potentially contributing to BACE1/γ-secretase mediated regulation of neuronal function.

BACE1 and presenilins are directly involved in AD pathology in specific groups of patients. BACE1 activity and levels are significantly increased in brains of a subset of AD patients, possibly contributing to Aβ accumulation [12,55,68]. Elevated BACE1 levels in AD mouse models increase Aβ generation and deposition [72]. Mutations in PS1 and PS2 are tightly associated with early-onset familial Alzheimer's disease (FAD) and all PS FAD mutations alter Aβ generation by modulating PS/γ-secretase activity [3,14,49]. Altered activities of these secretases may affect Na_v1 channel metabolism as well as Aβ generation through the regulation of $Na_v\beta$ cleavages. We have already found that $Na_v\beta_2$ C-terminal fragment and $Na_v1.1$ α-subunit levels are significantly increased in brains of AD patients with elevated BACE1 activity as compared to age-matched controls [28]. Altered Na_v1 channel metabolism may contribute to neuronal dysfunction and/or neurodegeneration in the course of the disease. Indeed, epileptic and myoclonic seizures are common in early-onset AD with familial presenilin mutations, but are also found in late-onset forms of the disease [17,52,58]. Increased excitatory neuronal activities, so called "silent seizures", are also detected in AD animal models [41–43]. Further studies will be required to test whether elevated BACE1 contributes to AD pathogenesis by altering Na_v1 channels.

Altered expression of sodium channels were reported in multiple sclerosis and chronic pain after nerve injuries [15,60–62]. Interestingly, animal model studies have shown that $Na_v\beta_2$ contributes to the pathogenic mechanism in these conditions by regulating sodium channel metabolism [40,44]. BACE1 levels and activity are increased in some other injury conditions including brain trauma [33] and ischemia [13,53,63]. O'Conor et al. proposed that BACE1 functions as a stress-response protein elevated by phosphorylation of the Translation Initiation Factor eIF2α [39]. The fact that BACE1 regulates Na_v1 channel metabolism through $Na_v\beta_2$ suggests the interesting possibility that BACE1 might modulate sodium channel metabolism not only in AD but also other disease conditions in which BACE1 levels are increased.

In summary, current data strongly suggest that BACE1 and PS/γ-secretase regulate Na_v1 channel metabolism at multiple levels *in vitro* and *in vivo* conditions. Further studies will be required to characterize the exact molecular mechanism underlying this function of Alzheimer's secretases.

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