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The Ups and Downs of BACE1: Walking a Fine Line between Neurocognitive and Other Psychiatric Symptoms of Alzheimer's Disease

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Abstract

Although neurocognitive deficit is the best-recognized indicator of Alzheimer's disease (AD), psychotic and other noncognitive symptoms are the prime cause of institutionalization. BACE1 is the rate-limiting enzyme in the production of Aβ of AD, and one of the promising therapeutic targets in countering cognitive decline and amyloid pathology. Changes in BACE1 activity have also emerged to cause significant noncognitive neuropsychiatric symptoms and impairments of circadian rhythms, as evident from clinical trials and reports in transgenic models. In this study, we consider key characteristics of BACE1 with its contribution to neurocognitive deficit and other psychiatric symptoms of AD. We argue that a growing list of noncognitive mental impairments related to pharmacological modulation of BACE1 might present a major obstacle in clinical translation of emerging therapeutic leads targeting this protease. The adverse effects of BACE1 inhibition on mental health call for a revision of treatment strategies that assume indiscriminate inhibition of this key protease, and stress the need for further mechanistic and translational studies.

Keywords

Nrg1/ErbB signaling, neuregulin, Aβ, peptide, synaptic plasticity, demyelination, neurodegenerative disease

Introduction

The vast majority of biological processes are maintained in a state of controlled equilibrium, warranting the integrity and survival of living organisms in a constantly changing environment. While a considerable shift in the balance is tolerated, providing a window for adaptation and plasticity, excessive and long-term changes in homeostatic indicators can have catastrophic consequences and are incompatible with life (Cannon 1939; Kotas and Medzhitov 2015). One of the best-known examples of controlled physiological equilibrium is the regulation of glucose metabolism by insulin. As the main anabolic hormone of the body, insulin plays a key role in carbohydrate, fat, and protein metabolism, facilitating glucose absorption from blood into the liver, skeletal muscles, and fat cells. Insulin also regulates protein synthesis in a wide variety of tissues (Havel 2002; Wilcox 2005). Due to such an important role, fasting levels of insulin in plasma is maintained within a narrow 20 to 48 pmol/L range. Lasting mild or moderate insulin deficiency is known to cause a devastating metabolic disease—diabetes mellitus, while its acute deficit is life threatening (DeWitt and Hirsch 2003; Nolan and Prentki 2019). On the other hand, an excessive rise of insulin in the blood leads to a severe diseased state known as insulinoma, manifested in seizure and coma, followed by brain damage and death if untreated.

Similar to the whole organism, balanced and finely adjusted processes are of prime relevance for adequate functioning of individual organs, and the brain in particular, where complex and regulated fluxes of ions and neurotransmitters warrant the coordinated activity of myriads of neurons and glial cells. To maintain such complexity in

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working order, a range of metabolically demanding electrochemical carriers and transporters are constantly at work (Ashley 1989; Bezanilla 2008; Nicholls 1994). Tight regulation of dopamine concentration and activity presents an illustrative case, with its pathological decline in basal ganglia linked to the motor symptoms of Parkinson's disease. The pathological rise of this monoamine in the mesolimbic system, on the other hand, leads to neuronal disinhibition in cortical and subcortical circuits, implicated in the positive symptoms of schizophrenia (Iarkov and others 2020; Kesby and others 2018).

Control of the amyloid beta-peptide (Aβ) level in the brain is another well-characterized example of functional equilibrium, with its physiological activity playing a key role in maintaining synaptic homeostasis and plasticity, whereas the pathological rise with conformational changes are viewed as key causatives of Alzheimer's disease (AD) (Long and Holtzman 2019; Panza and others 2019; Selkoe 2003). In extreme cases, a strong increase in extracellular Aβ concentrations has been shown to cause a dramatic inhibition of excitatory neurotransmission with learning and cognition deficits in animal models of AD, attributed largely to the inhibition of postsynaptic receptors, leading to the collapse of dendritic spines and loss of synaptic connections (Ovsepian and others 2018; Shankar and others 2007). Remarkably, cognitive impairments and synaptic dysfunctions have been also reported in association with the reduction in the Aβ activity, or its absence, as evident from studies with pharmacological inhibition of the β-site amyloid precursor protein cleaving enzyme (BACE1), or in experimental mice lacking the *bace1* gene (Filser and others 2015; Hampel and others 2020; Zhu ad others 2018). In light of these findings, it is not surprising that physiological activity and levels of Aβ are kept constant (~150-350 pM), with BACE1 protease playing a rate-limiting role in its production (Lazarevic and others 2017; Waters 2010).

Since its discovery (Vassar and others 1999; Yan and others 1999), BACE1 has attracted much interest due to its relevance to the pathobiology of AD and developing anti-Aβ therapy (see Box 1 in the Supplementary Material available online). Progress in elucidating the neurobiology of BACE1 and its role in neurocognitive deficit in AD has led also to the recognition of its contribution to a variety of noncognitive psychiatric symptoms (Egan and others 2019a; Egan and others 2019b; Forman and others 2019; Savonenko and others 2008), which present the main cause for early institutionalization. Remarkably, the noncognitive signs (see Box 2 in the Supplementary Material available online) have been shown to become more prominent in AD patients in trials of BACE1 inhibitors and can be induced even in healthy controls (Imbimbo and Pomara 2019). In the following, we consider the molecular and functional characteristics of BACE1 related to cognitive and other psychiatric manifestations of AD. We review recent progress in experimental and clinical studies, which suggests a major gap in the understanding of the biology of BACE1, and especially its contribution to mental dysfunctions extending beyond neurocognitive processes.

Biology of BACE1 and Its substrates

BACE1 and its homolog BACE2 are type-I membrane-anchored aspartyl proteases. While the former is highly expressed throughout the nervous system and pancreatic gland, with very low amounts also present in other organs, the latter dominates in the peripheral tissue, showing insignificant presence in the brain (Laird and others 2005; Marcinkiewicz and Seidah 2000; Vassar and others 2009). Within the nervous system, *BACE1* mRNA is primarily localized in neurons, with only trace amounts found in glial or endothelial cells. The two homologs of BACE exhibit strong structural similarity, possessing a conserved catalytic domain made of DSG and DTG active site motifs, a transmembrane domain, and an intracellular C-terminal domain (Cole and Vassar 2008; Shimizu and others 2008; Wang and others 2013). In humans, the *BACE1 gene* is mapped to chromosome 11q23.3, whereas *BACE2* is localized to the region of chromosome 21, which is implicated in diabetes and Down syndrome (Sinha and others 1999; Yan and others 2001). Four variants of BACE1 (432, 457, 476, 501AA) have been identified so far, which are produced via alternative splicing in exon 3 and 4. After initial translation as a pro-peptide BACE1 (pro-BACE1), the N-terminal domain provides a signal for sorting to the Golgi apparatus, where its cleavage by furin at the RLPR motif produces a mature BACE1, ready for trafficking to the functional destination at the cell surface (Benjannet and others 2001; Capell and others 2000). This process is facilitated by casein kinase I phosphorylation, which plays a key role in GGAs (Golgi-localized, gamma ear-containing Arf-binding proteins) guided sorting of BACE1 to transport endosomes and delivery to the surface membrane, where BACE1 is dimerized and recruited into lipid rafts (Bennett and others 2000; Haniu and others 2000; Kang and others 2010). The fully functional mature protease, thus, is made of the extracellular catalytic domain, followed by transmembrane and cytoplasmic intracellular domains. Figure 1a and b) presents a schematic of the molecular structure of BACE1 and its substrates.

