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Neurological dysfunctions associated with altered BACE1-dependent Neuregulin-1 signaling

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Abstract

Inhibition of BACE1 is being pursued as a therapeutic target to treat patients suffering from Alzheimer's disease because BACE1 is the sole β-secretase that generates β-amyloid peptide. Knowledge regarding other cellular functions of BACE1 is therefore critical for the safe use of BACE1 inhibitors in human patients. Neuregulin-1 (Nrg1) is a BACE1 substrate and BACE1 cleavage of Nrg1 is critical for signaling functions in myelination, remyelination, synaptic plasticity, normal psychiatric behaviors and maintenance of muscle spindles. This review summarizes the most recent discoveries associated with BACE1-dependent Nrg1 signaling in these areas. This body of knowledge will help to provide guidance for preventing unwanted Nrg1-based side effects following BACE1 inhibition in humans.

Graphical Abstract

To initiate its signaling cascade, membrane anchored Neuregulin (Nrg), mainly type I and III β1 Nrg1 isoforms and Nrg3, requires ectodomain shedding. BACE1 is one of such indispensable sheddases to release functional Nrg signaling fragment. The dependence of Neuregulin on the cleavage by BACE1 is best manifested by disrupting the critical role of Nrg in the control of axonal myelination, schizophrenic behaviors as well as the formation and maintenance of muscle spindles.

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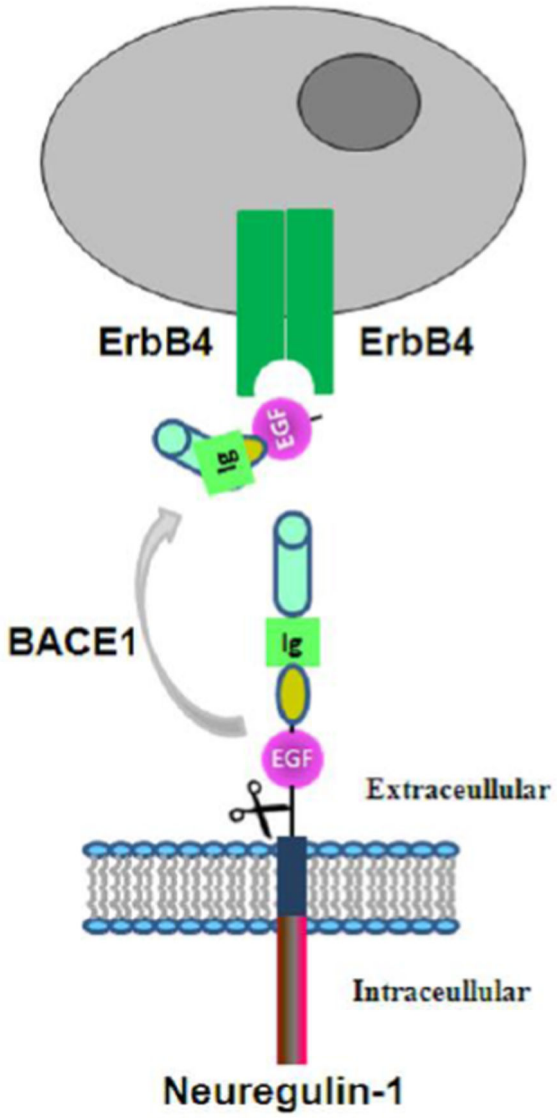

Keywords

BACE1; Alzheimer's β-secretase; neuregulin-1; myelination; myelin sheath; remyelination; schizophrenia; muscle spindle

INTRODUCTION

BACE, known as β-site amyloid precursor protein (APP) cleaving enzyme (Yan and Vassar 2014), is a membrane-anchored aspartyl protease required for the generation of β–amyloid peptides (Aβ) (Vassar *et al.* 1999;Yan *et al.* 1999; Hussain *et al.* 1999; Sinha *et al.* 1999; Lin *et al.* 2000). In brains of patients with Alzheimer's disease (AD), abnormally accumulated Aβ tends to oligomerize, aggregate and induce synaptic dysfunction and memory loss (Price *et al.* 2014;Tu *et al.* 2014; Haass and Selkoe 2007; Walsh *et al.* 2002; Wang *et al.* 2013; Gong *et al.* 2003). Aβ refers to peptide mixtures comprised of variants 38 to 43 amino acids

long, but 40 and 42 (Aβ40 and Aβ42) are the most common. Genetic mutations in presenilin-1 and −2 favor the production of Aβ42 (Borchelt *et al.* 1996; Citron *et al.* 1997; Duff *et al.* 1996; Tomita *et al.* 1997; Li *et al.* 2014; De *et al.* 2010), which is more frequently linked to AD pathogenesis. For example, Aβ42, but not Aβ40, has been found to induce tau pathogenesis (Gotz *et al.* 2001; Hu *et al.* 2014; Blurton-Jones and LaFerla 2006; Rank *et al.* 2002; Liraz *et al.* 2013), which is another major pathological feature in AD brains. Mice completely deficient of BACE1 show abolished Aβ production (Cai *et al.* 2001; Luo *et al.* 2001; Roberds *et al.* 2001), confirming that BACE1 is a critical and indispensable protease for Aβ release. Since BACE1 is critical for Aβ generation, inhibition of BACE1 should reduce levels of Aβ, particularly the more toxic Aβ42, which could benefit AD patients.

However, BACE1 cleaves other cellular substrates in addition to APP. Other BACE1 substrates that have been identified and characterized include neuregulin-1 (Nrg1) (Willem *et al.* 2006; Fleck *et al.* 2013; Hu *et al.* 2006; Hu *et al.* 2008; Luo *et al.* 2011), voltage-gated channel proteins such as sodium channel protein β-subunits (Kim *et al.* 2007; Kim *et al.* 2011; Wong *et al.* 2005), the potassium channel proteins KCNE1 and 2 (Sachse *et al.* 2013; Hitt *et al.* 2010), neural cell adhesion molecule close homolog of L1 (Zhou *et al.* 2012; Hitt *et al.* 2012; Kuhn *et al.* 2012), the Notch ligands Jagged-1 and Jagged-2 (He *et al.* 2014; Hu *et al.* 2013a), and contactin-2 (Gautam *et al.* 2014). BACE1 is more profoundly expressed in neurons than in non-neuronal cells (Vassar and Zheng 2014) and abolished processing of these substrates in BACE1-null mice is linked to changes in various brain functions.

Among these identified BACE1 substrates, Nrg1 receives considerable attention because Nrg1 is indispensable for neural and cardiac development (Meyer and Birchmeier 1995; Kramer *et al.* 1996). Additional studies have recently reported a functional link between BACE1 and Nrg1, which form the basis for this review. We will summarize recent findings associated with BACE1-dependent Nrg signaling in neural functions and in various stages of neural development.

Neuregulin signal transduction

I) Neuregulin genes

Neuregulin (Nrg) genes are typically recognized by the presence of exons coding for the epidermal growth factor-like (EGF-like) domain (Holmes *et al.* 1992; Chang *et al.* 1997). The Nrg gene family has four members (Nrg1 to Nrg4) in mammals, with more distant orthologues found in the *Xenopus laevis* and *Drosophila melanogaster* genomes and even in the emerging vertebrate lineage of the sea lamprey *Petromyzon marinus* (Libants *et al.* 2009; Yarnitzky *et al.* 1997; Yang *et al.* 1998; Marchionni 2014). Each gene is often expressed by specifically controlled transcription and splicing, which typically produces many mRNA and protein isoforms.

The Nrg1 gene is one of the largest genes in the human genome and its expression is the most complicated in the Nrg family. A single human Nrg1 gene (~1.5 Mb) produces 33 spliced isoforms due to specific uses of six different transcriptional initiation sites as well as multiple splicing isoforms (Brown *et al.* 2004; Steinthorsdottir *et al.* 2004; Liu *et al.* 2011; Tan *et al.* 2007; Mei and Xiong 2008). As depicted in Figure 1A, six types of Nrg1 are

defined by their differences at the N-terminal end. All six isoforms have an EGF-like domain, but only types I, II, IV, and V isoforms have an additional Ig domain. Exons coding for the linker region between the EGF-like domain and the transmembrane domain are often used to distinguish specific Nrg1 isoforms. The Nrg1 γ-isoforms have a stop codon preceding the transmembrane domain and are synthesized as secreted forms. Most Nrg1 α and β isoforms, except for the β3 variant, are synthesized as membrane-anchored molecules (Mei and Xiong 2008). Type III Nrg1 has a cycteine-rich domain (CRD), which is also intercalated into the lipid bilayer (Figure 1B).

While Nrg1 isoforms are pleiotropically expressed in various mammalian tissues, including the brain and heart, certain Nrg1 isoforms are expressed under the control of lineage-or development-specific signaling factors (Meyer *et al.* 1997; Canoll *et al.* 1996; Kerber *et al.* 2003). In human brains, all six types of Nrg1 are detectable, but the abundance of each form varies significantly (Liu *et al.* 2011). By comparing levels of unique mRNA, it has been shown that type III Nrg1 is predominant among all Nrg1 isoforms (accounting for 59–73%, dependent on the age group), while type I Nrg1 is only about 4% in all age groups. Although weakly expressed (less than 1%), type IV is predominantly brain-specific. Within the brain, types I, II, and III are mainly expressed by neurons; astrocytes also express type I, but not types IV, V, or VI Nrg1.

Only in recent years have the discriminative roles of other Nrg family members begun to receive attention. Nrg2 gene produces at least ten transcripts due to alternative splicing and has two different translational initiation sites. It is expressed in the developing nervous system, with the highest levels in granule cells and Purkinje cells of the cerebellum (Carraway, III *et al.* 1997; Chang *et al.* 1997), and it is often targeted to dendrites (Longart *et al.* 2004). Nrg2 is also expressed by motor neurons and Schwann cells (Rimer *et al.* 2004). Although less complicated compared to Nrg1, the Nrg3 gene still has two alternative ATG start sites and at least four isoforms (Zhang *et al.* 1997; Howard *et al.* 2005). Nrg3 is specifically expressed in the human embryonic central nervous system and is required for the survival of oligodendrocytes (Carteron *et al.* 2006). Nrg4 is the smallest Nrg member with only 115 amino acids, but it has five spliced isoforms (Harari *et al.* 1999; Hayes and Gullick 2008). Only two Nrg4 isoforms have the transmembrane domain encoded by exon 6. Expression of Nrg4 appears to be more restricted, mainly to pancreas and muscle, and is required for epithelial cell survival (Bernard *et al.* 2012; McElroy *et al.* 2014; Hayes *et al.* 2011). If not synthesized as secreted isoforms, Nrg2, Nrg3, and Nrg4 have a single pass type I membrane domain and all contain EGF-like domains (Figure 1B).

II) ErbB receptors

The discovery of Nrg genes originated from the search for specific ligands that bind to and activate ErbB2 receptors (Wen *et al.* 1992; Holmes *et al.* 1992; Falls *et al.* 1993; Marchionni *et al.* 1993). The ErbB family comprises four transmembrane tyrosine kinase receptors: ErbB1 (also called Epidermal Growth Factor Receptor, EGFR), ErbB2, ErbB3, and ErbB4. All ErbB proteins have a type I transmembrane topology flanked by a unique N-terminal ligand-binding domain and a C-terminal intracellular domain, which are variable in length and contain either a functional or pseudo tyrosine kinase. Nrg and its cognate receptor have

a specific binding preference by forming a functional binding partnership. Nrg1 and Nrg2 bind to ErbB3 and ErbB4, while Nrg3 and Nrg4 preferentially bind to ErbB4 only (Mei and Nave 2014; Hynes and Lane 2005; Yarden and Sliwkowski 2001). Nrg molecules usually do not bind ErbB1, which preferentially binds EGF and is also known as EGFR (Schlessinger 2002). Ligand binding induces dimerization of its cognate receptor. Interestingly, ErbB2 lacks the ligand binding pocket, while ErbB3 has only a pseudo-kinase domain; both require heterodimerization to be a functional unit. ErbB2 often forms a dimer with ErbB3 in many cell types.

III) Nrg-ErbB signal transduction

Upon ligand binding, ErbB intracellular receptor tyrosine kinase is intrinsically activated in response to dimerized structural changes (Weiss and Schlessinger 1998; Roskoski, Jr. 2014). The main activated signaling downstream molecules are the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)–AKT pathways; PLCγ and Stat proteins are recent additions (Britsch 2007; Roskoski, Jr. 2014; Carpenter 2003; Hynes and Lane 2005; Lai and Feng 2004; Yarden and Sliwkowski 2001). Each receptor has multiple intracellular phosphorylated sites, which dictate characteristic preferences for interacting with adaptor proteins. Multiple autophosphorylation sites have been identified in ErbB2 and mediate binding of adaptor molecules such as Grb2, Shc, Doc-R, and CRK for their unique signaling pathways, i.e., the MAPK pathway (Dankort *et al.* 2001b; Dankort *et al.* 2001a; Suenaga *et al.* 2003). Six phosphorylation sites in ErbB3 are normally transactivated, i.e., by the ErbB2 intrinsic kinase, and can be coupled to the p85 adaptor subunit of PI3K to activate the PI3K-AKT pathway. System-wide searches identified 19 potential Tyr sites in ErbB4, which can differentially mediate activation of PI3K-AKT, MAPK, and STAT1 signaling (Kaushansky *et al.* 2008; Junttila *et al.* 2000; Kainulainen *et al.* 2000; Elenius *et al.* 1999).

Proteolytic cleavage of neuregulin

Unless synthesized as functional secreted isoforms, Nrg molecules anchored on the lipid bilayer require proteolytic shedding to release EGF domain-containing fragments for binding to their receptors. Proteolytic cleavages of Nrg1 have been more extensively investigated than other Nrg molecules. Type I Nrg1 can be effectively cleaved at multiple sites by disintegrin and metalloproteinase 10 (ADAM10) and ADAM17 (Figure 2). *In vitro* MOLDI-TOF mass spectrometric mapping of the cleaved products showed that both ADAM10 and ADAM17 cleave β1 Nrg1 between the F-Y site, 18 residues before the membrane domain (La *et al.* 2011; Luo *et al.* 2011; Fleck *et al.* 2013). ADAM17 can also cleave the neighboring A-S site, while ADAM10 may additionally cleave the Y-K site in cells (Fleck *et al.* 2013). BACE1 specifically cleaves β1 Nrg1 isoforms at the F-M site (Hu *et al.* 2008; La *et al.* 2011; Fleck *et al.* 2013). Upon cleavage of Nrg1 by either enzyme, the N-terminal of Nrg1 is released for binding to its receptor. The sequence signature (M**A**SF**YK**HLGIE**F**MEAEELYQKR) comprising both ADAM and BACE1 cleavage sites is highly conserved among β1 isoforms in different species (human, rodent, dog, and chicken). Although almost all BACE1 substrates are also cleaved by ADAMs (Yan and Vassar 2014), the BACE1 cleavage site is downstream of the ADAM cleavage site, which is unique to Nrg1. This order may competitively favor BACE1 to cleave Nrg1 in early secretory

compartments in cells, as ADAM10 and ADAM17 are more enriched at the cell surface (Primakoff and Myles 2000; Deuss *et al.* 2008).

After ectodomain shedding, type I Nrg1 releases its N-terminal fragment (Nrg1-ntf) to the extracellular space, where it binds to ErbB receptors on nearby cells in a paracrine fashion, while type III Nrg1-ntf, which remains tethered on the lipid bilayer due to a hydrophobic CRD in its N-terminus, signals to adjacent cells in a juxtacrine fashion (Warren *et al.* 2006). A recent study suggested that type III Nrg1 may also mediate autocrine or paracrine signaling due to newly identified cleavage sites preceding the EGF-like domain (Figure 2). It shows that BACE1 cleaves an additional 16 residue site between L-Q, located before the EGF-like domain (Fleck *et al.* 2013). Enhanced expression of BACE1 facilitates this cleavage. ADAM17 also cleaves type III Nrg1 between L-V, at the N-terminal end of the EGF-like domain. A single cleavage of type III β1 Nrg1 by either BACE1 or ADAM17 may release the EGF-like domain for initiating signaling function (Fleck *et al.* 2013).