On the cell surface, BACE1 integrated into cholesterol-rich lipid rafts can interact and cleave multiple substrates. It is noteworthy that the disulfide bond in the C-terminal domain of BACE1 plays an essential role in maintaining its catalytic stability and quaternary structure (Shimizu and others 2008; Wang and others 2013), while

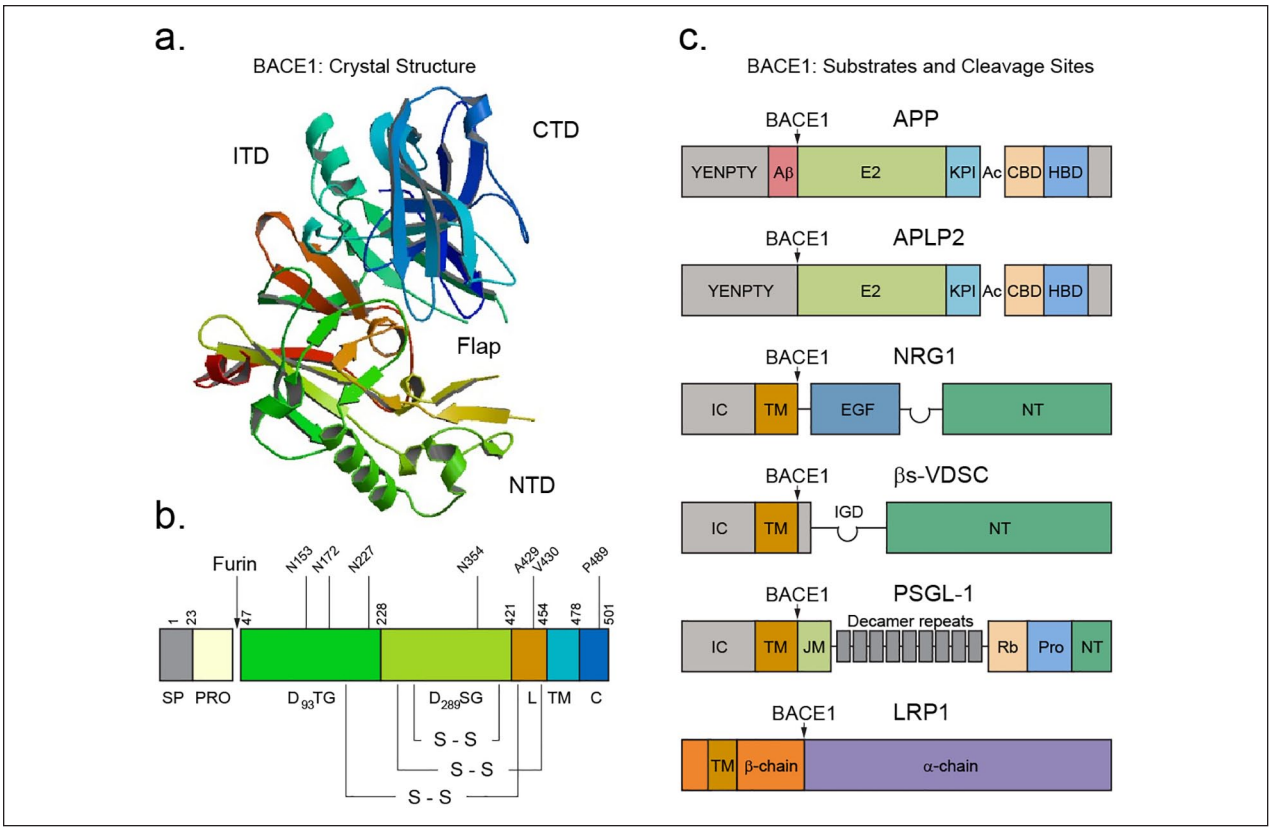

Figure 1. BACE1 structure, main substrates, and their cleavage sites. (a) Crystal structure of the active form of BACE1 at pH 4.0 as determined by X-ray diffraction at a resolution of 2.7 Å (Shimizu and others 2008). CTD = C-terminal domain; NTD = N-terminal domain; Flap = flexible antiparallel β-hairpin; ITD = inhibitor targeting domain. (b) Schematic representation of BACE1 structural organization and domains. Pro-BACE1 is cleaved by furin to become the mature form, BACE1. Numbers refer to the amino acid positions separating various domains or preferential post-translational modification sites. SP = signal peptide; PRO = pro-peptide domain; DTG (aspartic acid [D], threonine [T], and glycine [G]) and DSG (aspartic acid [D], serine [S], and glycine [G]) active site motifs; L = loop; TM = transmembrane domain; C = C-terminal domain. (c) Schematic representation of BACE1 substrates and sites of cleavage. BACE1 substrates include APP (amyloid precursor protein), APLP2 (APP-like protein 2), NRG1 (neuregulin 1), VGSCβs (voltage-gated sodium channel beta subunits), PSGL-1 (P-selectin glycoprotein ligand 1), and LRP1 (lipoprotein receptor-related protein 1). YENPTY = tyrosine–glutamic acid–asparagine–protein–threonine–tyrosine protein-sorting domain; Aβ = amyloid beta-protein domain; E2 = ectodomain 2; KPI = Kunitz protease inhibitor domain; Ac = acetylation site; CBD = copper-binding domain; ZnBD = zinc-binding domain; HBD = heparin-binding domain; IC = intracellular cytoplasmic domain; TM = transmembrane domain; EGF = epidermal growth factor; NT = N-terminal domain; IGD = immunoglobulin domain; JM = juxta-membrane peptide; Rb = receptor binding domain; Pro = propeptide; NPY-diL = NPxY (arginine, proline, random amino acid, tyrosine) motif and dileucine repeats.