While other ADAMs, including ADAM19, have been suggested to cleave membrane-anchored Nrg1 isoforms, these cleavage sites have not yet been identified (Montero *et al.* 2000; Kalinowski *et al.* 2010; Yokozeki *et al.* 2007; Shirakabe *et al.* 2001). Type I transmembrane Nrg2, Nrg3, and Nrg4 are also shedded for exerting their signaling activities under specific regulatory conditions. The broad-spectrum matrix metalloproteinase inhibitor, galardin (GM 6001), is capable of inhibiting Nrg4 cleavage (Hayes *et al.* 2008), although the details remain to be determined. A stretch of eleven residues spanning the BACE1 cleavage site, but not the ADAM cleavage site, is identical between Nrg1 and Nrg3; altered Nrg3 cleavage has been detected in BACE1-null mouse brains (Hu *et al.* 2008). Since the Nrg3/ErbB4 pathway has been found to regulate the survival of oligodendrocytes in cell cultures (Carteron *et al.* 2006), this pathway is likely to complement the function of Nrg1 in myelination upon genetic deletion of Nrg1. Amino acid sequences spanning the transmembrane domain of Nrg2 have high homology to those in Nrg1, but lack the canonical BACE1 cleavage site. It is not clear whether Nrg2 and Nrg4 are also physiological BACE1 substrates.

Functional changes via BACE1-dependent Nrg1 signaling

As outlined above, BACE1 mainly cleaves types I and III Nrg1 as well as Nrg3. BACE1 is richly expressed by neurons and its functions in brain development and diseases have recently gained attention (Vassar *et al.* 2014). Although Nrg1 is known to play roles in both cardiac and neural development, this review will focus on the recent findings related to common functional changes arising from BACE1-dependent Nrg1 signaling in the nervous system.

I) BACE1 and Nrg1 in myelination

In the vertebrate nervous system, most axons are wrapped by myelin membranes, which are specialized, spirally organized plasma membranes synthesized by oligodendrocytes in the central nervous system (CNS) and by Schwann cells in the peripheral nervous system (PNS) (Sherman and Brophy 2005). The protein composition of myelin in the CNS and PNS is significantly different, despite performing the same insulating function. Proteolipid protein

(PLP) is the major structural protein of CNS myelin, while P0 protein is the major structural protein of PNS myelin (Tuohy 1994;Lemke and Axel 1985). Myelin basic protein (MBP) and myelin associated glycoprotein (MAG) are present in both CNS and PNS myelin (Boggs 2006; Schachner and Bartsch 2000), but at different levels. A properly myelinated nerve efficiently transmits the electrical impulse by saltatory conduction, i.e. it “jumps” from node to node to ensure rapid axonal conduction.

Two of the well-identified phenotypes in BACE1-null mice are defects in axonal myelination and remyelination in the PNS and CNS. Immunohistochemical staining readily detects a significant reduction of myelin in BACE1-null sciatic nerves. Further electron microscopic analyses confirmed a marked reduction of myelin sheath thickness in BACE1-null mouse sciatic nerves (Hu *et al.* 2006; Willem *et al.* 2006). In BACE1-null zebrafish, anterior and posterior lateral line axons, typically ensheathed by Schwann cells, are also hypomyelinated (van *et al.* 2013). Consequently, abnormal PNS myelination causes impairments of neurological functions in BACE1-null mice, such as reduced grip strength (Hu et al. 2006).

Impaired myelination within the BACE1-null PNS resembles that in mice with type III Nrg1 haploinsufficiency (Nave and Salzer 2006). Mice heterozygous for type III Nrg1 exhibit hypomyelination and reduced nerve conduction velocity in their sciatic nerves (Taveggia *et al.* 2005; Michailov *et al.* 2004). This function is evolutionarily conserved, as knocking down type III Nrg1 in zebrafish results in a severe impairment in myelination of anterior and posterior lateral line axons (van *et al.* 2013). The identification of Nrg1 as a BACE1 substrate has led to molecular insights into BACE1-dependent hypomyelination. In BACE1-null mice, the abrogated cleavage of axonal Nrg1 increases full-length Nrg1 by reducing levels of axonal-anchored type III Nrg1 (Hu *et al.* 2006; Hu *et al.* 2008; Willem *et al.* 2006). This will reduce the transmission of Nrg-ErbB signaling by decreasing the active form of Akt (phosphorylated Akt) and phosphorylated Erk.

Although Nrg1 is also cleaved by ADAM10 and ADAM17, pan-inhibition of ADAM by GM6001 or treatment with ADAM10 siRNA in an *in vitro* co-culture myelination system shows minimal effects on normal myelination (Luo *et al.* 2011). Intriguingly, knockdown of ADAM17 in dorsal root ganglia neurons induces hypermyelination in co-cultures and rescues hypomyelination in type III NRG1 heterozygous mice (La *et al.* 2011), suggesting that ADAM17 is a negative regulator of myelination in the PNS. This effect is likely due to cleavage of Nrg1 within the EGF domain by ADAM17, but this cleavage was not observed with different biochemical mapping (Fleck *et al.* 2013). Instead, Fleck et al. have argued that either BACE1 or ADAM17 cleaves Nrg1 flanking the EGF-like domain by inducing paracrine Nrg-ErbB signaling (see cleavages in Figure 2). Despite this discrepancy, specific inhibition of BACE1 has been consistently shown to impair axonal myelination (Luo *et al.* 2011; La *et al.* 2011), further emphasizing the importance of BACE1-dependent Nrg1 signaling in myelination.

While Nrg1, mainly type III Nrg1, is indispensable for developmental PNS myelination, the effects of BACE1-dependent Nrg1 on developmental CNS myelination is more convoluted. Hypomyelination has been repeatedly observed in BACE1-null optic nerves (Hu *et al.* 2006), but was not detected in broad brain regions of BACE1-null mice by others (Treiber *et al.*

2012). In zebrafish, oligodendrocytes and Schwann cells can be highlighted by membrane-bound green fluorescent protein (GFP) under the control of the myelin specific *claudin k* promoter (Munzel *et al.* 2012). Mauthner axons are typically myelinated by zebrafish oligodendrocytes and GFP-marked myelin in the Mauthner axons of *bace1−/−; claudin k:GFP* appears indistinguishable from *claudin k:GFP* larvae, indicating no obvious effect on CNS myelin in BACE1-null zebrafish (van *et al.* 2013). Despite this difference in various models, reduced levels of compact MBP, PLP, and MOG were evident in the young BACE1-null mouse hippocampus (Hu *et al.* 2006). Such a reduction of myelin proteins is visible in hippocampal sections stained by MBP or PLP antibody (Hu *et al.* 2006) and is more evident during early developmental stages (Figure 3). The eventual normal levels of myelination in this brain region suggest a compensatory mechanism that remains to be determined. Although no obvious changes in myelin sheath thickness in normal adult BACE1-null white matter have been observed, this is remarkably not the case during remyelination. In a cuprizone-induced demyelination model, reduction of myelin sheath thickness was observed in remyelinated axons within the BACE1-null mouse corpus callosum (Treiber *et al.* 2012).

One study suggests that type III Nrg1 is a more restricted instructive signal in promoting oligodendrocyte myelination, as mice heterozygous for type III Nrg1 are hypomyelinated only in the forebrain (Taveggia et al. 2008). However, a separate study, using a conditional deletion of the Nrg1 gene in neurons or ErbB3/ErbB4 genes in oligodendrocytes at different time points during development, showed normal myelinated fibers in the grey matter and spinal cord (Brinkmann *et al.* 2008). Knocking down type III Nrg1 in zebrafish also resulted in normal myelination in the central nerve (van *et al.* 2013). While the loss-of-Nrg1 function in CNS myelination in animals is controversial, it is no doubt that the enhanced Nrg-ErbB signaling pathway regulates CNS myelination for the following observations. First, in cell cultures, Nrg1 is a mitogen to pro-oligodendrocytes by facilitating lineage development and enhancing survival of oligodendrocytes (Flores *et al.* 2000; Vartanian *et al.* 1997; Fernandez *et al.* 2000; Canoll *et al.* 1996). In rat optic nerves, injected Nrg1 significantly increases the number of survival oligodendrocytes in the nerve (Fernandez *et al.* 2000), indicating an important role of Nrg1 in maintaining functional oligodendrocytes. Second, overexpression of either type I or type III Nrg1 has been shown to promote CNS myelination in animals (Taveggia *et al.* 2008; Brinkmann *et al.* 2008). Third, disrupting ErbB function by expressing the dominant negative form of ErbB4 induces hypomyelination (Roy *et al.* 2007). Fourth, Nrg3, another substrate of BACE1 (Hu *et al.* 2008), is broadly expressed in neurons, is able to activate Akt similar to Nrg1, and acts as a survival factor for oligodendrocytes in cell cultures (Carteron *et al.* 2006). Nrg3 may potentially compensate for the loss of Nrg1 considering its binding to ErbB receptor like Nrg1. Finally, gain-of-function studies support a role for Akt, a downstream molecule of the Nrg-1/ErbB pathway, in enhancing CNS myelination. Mice overexpressing Akt-DD for gaining Akt function under the control of PLP promoter develop hypermyelination of the central axons (Flores *et al.* 2008; Barros *et al.* 2009). Augmenting Akt activity by targeting its downstream mTOR function or inhibiting PTEN by disruption of Pten in Schwann cells also increases hypermyelination (Zou *et al.* 2014; Narayanan *et al.* 2009; Lebrun-Julien *et al.* 2014; Goebbels *et al.* 2012). Hence, properly enhancing PI3K-Akt signaling function can facilitate myelination in the CNS (Macklin 2010). Consistent with this, BACE1-null mice overexpressing constitutively active

Akt (Akt-DD; mutations with D308T and D473S) in oligodendrocytes show reversal of hypomyelination of optic nerves (Hu *et al.* 2013b). The effect of Akt in oligodendrocytes is also more critical for CNS myelination. Hence, it is likely that BACE1-dependent Nrg signaling can have spatial and temporal effects on CNS myelination.

II) BACE1 and Nrg1 in remyelination

Genetic deletion of BACE1 also affects sciatic nerve remyelination, as demonstrated in the adult sciatic nerve crush model (Hu *et al.* 2008). When a nerve is severely injured in this manner, the segment proximal to the crush site is subjected to axonal degeneration due to Wallerian degeneration; during recovery, remyelination is initiated by Schwann cells contacting the regenerating axons in the proximal band of Büngner. Myelin sheath thickness remains thinner in BACE1-null regenerated axons and levels of the major myelin proteins P0 and MBP are significantly lower in the distal stump of BACE1-null sciatic nerve (Hu *et al.* 2008), indicating that BACE1 deficiency also impairs remyelination in peripheral nerves. BACE1 also appears to be required for optimal remyelination of corpus callosum axons, which can be demyelinated by cuprizone treatment (Treiber *et al.* 2012).

Impaired remyelination can stem from the loss of Nrg1 cleavage by BACE1, as axonal deletion of Nrg1 disrupts remyelination of sciatic nerves in adult mice (Fricker *et al.* 2011). Peripheral nerve remyelination is also more efficient in transgenic mice overexpressing type III Nrg1. Although it has been suggested that type I Nrg1 has no effect on developmental myelination, transgenic mice overexpressing type I Nrg1 exhibit more efficient remyelination of injured sciatic nerves (Stassart *et al.* 2013). Moreover, nerve injury triggers expression of type I Nrg1 by Schwann cells, which is normally undetectable in intact nerves (Stassart *et al.* 2013). Intriguingly, in mice with a conditional deficiency of Nrg1, remyelination is reduced at early stages (up to 2 months post-nerve injury), but not at later recovery stages (Fricker *et al.* 2013). This late normalization is likely due to compensation by other growth factors. Overall, Schwann cell-derived Nrg1 appears to be dispensable for developmental myelination and myelin maintenance, but exerts an autocrine signaling function for remyelination, as loss of Nrg1 expression in Schwann cells severely impairs remyelination after nerve crush.

We have recently shown that BACE1 in Schwann cells is equally important to axonal BACE1 for remyelination (Hu *et al.* 2015). In a nerve transplantation experiment, axons in the transplanted sciatic nerve are degenerated, similar to the distal side in the nerve crush model. However, Schwann cells in the transplanted sciatic nerve remain and will form a “Schwann tube”, which can remyelinate the regenerated axons from the recipient proximal segment. We show that in the case of either a BACE1-null nerve segment transplanted into a WT recipient or a WT nerve segment transplanted into a BACE1-null recipient, remyelination is equally impaired, as the increase in g-ratio is almost identical (Hu *et al.* 2015). Nerve injury not only induces expression of BACE1, but also type I Nrg1 by Schwann cells. Expression of type III Nrg1 in Schwann cells is barely detected, in line with the prior observation that conditional deletion of type I Nrg1, but not type III Nrg1, in Schwann cells is required for optimal remyelination. Hence, axonal and Schwann cell

BACE1-dependent Nrg1 signaling differentially contribute to developmental myelination and remyelination of regenerated axons.

III) BACE1 and Nrg1 in schizophrenia

Schizophrenia (SCZ) is a severe chronic neuropsychiatric disorder affecting approximately 1% of the population worldwide, with the average age of onset being between 19 and 25 years (Nasrallah *et al.* 2011). Clinically, the symptoms include auditory and visual hallucinations, delusions, social withdrawal, and cognitive dysfunction. Although the etiology of SCZ remains contentious, it is commonly accepted that this disease is a multi-factorial neurodevelopmental disorder influenced by both genetic and environmental factors (Shorter and Miller 2015; Purcell *et al.* 2009; Glessner and Hakonarson 2009; Insel 2010; Lee *et al.* 2012; Steinberg *et al.* 2011; Fromer *et al.* 2014; Purcell *et al.* 2014; 2014; Ibi and Gonzalez-Maeso 2015). An association study of SCZ families in Iceland initially revealed Nrg1 to be a SCZ-susceptible gene (Stefansson *et al.* 2002), and this finding was quickly replicated in various ethnic populations (Williams *et al.* 2003; Li *et al.* 2004; Stefansson *et al.* 2003; Yang *et al.* 2003). Further analyses of Nrg1 polymorphisms support the linkage of altered Nrg1 function as a risk factor for SCZ (Corvin *et al.* 2004; Tang *et al.* 2004; Norton *et al.* 2006). Initial functional studies suggest that mutations in Nrg1 likely lead to loss-of-function, as mice heterozygous for Nrg1 show SCZ-related behavioral deficits such as impaired reciprocal social interaction behaviors as well as impaired short-term and long-term plasticity in the CA3-CA1 pathway (Stefansson *et al.* 2002; O'Tuathaigh *et al.* 2008). Biochemical pathway analysis of this risk effect also indicates acting through the receptor level, as mice with haplo-insufficiency of ErbB4 display SCZ-like behaviors, including impaired pre-pulse inhibition (Stefansson *et al.* 2002). The first clinical evidence of haploinsufficiency of ErbB4 was found in a patient with early myoclonic encephalopathy and profound psychomotor delay with the ErbB4 gene disrupted due to a *de novo* reciprocal translocation t(2;6)(q34;p25.3) (Backx *et al.* 2009). An array CGH analysis identified another case of *de novo* deletion of the ErbB4 gene in a patient with SCZ behaviors (Kasnauskiene *et al.* 2013). Functional neuroimaging analysis of SCZ patients together with case controls confirmed that individuals carrying risk genotypes for Nrg1 and ErbB4, or these two together with AKT1, are disproportionately less efficient at dorsolateral prefrontal cortex processing (Nicodemus *et al.* 2010). This epistatic and functional interaction analysis is consistent with prior findings of decreases in AKT1 protein levels and in levels of phosphorylation of GSK3beta at Ser9 in the peripheral lymphocytes and brains of individuals with SCZ (Emamian *et al.* 2004). Hence, a body of evidence supports the hypothesis that impaired Nrg1-ErbB-AKT1/GSK3 signaling is a risk factor for SCZ (Emamian 2012), although growing evidence also supports association of gain-of-function in Nrg1 with SCZ to be discussed later.