the other two disulfide bonds of BACE1 ensure its correct steric orientation and activity. The C-terminal domain, together with the transmembrane domain of BACE1 also plays a key role in its dimerization, which is necessary for optimal activity and substrate recognition (Shimizu and others 2008; Wang and others 2013). Although under physiological settings, pro-BACE1, monomeric- dimeric- and higher-order BACE1 complexes coexist, the dimeric and oligomeric BACE1 complexes have faster kinetics and therefore set the rate of protease activity (Westmeyer and others 2004; Yan and others 2001). The baseline activity of BACE1 depends not only on its substrate binding and catalytic efficiency but also on interactions with multiple regulatory proteins and peptides, as well as a variety of environmental factors. For optimal functionality, BACE1 must interact with several other molecular partners. Amongst these, SorLAs and sortilins, reticulonogo proteins (RTN3, RTN4-B/C, or Nogo-B/C), Golgi-localized GGAs and phospholipid scramblase 1 (PLSCR1), prostate apoptosis response-4 protein, Presenilin 1 (PS1), cellular prion protein (PrPC) are the best characterized (Gersbacher and others 2010; Hu and others 2008; Kang and others 2000; Marquer and others 2011; Nikolaev and others 2009). These interactions are important for multiple biological processes and functions, from the governance of transport and sorting of

BACE1 to acidifying endosomes or lysosomes, influencing the rate of substrate cleavage, stabilizing the quaternary structure of BACE1 via positive effector properties (e.g., RTNs), or modulating oxidative stress responses, via N-terminal domain CCS and SOD1 interactions.

Although BACE1 is acknowledged mostly for cleavage of APP, with production the Aβ of AD, it also cleaves several other substrates. These include but are not limited to the membrane-bound α2,6-sialyltransferase, localized in the Golgi complex (Kitazume and others 2003), the APP homolog proteins APLP1 and APLP2 (Eggert and others 2004; Li and Sudhof 2004), the voltage-gated sodium channel (Nav1) β2 subunit (Navβ2) (Kim and others 2007; Kim and others 2011), P-selectin glycoprotein ligand-1 (PSLG-1) (Lichtenthaler and others 2003), low-density lipoprotein receptor-related protein (LRP) (von Arnim and others 2005), neuregulin-1 (NRG1) (Hu and others 2006; Hu and others 2008; Willem and others 2015), and neuregulin-3 (NRG3) (Hu and others 2008) (Fig. 1c). Such impressive versatility of BACE1 not only infers its potential role in multiple neurobiological processes and functions but is also of importance for developing therapies modulating its activity (Barao and others 2016; Vassar and others 2009). The emerging results of preclinical and clinical trials with disconcerting psychiatric symptoms in patients and healthy individuals treated with inhibitors point toward a previously unrecognized role of BACE1 in higher brain mechanisms, and extend its role beyond described below neurocognitive processes.

BACE1 and Cognitive Impairments of AD

In the adult brain, BACE1 is enriched primarily in axons and presynaptic terminals, where it plays an essential role in a variety of fundamental neurobiological processes, including neurite outgrowth, synapse formation, regulation of neurotransmitter release and synaptic plasticity (Baratchi and others 2012; Chasseigneaux and others 2011; Furukawa and others 1996). Presynaptic terminals are also the prime location of APP cleavage by BACE1, leading to the formation and release of the Aβ peptide. As shown in Figure 2a and b, BACE1 dependent production of Aβ is a two-step process. At first, BACE1 cuts APP to generate the sAPPβ fragment and CTFβ membrane-anchored domain, which subsequently is cleaved by the γ-secretase complex at 40-43AA, releasing Aβ (De Strooper 2010; Haass and Selkoe 1993, 2007). BACE1 is also an essential player in more recently described η-β cleavage of APP, in close cooperation with η-secretase (Willem and others 2015). When in excess, both, Aβ and Aη-β can induce impairment of synaptic function and plasticity, with cognitive deficit, initiating the degeneration of synaptic connections and neuronal loss (Ovsepian and others 2018; Selkoe 2002).

From the ample data published over recent years, it emerges that the detrimental effects of enhanced BACE1 activity with the build-up of β-γ and η-β cleavage products of APP can be mediated via a variety of mechanisms. Figure 3a and b illustrates examples of the enrichment of BACE1 proteases in normal presynaptic terminals of the hilar region of the hippocampal dentate gyrus, as well as presynaptic dystrophies surrounding amyloid plaques of 5XFAD AD mice (Kandalepas and others 2013), where BACE1 meets and cleaves its substrates. In the case of APP cleavage and release of fragments in the extracellular space, the disruptive effects of BACE1 hyperactivity are attributed to the pre- and postsynaptic action of the higher concentrations of Aβ and other fragments. The accumulation of Aβ outside of neurons can have harmful effects through interference with the functioning of an array of receptors and ion channels, and most notably, with glutamatergic and cholinergic receptors, and voltage-gated Ca^{2+} channels (Flynn and others 1995; McClean and others 2011; Ovsepian and others 2014; Renner and others 2010; Snyder and others 2005). Besides, extracellular Aβ can act directly on the surface membrane of neurons, disturbing its integrity with knock-on effects on Ca^{2+} homeostasis and mitochondrial functions, resulting in cytotoxicity (Ovsepian and others 2019). Amassing inside neurons, on the other hand, Aβ can cause impairments of synaptic vesicle cycle at presynaptic terminals, affecting synaptic vesicle docking, priming, and fusion, as well as postfusion membrane recovery (Alzheimer's Association Calcium Hypothesis Workgroup 2017; Arispe and others 1993; Khachaturian 1994; Ovsepian and others 2018). The conclusion that can be drawn from these and numerous other reports is that the pathological increase in BACE1 activity can lead to impairments in synaptic transmission and plasticity, which contribute to the cognitive decline and memory loss of AD. Accordingly, a rare loss-of-function human mutation at the BACE1 cleavage site of APP has been identified, which is characterized by reduced Aβ production, enhanced cognition in older age, and lower risks of developing AD (Jonsson and others 2012).

In light of these findings, cognitive impairments with memory loss, and reduced synaptic plasticity reported in a loss-of-function *bace1* transgenic mice came as a major surprise (Ma and others 2007). Several follow-up studies with the use of pharmacological and transgenic approaches confirmed that partial inhibition of BACE1 can have disruptive effects on cognition and synaptic plasticity, inferring bidirectional effects of BACE1 (Habib and others 2017; Hampel and others 2020; Ma and others 2007). The data from *bace1* KO mice lacking all products of β-cleavage of APP also highlight

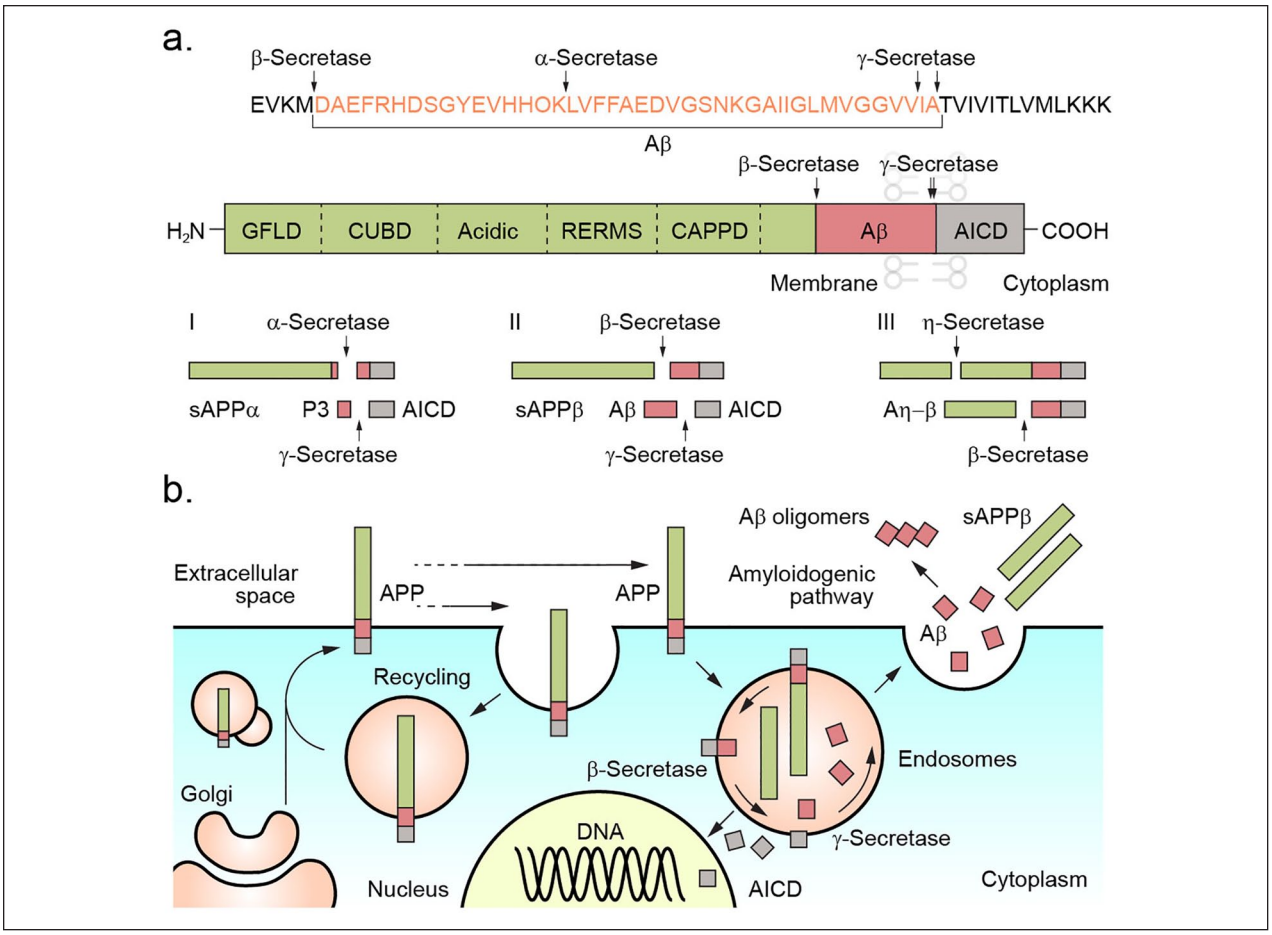

Figure 2. Amyloid precursor protein (APP) processing and production of the Aβ peptide. (a) The amino acid sequence of Aβ and the C-terminal adjacent region are displayed in single letter code with cleavage sites (arrows) of three secretases (α. β, and γ) resulting in Aβ production—upper. Schematic illustration of APP with secretase (β and γ) cleavage sites shown as arrows. GFLD = growth factor-like domain; CUBD = copper-binding domain; Acidic = acidic domain; RERMS = peptide sequence composed of arginine, glutamic acid, methionine, and serine; CAPPD = peptide sequence composed of cysteine, alanine, prolines, and aspartic acid; AICD = APP intracellular domain—middle. Representation of Aβ production through the sequential cleavage of APP by various secretases—lower. Three scenarios are illustrated as follows: I—APP is cleaved by α-secretase and γ-secretase to form sAPPα (soluble amyloid precursor protein alpha) and the P3 fragment respectively; II—APP is cleaved by β-secretase generating sAPPα. AICD and Aβ are released subsequently by γ-secretase cleavage of C99 fragment; III—η-secretase cleaves APP releasing a truncated, soluble APP ectodomain (sAη-β), which is further processed by β secretase to produce the short Aη-β peptide. (b) Illustration of the intracellular trafficking and proteolytic processing of APP leading to Aβ production. APP matures going through the secretory pathway (left). On reaching the cell surface, some of the APP is recycled, while the rest is recruited in lipid rafts, and internalized within acidifying endosomes, where favorable pH facilitates its cleavage with the extracellular release of sAPPβ and Aβ, and cytoplasmic release of AICD nuclear-signaling fragments (right).

significant memory and learning deficit, with synaptic plasticity impairments (Filser and others 2015; Savonenko and others 2008). Longitudinal analysis of the effects of BACE1 inhibitors and *bace1* KO on structural synaptic plasticity demonstrated a reduction in the density of excitatory synaptic connections in mice, with loss of dendritic spines, which correlated with reduced activity-dependent LTP, impaired spatial working memory and worsened cognition (Filser and others 2015; Savonenko and others 2008; Zhu and others 2018). As illustrated in Figure 3c and d, pharmacological inhibition of BACE1 leads to a reduction in the frequency of mini EPSCs (excitatory postsynaptic currents) in cortical pyramidal cells with attenuation of evoked synaptic transmission and dose-dependent decrease in the hippocampal LTP. Taken as a whole, these findings restate an essential role of the constitutive activity of BACE1 in the maintenance of learning and memory processes, with synaptic plasticity mechanisms (Ashe and Zahs 2010; Filser and others 2015).