In 2003, BACE1-null mice were reported to display timid behavior and reduced serotonin and dopamine (DA) levels in the hippocampus and striatum, respectively (Harrison *et al.* 2003); dopamine and serotonin dysfunctions are the basis for many antipsychotic drugs (typical or atypical) developed to ameliorate SCZ positive and negative symptoms (Strange 2008; Amato 2015; Guidotti *et al.* 2005). However, the link between BACE1 and SCZ pathogenesis has gained recent attention due to the observed SCZ-like endophenotypes in

BACE1-null mice and BACE1 cleavage of Nrg1. Specifically, BACE1-null mice display significantly impaired pre-pulse inhibition, hypersensitivity to glutamatergic psychostimulants, reductions in spine density, and hyperactivity (Savonenko *et al.* 2008). Behavioral studies of BACE1-null mice have also shown poor performance on spatial and temporal hippocampus-dependent memory tasks (Kobayashi *et al.* 2008; Laird *et al.* 2005; Eimer and Vassar 2013). All these defects resemble those seen in Nrg1 mutant mice, phenotypically connecting BACE1 and Nrg1 in the same pathway.

Functionally, Nrg1 regulates signaling via inhibitory gamma-aminobutyric acid (GABA)-mediated inhibitory functions and N-methyl-D-aspartate receptor (NMDAR)-mediated glutamatergic excitatory functions (Fazzari *et al.* 2010; Lu *et al.* 2014; Okada and Corfas 2004; Woo *et al.* 2007; Yin *et al.* 2014; Ting *et al.* 2011). While the detailed pathways have been well-summarized in several comprehensive reviews (Corfas *et al.* 2004; Mei and Xiong 2008; Buonanno *et al.* 2008; Harrison and Law 2006; Mei and Nave 2014; Banerjee *et al.* 2010), here we mainly discuss Nrg1 function in the hypofunctional NMDAR-mediated glutamatergic system, a hypothesis increasingly gaining attention in SCZ pathogenesis over the past two decades (Coyle 2012; Cohen *et al.* 2015; Snyder and Gao 2013; Javitt 2012; Stahl 2007; Vukadinovic 2014). Current publications linking BACE1 to SCZ focus mainly in this system (Savonenko *et al.* 2008). Although altered function of Nrg2-ErbB4 has been shown to regulate NMDA receptor internalization in GABAergic interneurons (Vullhorst *et al.* 2015), Nrg2 is not a BACE1 substrate and thus will not be included in this discussion. Although Nrg3 is also BACE1 substrate and Nrg3 polymorphisms, perhaps more clustered in the brain-specific exon b, have high ‘delusion factor’ scores and modulate early attentional processes for perceptual sensitivity and vigilance (Kao *et al.* 2010; Morar *et al.* 2011; Chen *et al.* 2009; Wang *et al.* 2008), its signaling pathway is similar to Nrg1.

Nrg1 impacts NMDA receptors through multiple mechanisms, such as altered expression and internalization of NMDA receptors (Geddes *et al.* 2011; Mei and Xiong 2008). (internalization of NMDA or AMPA receptors is artefacts. This cannot be the case, because erbb4 is not expressed in pyramidal neurons as claimed). A binding study using MK-801 in forebrain homogenates from *Nrg1* hypomorphs showed reduction of NMDA receptors (Stefansson *et al.* 2002), supporting an earlier finding that Nrg1β signaling regulates NMDA-mediated excitatory functions by inducing expression of NMDA receptor subunits (Ozaki *et al.* 1997). Several groups investigated NMDAR expression in postmortem samples from SCZ patients and show reduced NMDA receptor subunit density in the prefrontal cortex, hippocampus, and thalamus (see summary in table 1 by Geddes *et al.* 2011). Interestingly, both ErbB4 and the NR2 subunit of the NMDA receptor bind to the same adaptor molecule, postsynaptic density protein-95 (PSD-95) (Figure 4), a PDZ domain-containing synaptic scaffold protein (Garcia *et al.* 2000; Lin *et al.* 2004; Huang *et al.* 2000). The interaction between PSD-95 and C-terminal tails of the NR2 subunit increases the number of functional channels at the cell surface and channel opening rate of NMDARs, and this interaction is regulated by phosphorylation of residues within the PDZ-binding domain of NR2 (Chung *et al.* 2004). The activated ErbB4 receptor, upon Nrg1 binding, is also able to interact with PSD-95 and transduces the downstream signaling cascade. Hence, PSD-95 is clearly the bridging molecule between these two receptors, and impaired binding might contribute to NMDAR hypofunction or altered activities of signaling kinases (Steigerwald *et al.* 2000;

Mori *et al.* 1998; Rossi *et al.* 2002). Among various kinases that regulate NMDAR activity, Src/Fyn kinases are particularly important because they are modulated by PKC, Pyk2, and PKA, and thus can serve as a hub of various pathways influencing NMDAR activation (Hahn 2011). ErbB4 has been shown to interact with Fyn, which phosphorylates tyrosine residues on both NR2A and NR2B subunits, affecting channel gating and increasing NMDAR currents (Bjarnadottir *et al.* 2007; Takasu *et al.* 2002). Reduced phosphorylation on NR2B Y1472 by Fyn is seen in NRG1+/− mutant mice. Alternatively, overexpressing ErbB4 enhances AMPA synaptic currents and increases dendritic spine size, while reducing Nrg1-ErbB4 activity can destabilize synaptic AMPA receptors, leading to loss of synaptic NMDA currents and dendritic spines (Li *et al.* 2007). Collectively, these data support the hypothesis that the glutamatergic hypofunction contributing to SCZ is associated with loss-of- function in Nrg1.

Conversely, genetic studies also found increased Nrg1 or ErbB4 transcripts and proteins in SCZ patients (Harrison and Law, 2006; Geddes et al., 2011), as well as substantial increases in ErbB4-PSD-95 interactions (Hahn *et al.* 2006). SCZ-like behaviors are indeed observed in mouse models overexpressing Nrg1 (Yin *et al.* 2013; Luo *et al.* 2013; Kato *et al.* 2010; Agarwal *et al.* 2014), indicating that balanced Nrg1 function is of critical importance for normal psychiatric behaviors. This notion is strongly supported by studies in two different mouse models utilizing the same tetracycline-inducible promoter system. The Mei lab generated inducible transgenic mice overexpressing full length Nrg1 (Yin *et al.* 2013), while we developed inducible transgenic mice overexpressing the N-terminal fragment of BACE1-cleaved Nrg1 (Nrg1-ntf$_\beta$) (Luo *et al.* 2013). In both cases, increased transgene expression was found to cause SCZ-like behaviors. After turning off transgene expression, behavioral deficits and synaptic dysfunction in these mice were reversed, indicating that the abnormal functions were due to significant gain-of-function in either full length Nrg1 or Nrg1-ntf$_\beta$. In a separate study, transgenic mice with constitutive overexpression of type I full length Nrg1 also exhibited SCZ-like behaviors (Kato *et al.* 2010). Molecular studies have shown that protein levels of NMDARs are reduced in both transgenic mouse models, which may underlie the observed social and cognitive behavioral impairments. Enhanced Nrg1 reducing NMDARs has been shown to be dependent on functional ErbB receptors (Gu *et al.* 2005). In an *in vitro* assay with acutely isolated and cultured prefrontal cortical (PFC) pyramidal neurons, bath perfusion of Nrg1 was found to significantly reduce whole-cell NMDA receptor currents, and this reduction was blocked by application of an ErbB receptor tyrosine kinase inhibitor. The reduced NMDA currents resulting from Nrg1 treatment are attributable to the induced internalization of NR1 subunit of NMRA receptors as demonstrated in cultured PFC neurons, and the membrane-permeable actin stabilizer phalloidin oleate blocks the Nrg1-mediated NR1 internalization (Gu *et al.* 2005). Nrg1 will not suppress NMDAR currents if NMDAR endocytosis is inhibited by the dynamin inhibitory peptide, suggesting involvement of clathrin/dynamin-dependent endocytosis in Nrg1-induced downregulation of NMDAR currents. Alternatively, others have suggested that Nrg1 is normally required for the physiological upregulation of NMDA receptors in a Src-dependent manner during theta-burst stimulation in the hippocampus and PFC (Pitcher *et al.* 2011), and enhanced Nrg1 signaling suppresses Src-mediated synaptic NMDAR function (Figure 4). This observation is consistent with the clinical finding of decreases in phosphorylation of Src and Pyk2 in

human postmortem brains (Banerjee *et al.* 2014). Hyperactive ErbB4 is also found in the PFC of patients with SCZ, and reduced tyrosine phosphorylation of NR2A is also observed (Hahn *et al.* 2006).

Overall, Nrg1-ErbB4 activity can mediate the interaction between synaptic activity and dendritic spines, suggesting that this pathway provides trophic support for glutamatergic functions in development, maturation, and stabilization. Most relevantly, loss of BACE1 activity will reduce Nrg1-ErbB function, which will impair NMDA-mediated synaptic plasticity. Hence, the effect of BACE1 on the pathogenesis of SCZ is likely mainly through impaired Nrg1 signaling. There is no evidence thus far showing that increased BACE1 activity causes SCZ pathogenesis, although abnormally elevated Nrg1 signaling can also contribute to dysfunction of NMDA-mediated pathways.

IV) BACE1 and Nrg1 in muscle spindles

Immuno-electron microscopic analyses in 35 human muscle biopsies, including 5 sporadic inclusion-body myositis (s-IBM), 5 chromosome-9p1-linked quadriceps-sparing inclusion-body myositis (hereditary-IBM), and 25 control muscle biopsies demonstrated that BACE1 is localized in normal adult muscle at the postsynaptic domain of neuromuscular junctions, as well as in cultured human muscle (Vattemi *et al.* 2003). The role of BACE1 in muscle dystrophy has been suggested due to the finding of elevated expression of BACE1 in s-IMB and h-IMB, which correlated with abnormal Aβ accumulation and oligomerization in necrotizing muscle fibers (Vattemi *et al.* 2009; Wojcik *et al.* 2007; Vattemi *et al.* 2001). Most recently, the important role of BACE1 in muscle spindles has become increasingly clear (Cheret *et al.* 2013); the functional dependence of Nrg1-ErbB signaling for proper formation of muscle spindles has long been described (Hippenmeyer *et al.* 2002; Andrechek *et al.* 2002). The role of BACE1-dependent Nrg1 signaling in this aspect is consistent with observed localization of BACE1, Nrg1, and ErbB4 at the axonal terminus and in synapses (Jaworski and Burden 2006; Kandalepas *et al.* 2013; Garcia *et al.* 2000; Rimer 2007; Jo *et al.* 1995).

Muscle spindles are composed of specialized intrafusal muscle fibers, which are innervated by afferent axons extending from sensory neurons (Hunt 1990). Previous *in vitro* studies have demonstrated that decreases in Nrg1 in sensory neurons, or its receptor ErbB2 in muscles, reduces the formation of muscle spindles (Andrechek *et al.* 2002; Hippenmeyer *et al.* 2002; Leu *et al.* 2003), which require proper contacts between proprioceptive sensory afferents and developing muscle fibers. This knowledge has driven further examination of coordinated muscle function in BACE1-null mice in the context of Nrg1 cleavage by BACE1 (Cheret *et al.* 2013). BACE1-null mice show a swaying walking pattern, which is attributable to impared coordination between forelimbs and hindlimbs. Such an ambulatory defect is likely due to dysfunctional proprioception, as governed by muscle spindles. Newborn BACE1-null mice have a more dramatic reduction in the number of muscle spindles, while this reduction is less severe in BACE1-null adult or heterozygous mice (Cheret *et al.* 2013). In mice treated for 29 days with the compound Ly2811376, which is a specific and nerve-penetrable inhibitor of BACE1 (May *et al.* 2011), up to 40% of muscle spindles are lost. This role of BACE1 in reduced muscle spindle maintenance is due to abrogated or reduced

cleavage of type I Nrg1, which has an Ig domain. The Ig domain-containing Nrg1 isoforms are preferentially expressed by proprioceptive sensory neurons and are sufficient to induce muscle spindle differentiation in animals (Hippenmeyer *et al.* 2002). Consistently, transgenic mice overexpressing IgNrg1β1 develop supernumerary muscle spindles (Rumsey *et al.* 2008). Mechanistically, Nrg1 induces expression of members of the early growth response (Egr) family of transcription factors, Egr1, Egr2, and Egr3 (Jacobson *et al.* 2004); Egr3 expression is regarded as the muscle spindle-specific gene required for the formation of muscle spindle fibers (O'Donovan *et al.* 1999). Induction of Egr3 expression in intrafusal fibers requires ectodomain-shedded Nrg1 to activate ErbB2 on the muscle fibers and the downstream MAPK pathway; Erg3 promoter contains binding sites for two transcription factors, SRF and CREB, which are inducibly expressed by MAPK signaling activity (Herndon *et al.* 2013; Herndon *et al.* 2014). Hence, these data support the concept that BACE1-dependent type I Nrg1 signaling is critical for motor coordination.

Perspective summary

BACE1 inhibitors are currently under clinical trials aimed at treating patients with Alzheimer's disease (Yan and Vassar 2014). The compound from Merck has shown potent inhibition and safety profiles in phase I trials and is currently in phase II and III combined trials (see reviews by Menting and Claassen 2014; Vassar 2014). Several other companies have also shown great promise with their BACE1 inhibitors in phase I trials. Hence, there is growing optimism that BACE1 inhibitors can reverse Aβ-mediated cognitive failures. Because chemical inhibition of BACE1 in animals has been shown to alter maintenance of muscle spindles and to impair synaptic functions (Filser *et al.* 2015), monitoring of potential alterations in BACE1-dependent Nrg1 signaling functions in patients who will take BACE1 inhibitor drugs over the long term should receive increasing basic and clinical attention.

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Abbreviation

BACE1	β-site APP convertases enzyme
Nrg1	neuregulin-1
ErbB, APP	amyloid precursor protein
Aβ	β–amyloid peptides
CNS	central nervous system
PNS	peripheral nervous system

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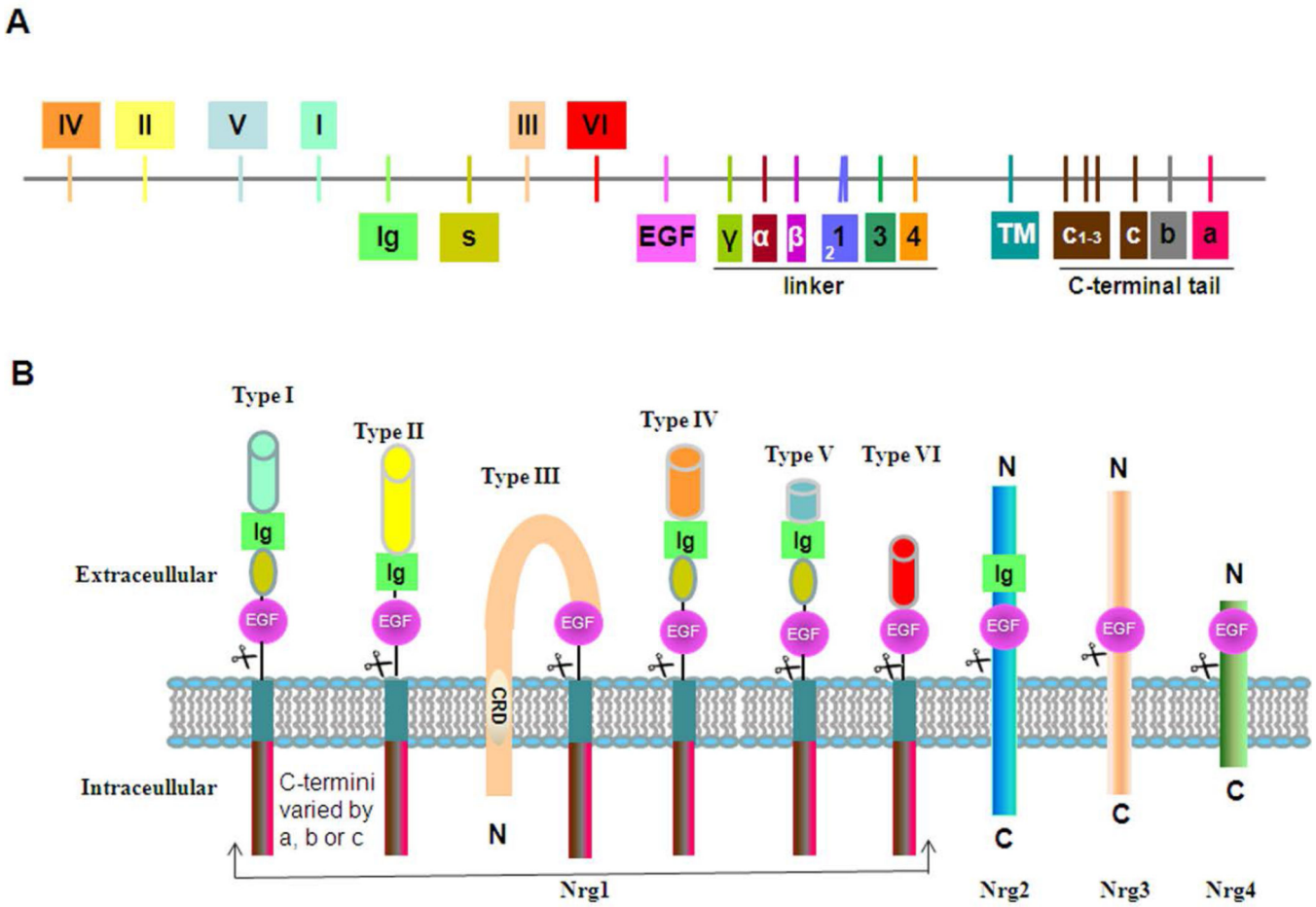