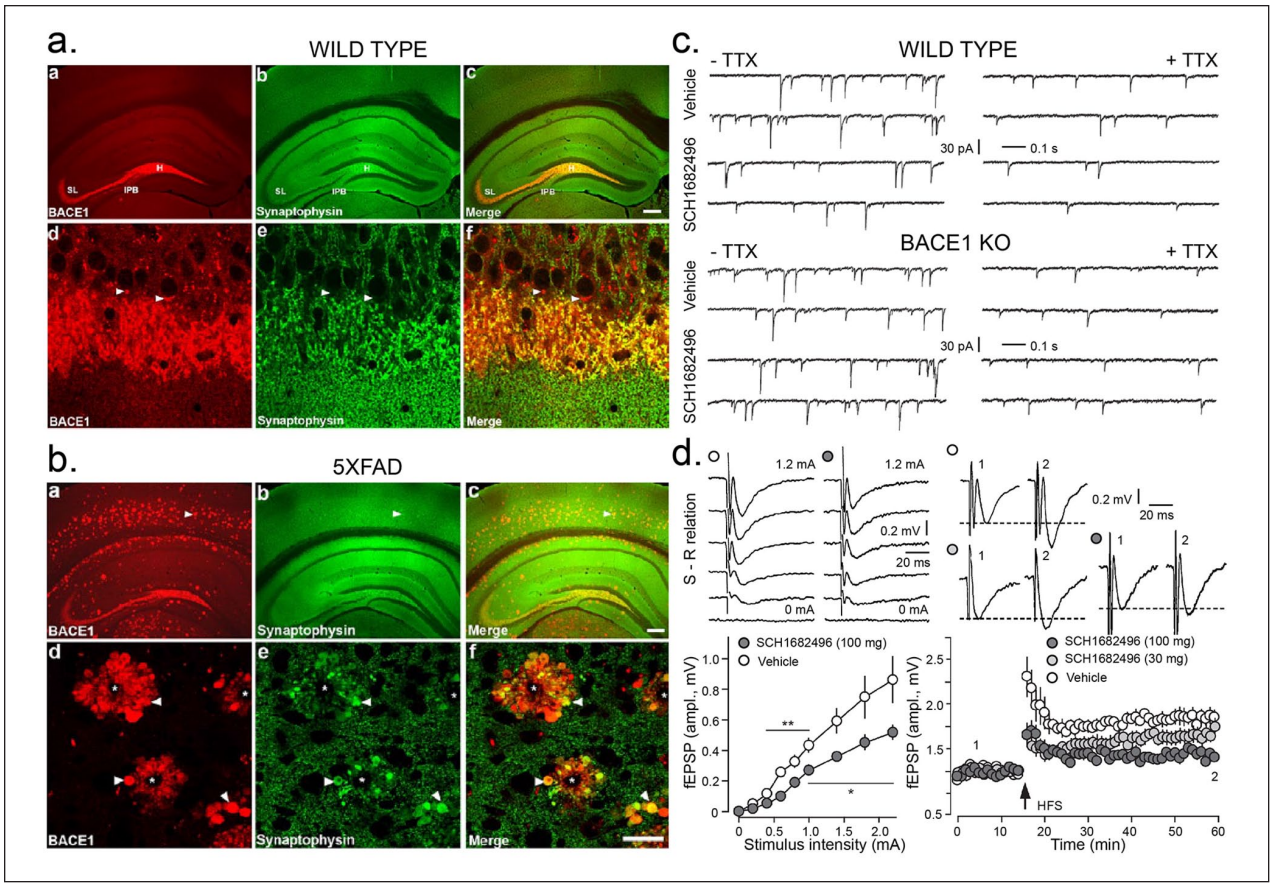

Figure 3. Localization of BACE1 in neurons and the effects of its inhibition on glutamatergic transmission and synaptic plasticity. (a) BACE1 enrichment in presynaptic terminals visualized with immune-fluorescence confocal microscopy. Representative images of hippocampal coronal sections from adult wild-type mice co-stained with BACE1 (red) and synaptophysin (green). (*a-c*) Low magnification images showing strong BACE1immunoreactivity in the hilar region of the dentate gyrus (H), and in the infra-pyramidal bundle (IPB) and stratum lucidum (SL) of the hippocampal mossy fiber pathway, where extensive labeling with synaptophysin signifies presynaptic localization of BACE1. (*d-f*) Higher magnification of BACE1 and synaptophysin immunoreactivity within the stratum lucidum. Note strong colocalization of BACE1 and synaptophysin. The punctate BACE1 signals within neuronal soma (white arrowheads), which do not overlap with synaptophysin represent BACE1 in TGN and endosomes. Scale bar *a-c*, 200 μm; *d-f*, 25 μm. (b) BACE1 accumulates presynaptically around amyloid plaques in 5XFAD transgenic mouse. Representative confocal images of 5XFAD transgenic mouse (~6 months old) brain co-stained with BACE1 (red) and synaptophysin (green) antibodies. (*a-c*)At low magnification, in addition to typical BACE1 localization in presynaptic terminals of hippocampal mossy fibers, BACE1 immunoreactivity (red) displays a plaque-like staining pattern that overlaps with synaptophysin (green) immunoreactivity (white arrowheads point onto plaque). (*d-f*) Higher magnification images showing strong co-localization of BACE1 and synaptophysin around amyloid lesions (white asterisks) in 5XFAD brain, demonstrating accumulation of BACE1 in swollen and dystrophic terminals. Adapted with permission from (Kandalepas and others 2013). (c) Whole-cell recordings of spontaneous and mini excitatory postsynaptic currents (EPSCs) (−TTX and +TTX) showing the effects of BACE1 inhibitor SCH1682496 on the frequency of EPSCs in cortical pyramidal cells of wild type mice. Representative spontaneous EPSCs (left) and miniature EPSCs (right) of somatosensory cortical neurons from mice treated over 16 days with a vehicle or 100 mg/kg SCH1682496. Note lower synaptic activity in neurons of mice treated with 100 mg/kg SCH1682496. Similar experiments using brain slices of BACE1 KO mice revealed no changes in synaptic transmission-related with 100 mg/kg SCH1682496 (not shown). (d) Inhibition of BACE1 attenuates evoked synaptic transmission (S-R relation) (left) and activity-dependent long-term potentiation (LTP) in CA1 neurons of a wild type mouse (right). Representative traces of Schaffer collateral field EPSPs for each experimental condition shown along with corresponding graphs. *$P < 0.05$; **$P < 0.01$. Adapted with permission from Filser and others (2015).

Overall, while it is clear that the inhibition of BACE1 can slow down amyloid pathology and related cognitive deficit in some AD mouse models, there is rising evidence that warrants a great degree of caution and restrained optimism concerning the use of BACE1 inhibitors for the treatment of cognitive decline and synaptic

protection in AD, given the emerging wider role of this protease in synaptic homeostasis and processes related to higher brain mechanisms (Barao and others 2016; Castellani and others 2019). Additional complexity has been added to the clinical translation of BACE1 inhibitors by the experimental demonstration that the effects BACE1 inhibitors can extend beyond neurocognitive mechanisms, leading to increased anxiety, depression, emotional instability, aggression, and signs of schizophrenia, as described below.

BACE1 and Neuropsychiatric Symptoms of AD

Two recent publications of the results of clinical trials with BACE1 inhibitors verubecestat and atabecestat in prodromal AD and in elderly at risk of developing AD reported a significant and progressive cognitive decline, despite the reduction of amyloid burden (Egan and others 2019a; Henley and others 2019). These effects induced by BACE1 inhibitors were associated with varying degrees of neuropsychiatric impairments, including depression, sleep impairments, anxiety, and psychotic symptoms, which were dose dependent. In the case of verubecestat, for instance, significant increases in the frequency of non-cognitive neuropsychiatric symptoms were observed in the highest dose group (40 mg/day) compared with placebo: 10.3% versus 5.2% for depression; 9.1% versus 4.3% for anxiety; 9.1% versus 4.5% on sleep disturbances; 5.6% versus 2.3% on psychotic symptoms. The effects in the group receiving lower doses of verubecestat (20 mg/day) were mild and did not differ from the placebo group (Egan and others 2019a). Although these studies did not discuss the underlying mechanisms for noncognitive symptoms, such effects cannot be explained within the amyloid cascade hypothesis, as the latter refers only to cognitive functions and mechanisms of learning and memory (Castellani and others 2019). Remarkably, BACE1 inhibition caused also noncognitive neuropsychiatric signs in cognitively normal elderly volunteers (Forman and others 2019). These recent discoveries show that BACE1, in addition to cognition and hippocampal-dependent learning and memory, might influence processes underlying wider mechanisms and functions of the brain, affecting emotional and perceptive spheres, decision making, circadian activity, and others.