Figure 1. Neuregulin-1 isoforms and membrane anchoring

(**A**) Schematic illustration of the genetic structure of neuregulin-1 (Nrg1). The Nrg1 gene has 33 exons; each bar represents one or more exons coding for the major structural domain. Exons coding for six different types of Nrg1 are specified as I-VI. Sequences in the space region(s) contain glycosylation sites. Exons coding for the linker region between the EGF-like and transmembrane domains are often alternatively spliced. Each Nrg1 variant can be identified by the presence of exons coding for α, β, or γ-specific sequences. For example, β1 Nrg1 contains both exons for β- and 1-specific sequences. The exon for 2-specific sequence lacks the sequence of KHLGIEFME. The c1, c2 and c3 exons are shared by all membrane-anchored Nrg1 in the C-terminal tail, but vary by either stopping in c or being spliced to include either exon a or b. The γ- and c-exon have an in-frame stop codon; the Nrg1 γ-isoforms are naturally secreted due to this organization. (**B**) Nrg1 is classified as having six different forms, which differ mainly in their N-terminal part. All six isoforms have an EGF-like domain, but only types I, II, IV, and V contain the Ig domain. The unique N-terminal region of type III Nrg1 has a cysteine rich domain (CRD), which is expected to embed this region in the lipid bilayer. Hence, ectodomain shedding of Nrg1 will only have an EGF-domain containing the type III Nrg1 N-terminal side tethered on the membrane. Although not depicted, Nrg3 has a hydrophobic stretch in the N-terminal domain (residue 61 to 91), and is potentially adopt a membrane topology similar to type III β1 Nrg1.

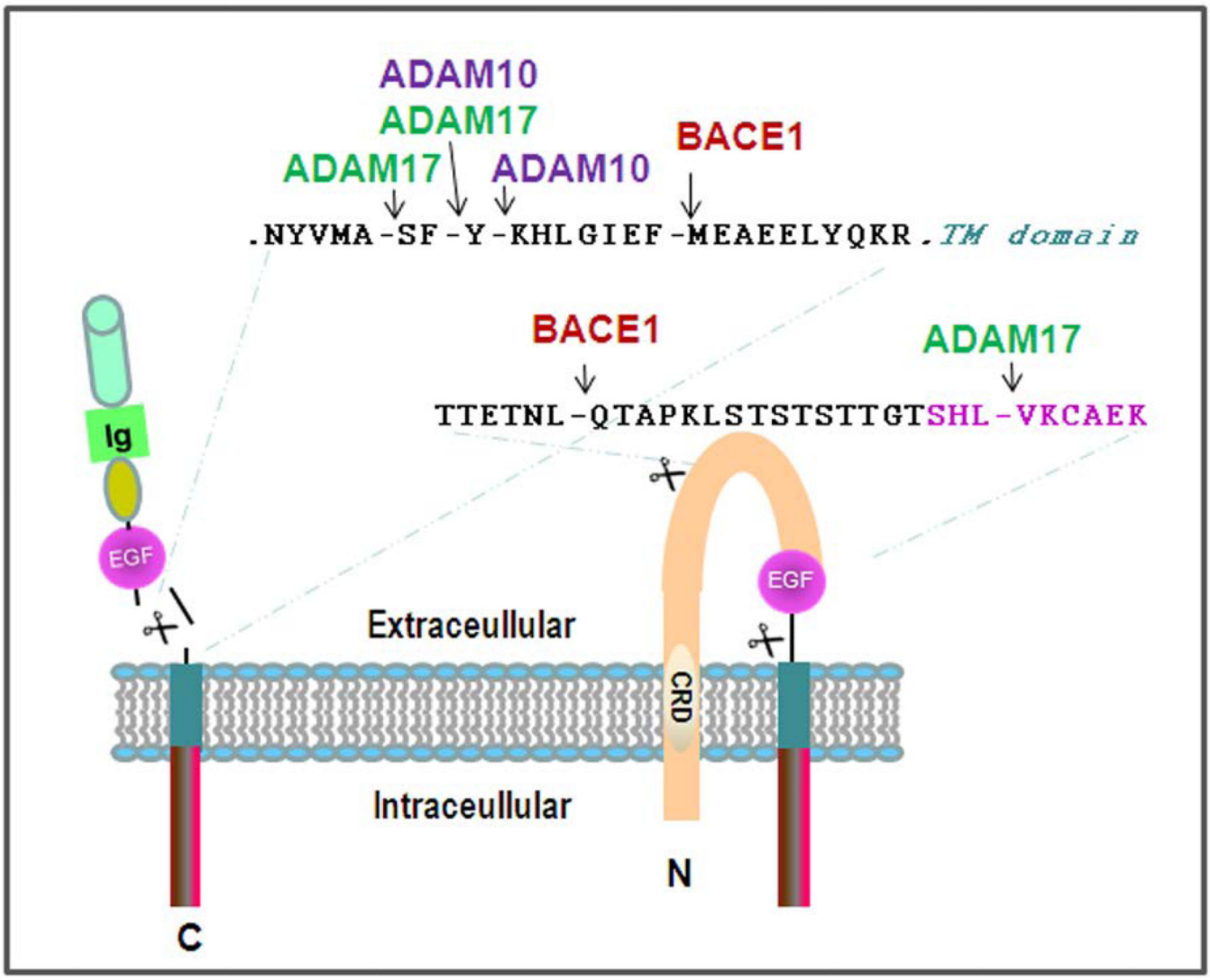

Figure 2. Cleavage of Nrg1 by BACE1 and ADAMs

The characterized cleavages of Nrg1 β1 isoforms are illustrated. The β1-containing exons coding for sequences are cleavable by ADAM10, ADAM17, and BACE1. Compared to the β1-isoform, the β2-isoform only lacks the sequence of KHLGIEFME, and is not cleavable by BACE1. The sequences as shown in type III Nrg1 isoforms can also be specifically cleaved by BACE1 and ADAM17, respectively. The EGF-like domain is presumably released after a single enzyme cleavage, such as BACE1 or ADAM17. Letters in pink are residues in the EGF-like domain.

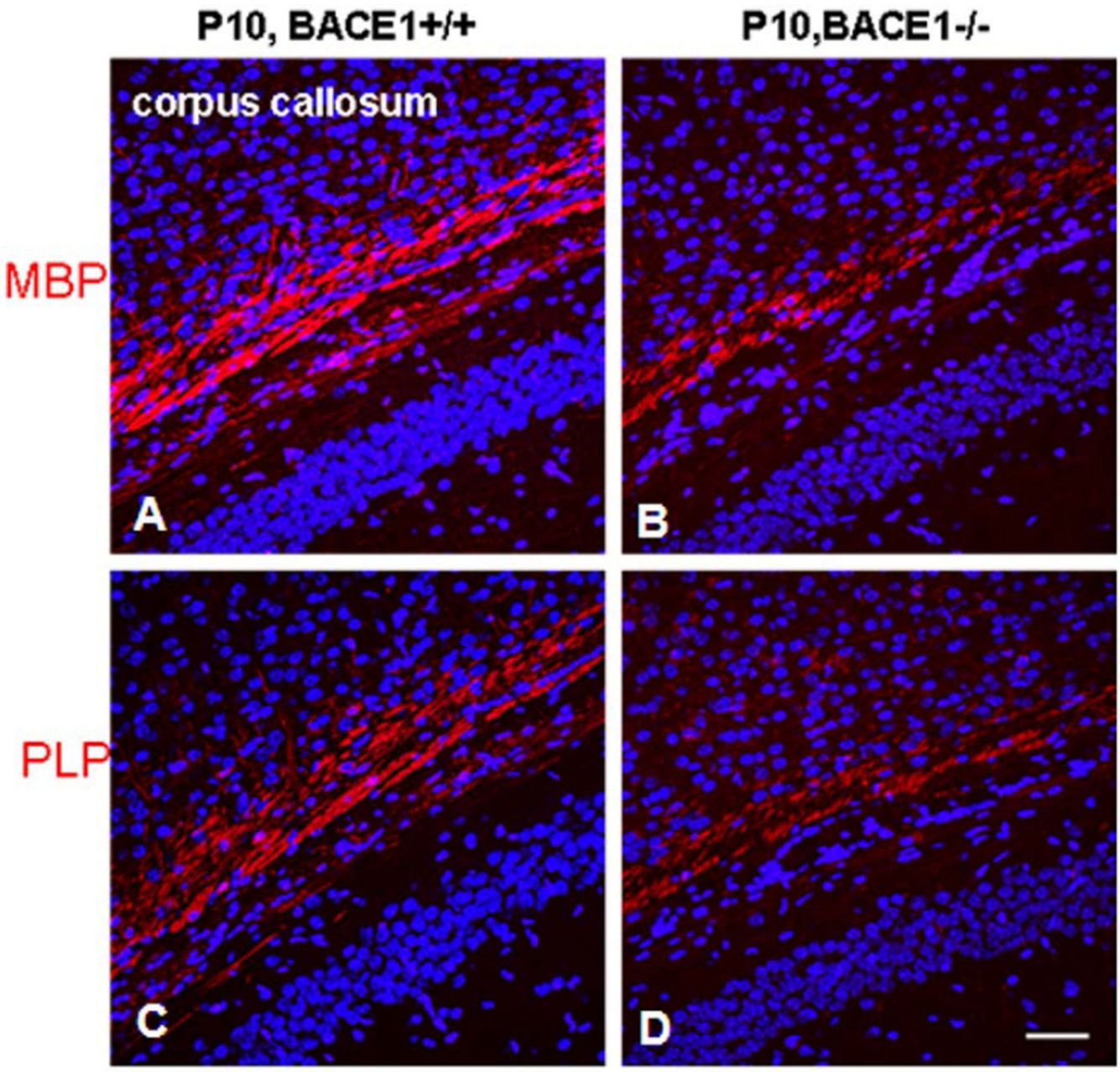

Figure 3. Delayed myelination of axons in corpus callosum of BACE1-null brains

Postnatal day 10 (P10) brain sections were fixed for immunohistochemistry with antibody to MBP (A–B) or PLP (C–D). Significantly delayed myelination in the corpus callosum of BACE1-null brain sections was evident with both antibodies, suggesting delayed myelination due to deletion of the BACE1 gene in mice.

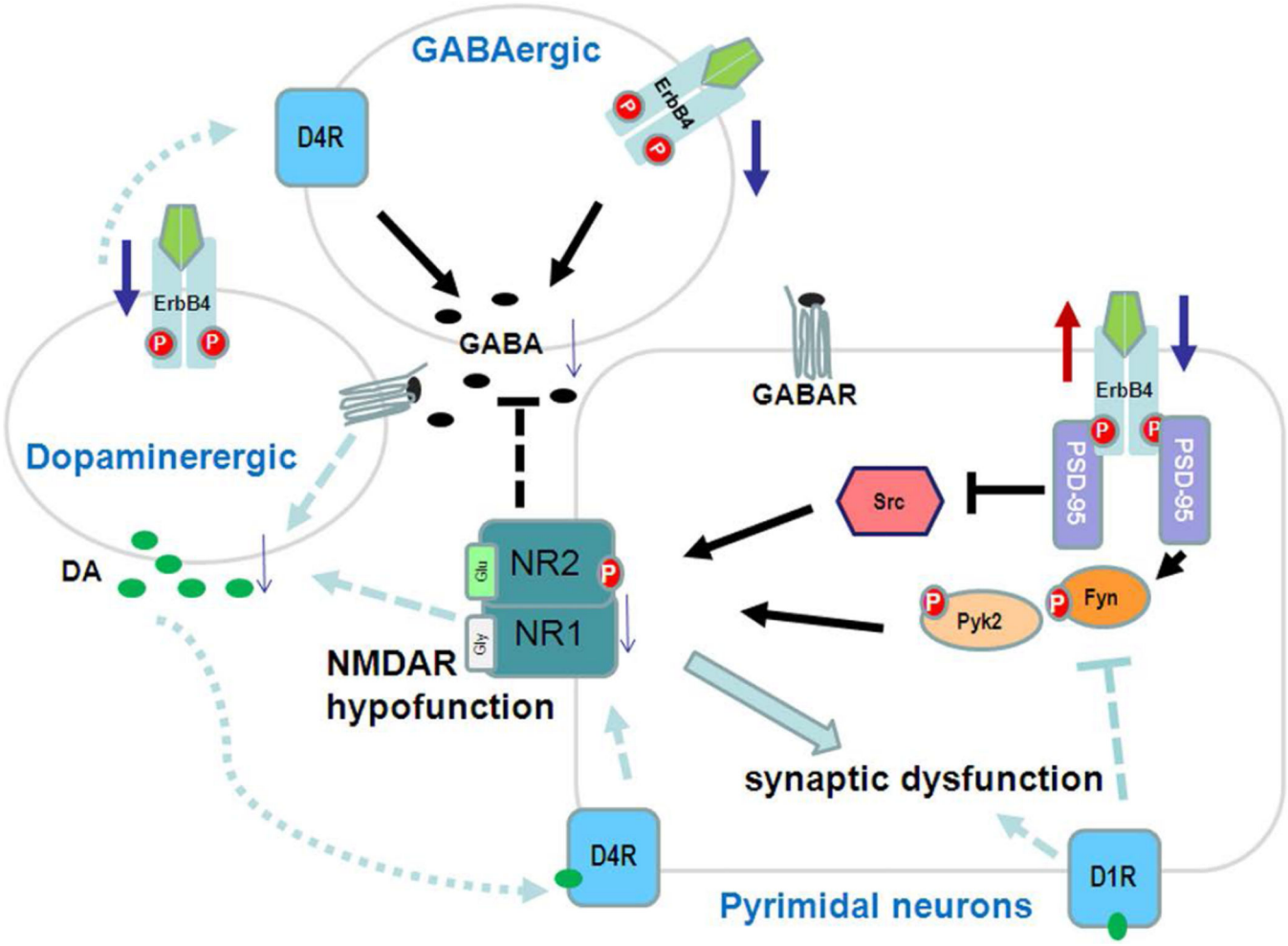

Figure 4. The Nrg1-ErbB4 pathway in schizophrenia

Disrupted functions in dopamine receptor-, GABA receptor-, and NMDAR-mediated neurotransmission are commonly suggested to contribute to schizophrenia etiologies. The ErbB4 receptor is present in pyramidal glutamatergic neurons, GABA-producing interneurons, and dopamine (DA)-producing neurons. Reduced Nrg1 levels decrease ErbB4 signaling in these cells. The consequent reduction in DA transmission will impair synaptic function via the DA-D4R or DA-D1R pathway or decreased stimulation of GABA-producing interneurons. ErbB4 signaling is required for GABA release, which is required for synchronizing synaptic function in glutamergic neurons. Decreased Nrg1-ErbB4 signaling in glutamergic neurons can have a direct impact on NR2 (NR2A and NR2B) phosphorylation via fyn and pyk2 activity, while increased Nrg1 may inhibit src-mediated phosphorylation of NMDARs. PSD-95 has a PDZ domain, which mediates binding of Src/fyn to the ErbB4 receptor.