In experimental animals, the neuropsychiatric symptoms induced by BACE1 deficiency have been recognized for some time. Analysis of *bace1* KO mice revealed behavioral traits resembling the symptoms of schizophrenia (Savonenko and others 2008). Indeed, in habituation tests, *bace1* null mice displayed a decline in a startle response as evident from reduced prepulse inhibition (PPI). In the open field plus maze, these animals also exhibited hyperactivity when exposed to novel stimuli, with poor working memory, mimicking schizophrenia-like agitation. Of note, in pharmacological tests, *bace1* null mice display higher sensitivity to psychostimulants and *N*-methyl-D-aspartate (NMDA) antagonist MK-801, implying a cusp of psychosis (Savonenko and others 2008), while atypical antipsychotics such as clozapine phased out the hyperactivity and restored normal PPI. Surprisingly, a more recent report showed that the schizophrenia-like symptoms of *bace1* KO mice can be mimicked by overexpression of BACE1-cleaved Nrg1:N-terminal fragment (Neuregulin-NTF) (Luo and others 2014). The behavioral changes in animal models were accompanied by enhanced levels of myelin basic protein and reduced expression of NR1 and NR2A/2B subunits of NMDA receptors. These data imply that impairments of Nrg1 function downstream to BACE1 could present a high risk for schizophrenia. Compatibly, postmortem studies in humans showed region-specific bilateral changes of Nrg1 cleavage in schizophrenia subjects, with a strong increase in Nrg1-NTF in the BA9 region (Marballi and others 2012).

As the second best-characterized substrate of BACE1, NGR1is encoded by *NRG1*—one of the key schizophrenia-associated genes identified so far. Its role in higher brain mechanisms is related with controlling neuronal development, regulation of the expression of NMDA receptor, tuning of the excitability of neuronal membrane as well as axonal myelination (Liu and others 2001; Rieff and others 1999; Stedehouder and Kushner 2017). Figure 4a and b illustrates Nrg1 isoforms and their proteolytic cleavage by BACE1. As can be seen, all Nrg1 isoforms share common structural features, including immunoglobulin, epidermal growth-like factor domain, transmembrane, and an unequal length of intracellular domains (Falls 2003). Nrg1 fragments produced by BACE1 cleavage are known to activate the ErbB receptor with the downstream signaling. In addition to BACE1, this process involves ADAM17 or ADAM10, which leads to the release of the extracellular EGF-domain, causing paracrine effects (Vullhorst and others 2017). In the context of schizophrenia and schizoaffective disorders, BACE1 Nrg interactions and signaling are discussed mostly with dysfunctional NMDA receptors and allied synaptic impairments and degeneration of dendritic spines, with loss of myelination (Gu and others 2005; Lundgaard and others 2013; Yarden and Sliwkowski 2001). Figure 5a-e presents a summary of key results illustrating the effects of Nrg1 dysfunctions on dendritic spine density and axonal myelination in *Nrg1* +/− heterozygote mice (Chen and others 2008; Taveggia and others 2005). Like in humans with schizophrenia, adult heterozygous mice have enlarged lateral ventricles and reduced dendritic spine density of pyramidal neurons, with functional magnetic

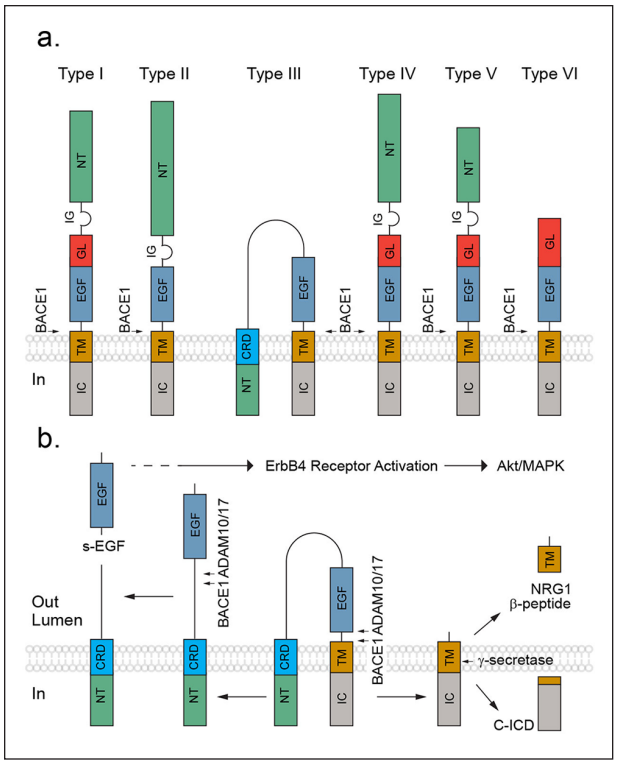

Figure 4. Neuregulin-1 (NRG1) isoforms (types I-VI): their cell membrane location and cleavage by BACE1. (a) A schematic representation of neuregulin-1 isoforms: structure, various subdomains, and membrane location. While all NRG1 isoforms contain an EGF domain, they are distinguished from each other mainly by their N-terminal peptides. NRG1 types I, II, IV, and V have an Ig (IG) domain. NRG1 types I, IV, V, and VI have a glial growth factor-like domain (GL). NRG1 type III contains a cysteine-rich domain (CRD) embedded in the lipid bilayer which results in its N-terminal being tethered to the cell membrane. (b) NRG1 processing with activation of NRG1/ErbB4 signaling alleged in schizophrenia. NRG1 type III is cleaved by BACE1 or ADAM10/17, releasing the EGF domain into the extracellular space (left). The soluble EGF domain (s-EGF) binds to the ErbB4 receptor, activating Akt/MAPK phosphorylation in neurons. The intracellular fragment of NRG1 (type III) composed of transmembrane (TM) and intracellular (IC) domains are cleaved by γ-secretase (right). This results in the release of the NRG1 β-peptide into the extracellular space, and cleaved intracellular domain (C-ICD), which activates the nuclear signaling regulating neuronal development.

resonance imaging (fMRI) data demonstrating hypofunction of the medial prefrontal cortex. Importantly, *Nrg1* +/− also show impaired performance in delayed alteration tasks and deficit in PPI (Chen and others 2008). In the prefrontal cortex, Nrg1 signaling is also known to regulate the internalization of the NR1/NR2A/2B subunit, causing inhibition of NMDA receptors (Ozaki and others 1997; Yarden and Sliwkowski 2001). In addition to direct effects at synapses, Nrg1 also modulates the neuronal excitability and neural network function through regulation of axonal conductivity, myelin sheath formation, and postinjury remyelination. In Schwann cells, for instance, Nrg1/ErbB activation stimulates myelin formation and development of axons, which depends mainly on ErbB2 and ErbB3 signaling (Boerboom and others 2016; Miyamoto and others 2017). The latter is of major relevance to schizophrenia given the causal link between retarded myelination and the onset of this devastating disorder (Chavarria-Siles and others 2016; Stedehouder and Kushner 2017).

Overall, the data from clinical trials and preclinical studies in animal models show that inhibition of BACE1, in addition to neurocognitive impairments, can induce a range of schizoaffective and other noncognitive psychiatric symptoms. While the direct link between BACE1, Nrg1, and schizophrenia in humans remains to be established, the results from animal studies suggest impairments of BACE1-Nrg1-nft signaling as a potential contributor. Other players and molecular mechanisms underlying a wide spectrum of neuropsychiatric symptoms related to BACE1 dysfunctions remain to be determined, along with the assessment of the safety margins for their pharmacological modulation, to ensure the most favorable therapeutic outcome.

Concluding Remarks

Although BACE1 has been named after its most widely recognized substrate APP, its role extends beyond the cleavage of APP and production Aβ and other fragments (Fig. 6). Discussed above evidence from animal and human studies imply BACE1 as a key regulator of many fundamental neurobiological processes related to the proliferation of neuronal progenitors, neurodevelopment, axonal growth and myelination, cell excitability, synaptic homeostasis, and plasticity. Some of these are governed by fragments of the same substrate cleaved by BACE1, while others involve cleavage products of different substrates. Over the past decade, much progress has been made in the development of potent and selective BACE1 inhibitors, raising hopes for their use as therapeutics in the treatment of the amyloid pathology of AD. Despite the successful target engagement of potential drug leads and significant reduction of the amyloid burden, including toxic soluble variants Aβ species, the results of clinical trials have been less than satisfactory. Major issues remain with replicating and clinical translation of preclinical results with BACE1 inhibitors like verubecestat, lanabecestat, elembecestat, umibescetat, and others, calling for more rigorous quality control of the data and careful consideration of research models. Reports of cognitive decline and psychiatric symptoms induced by BACE1 inhibitors in AD risk groups and

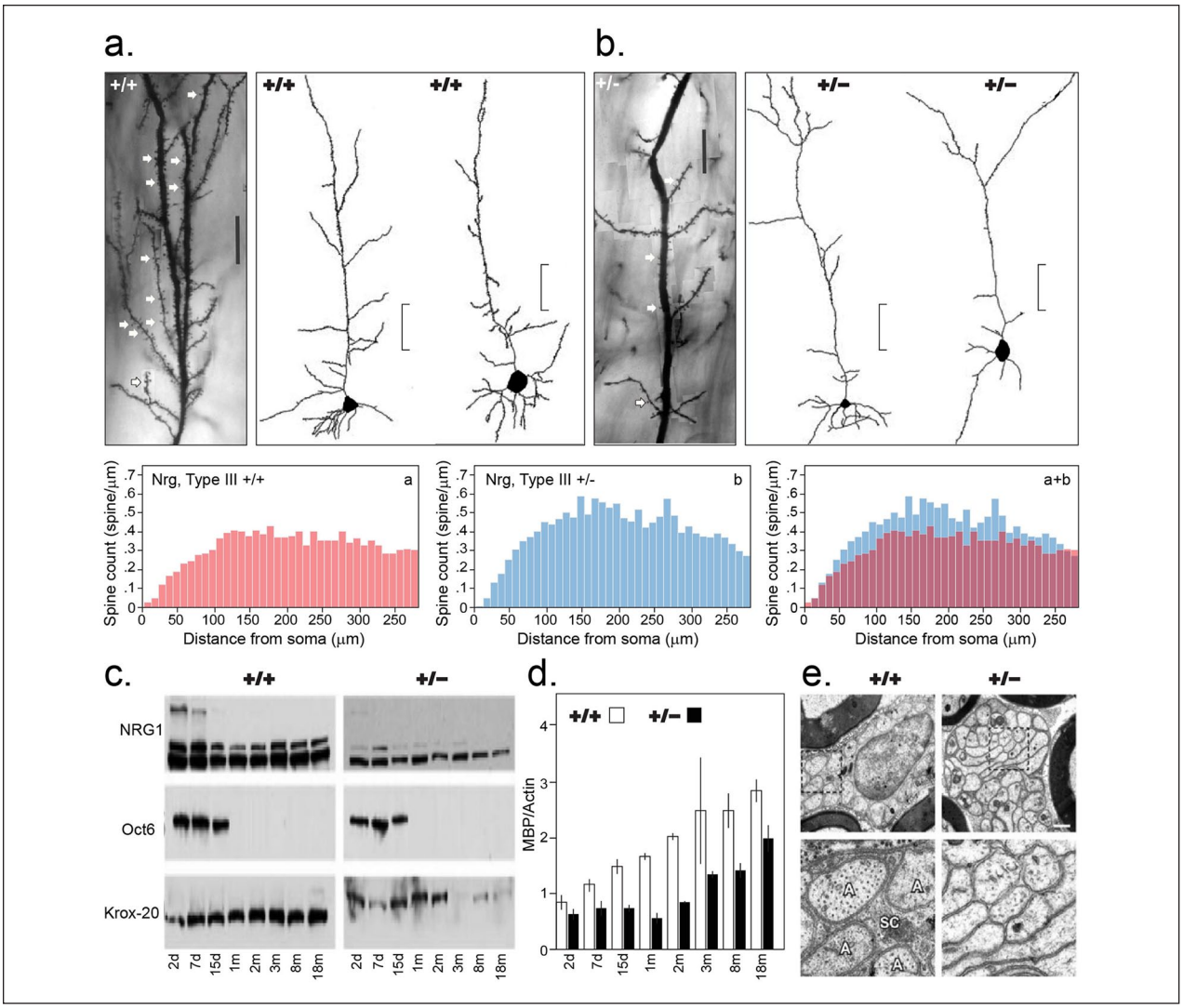

Figure 5. Neuregulin maintains high-density of dendritic spines and myelination of axons in mice. (a, b) Montage and reconstruction of high-resolution images of Golgi stained apical dendrites of pyramidal neurons and neurolucida reconstructed three-dimensional structures of typical wild type and from Nrg+/− mice (top) cells. Scale bars, 100 μm, and 10 μm, respectively. Note that there are many more spines (examples indicated by white arrows) on dendrites from wild type (+/+) as compared to (+/−) mice. (Bottom) Spine densities plotted against increasing shell radius from the center of the soma. The results are from 30 wild type neurons of five mice (pink) and 44 neurons of five transgenic (blue) animals. Data present mean values. Heterozygous mice have significantly lower spine densities at the 50 to200 shell radius compared with wild type. Adapted with permission from (Chen and others 2008). (c) Detection of the expression of NRG1 with myelination of the sciatic nerve in developing wild type and NRG +/− mice. Extracts were prepared from sciatic nerve at the postnatal time points shown and fractionated by SDS-PAGE (sodium dodecyl sulfate–polyacrylamide gel electrophoresis), blotted, and probed with anti-NRG1 antibody and the transcription factors Oct-6 and Krox-20. (d) Summary histogram of the myelin basic protein/actin ratio changes in wild type and NRG +/− during development. Myelin protein levels are normalized to actin as indicated; the means (±SEM) from two different experiments are shown. (e) Electron micrographs of Remak bundles in sciatic nerves from wild type (left panels) and NRG +/− (right panels) adult mice show altered axonal segregation; insets are shown at higher magnification in the lower panels. In the wild type mice, axons are fully ensheathed by Schwann cell processes (Sc), whereas NRG +/− axons frequently directly oppose each other without intervening Schwann cells processes. Scale bar, 1 μm. Adapted with permission from Taveggia and others (2005).

healthy individuals brings another major complexity to the field, casting doubts over the possibility of simple solutions to impairments of neuronal activity and restoration of brain mechanisms by inhibitors of this key protease. Given the functional versatility of BACE1, it is hardly surprising that both, genetic and pharmacological modulation of its activity leads to deterioration of higher integrative processes and functions of the brain, with a

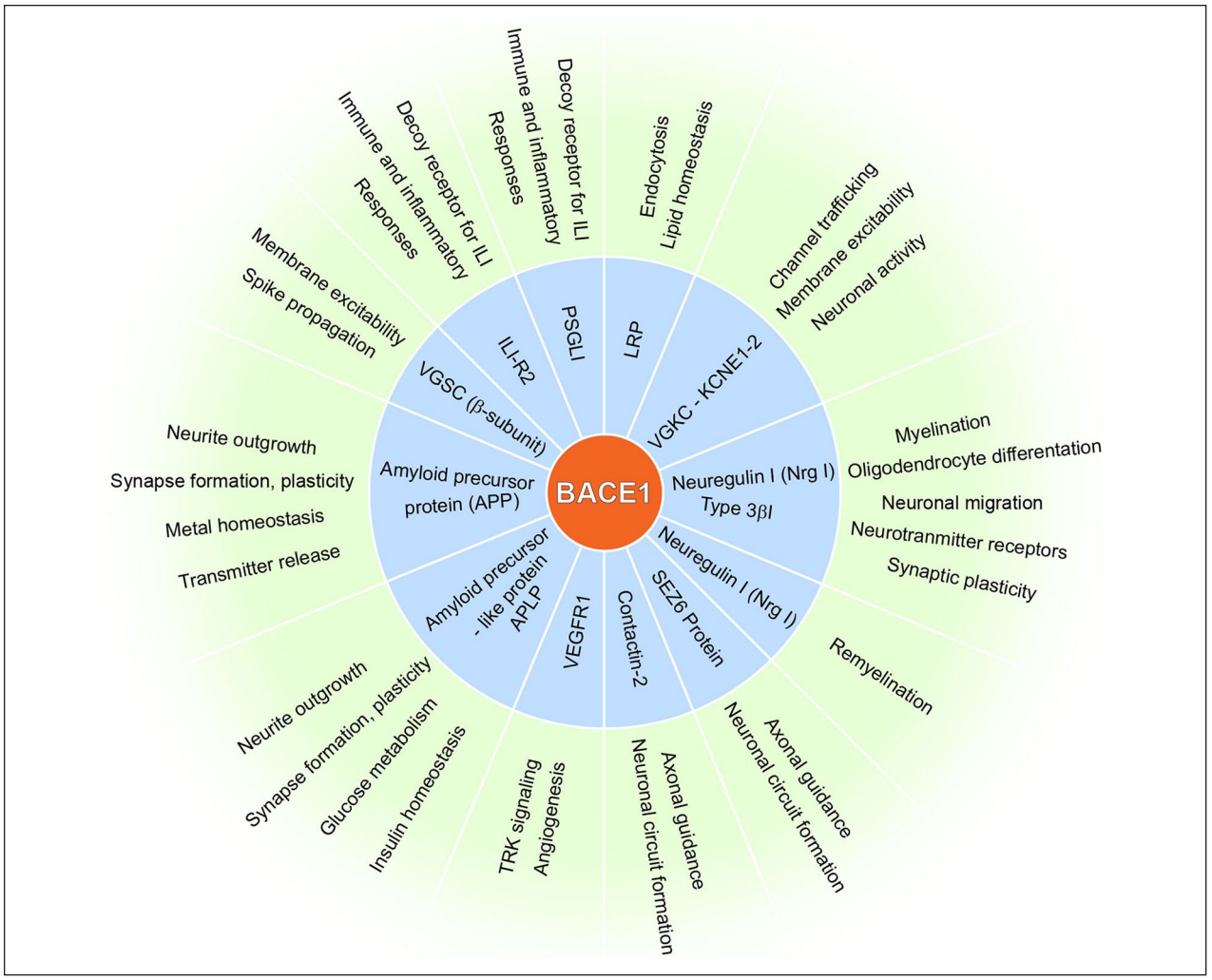

Figure 6. BACE1 signaling and functions in the brain. A schematic illustration of the main substrates of BACE1 and their alleged role in the central nervous system. BACE1 substrates: APP (amyloid precursor protein), APLP (APP-like protein), Nrg1 (neuregulin 1), VGSCβs (voltage-gated sodium channel beta subunits), PSGL1 (P-selectin glycoprotein ligand-1), LRP (lipoprotein receptor-related protein), VGKC-KCNE1-2 (ancillary KCNE1-2 subunits of voltage-gated potassium channel), SEZ6 (seizure related 6 homolog protein), VEGFR1 (vascular endothelial growth factor receptor 1), and IL1-R2 (interleukin 1 receptor 2).

detrimental impact on mental health. At this stage, the most consistent theme that traverses the majority of preclinical and clinical studies is that the physiological activity of BACE1 is maintained at a homeostatic state of equilibrium, with tipping the fine balance in any direction carrying risks of functional impairment extending beyond neurocognitive spheres. In addition to highlighting the pressing need for research of the biology and biochemistry, the results of clinical trials and preclinical animal studies call for a careful revision of therapeutic strategies and models that assume the indiscriminate inhibition of BACE1 activity, and work toward the targeted restoration of its functional balance in affected neurons and synapses.

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Supplemental Material

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