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Molecules in focus

PSA–NCAM: Synaptic functions mediated by its interactions with proteoglycans and glutamate receptors

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ABSTRACT

Dynamic regulation of glycosylation of the neural cell adhesion molecule (NCAM) by an unusual large negatively charged polysialic acid (PSA) is the major prerequisite for correct formation of brain circuitries during development and for normal synaptic plasticity, learning and memory in the adult. Traditionally, PSA is viewed as a de-adhesive highly hydrated molecule, which interferes with cell adhesion and promotes cellular/synaptic dynamics by steric hindrance. Analysis of synaptic functions of PSA–NCAM highlighted additional features of this molecule. First, PSA promotes interaction of NCAM with heparan sulfate proteoglycans and thus stimulates synaptogenesis. Second, PSA–NCAM modulates glutamate receptors: it restrains activity of extrasynaptic GluN2B-containing NMDA receptors and facilitates activity of a subset of AMPA receptors. Perturbation in polysialylation and/or NCAM expression in mouse models recapitulates many symptoms of human brain disorders such as schizophrenia, depression, anxiety and Alzheimer's disease.

1. Introduction

Neural cell adhesion molecule (NCAM) belongs to the immunoglobulin (Ig) superfamily of glycoproteins (Maness and Schachner, 2007). NCAM mediates Ca^{2+}-independent homophilic and heterophilic cell–cell and cell-extracellular matrix (ECM) interactions, promoting neurite outgrowth and targeting, cell migration, fasciculation, axonal branching and synaptogenesis. Its polysialylated form PSA–NCAM exhibits de-adhesive properties and is also a key player in morphogenetic events during development (Kleene and Schachner, 2004). In addition, a solid body of evidence suggests an important role for NCAM and PSA–NCAM in synaptic plasticity, learning and memory in the adult nervous system (Dityatev et al., 2008).

2. Structure

NCAM is encoded by a single gene (Ncam1), which is located on different chromosomes in different species: 11th in humans, 9th in mouse and 8th in rat. In mice, NCAM gene consists of 24 exons (see Fig. 1): 15 (0–14) exons encode extracellular part of NCAM. Expression of exon 15 results in production of 725 amino acid (aa)-long NCAM-120, which is attached to the membrane by a glycosylphosphatidylinositol (GPI) anchor. Alternatively, the transcript can include exon 16, which encodes a transmembrane domain, and exons 17–19, which encode the intracellular part of NCAM. If a transcript includes exon 18, the result is 950 aa-long NCAM-180. If exon 18 is excluded from the transcript, 850 aa-long NCAM-140 is generated. Due to alternative RNA splicing, about 27 different NCAM isoforms can be generated, among which three major membrane isoforms are distinguished (NCAM-120, NCAM-140 and NCAM-180). The extracellular domain of these NCAM isoforms is composed of five Ig-like domains and two fibronectin type-III modules. Based on crystallographic data (Soroka et al., 2003, Table 1), it is plausible that NCAM–NCAM interactions occur either in a fully antiparallel (*trans*) fashion requiring Ig2–Ig3, Ig1–Ig3, Ig2–Ig2 interactions between NCAM domains, or in parallel (*cis*) mode, when Ig1 and Ig2 modules mediate dimerization of NCAM situated on the same cell surface, and such dimers trans-interact to form various zipper-like adhesion complexes. The extracellular domain of NCAM is also engaged in heterophilic interactions with the neural adhesion molecule L1, heparan and chondroitin sulfate proteoglycans, FGF receptor, GDNF and GDNF receptor GFR1, prion protein, TAG-1/axonin-1, and collagens (Table 1). In addition to the three main membrane isoforms of NCAM, there are several secreted forms. One of these is produced by expression of a small SEC-exon

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Table 1
NCAM-mediated interactions and brain disorders. The upper part of the table summarizes studies on interactions mediated by extracellular domain (ED), intracellular domain (ID) of NCAM and PSA. The lower part of the table depicts major evidence from human patients (blue) and animal models (black) on involvement of PSA–NCAM in different psychiatric disorders.

NCAM/PSA-mediated interactions

Binding partner	Binding domain	References
NCAM	Ig1-3, Ig1-2 Ig1-5	Soroka et al. (2003) Structure 10:291–301; Wieland et al. (2005) J Biol Chem 280:41037–46 Ranheim et al. (1996) PNAS 93:4071–75; Carl et al. (2001) PNAS 98:1565–70
L1	Ig4	Horstkorte et al. (1993) J Cell Biol 121:1409–21; Heiland et al. (1998) Eur J Cell Biol 75:97–106
FGFR	Fn1-2	Kiselyov et al. (2003) Structure 11:691–701
Heparin	Ig2	Cole and Akeson (1989) Neuron 2:1157–65; Reyes et al. (1990) Cell Regul 1:567–576
HSPG	Ig2	Cole and Akeson (1989) Neuron 2:1157–65; Storms et al. (1996) Exp Cell Res 223:385–394; Kulahin et al. (2005) J Neurochem 95:46–55
Chondroitin sulfate	Ig2	Kulahin et al. (2005) J Neurochem 95:46–55
CSPG	Ig2	Retzler et al. (1996) J Biol Chem 271:27304–10
GDNF	Ig3	Paratcha et al. (2003) Cell 113:867–79; Nielsen et al. (2009) J Neurosci 9:11360–76
GFRα1	Ig3	Ibáñez (2010) Biochem Biophys Res Commun 396:24–7
GDNF, GFRα1	Ig3	Sjostrand et al. (2007) J Biol Chem 282:12734–40
ATP	Fn2	Dzhandzhugazyan, Bock (1997) Biochem 36:15381–95; Skladchikova et al. (1999) J Neurosci Res 57:207–18
ST8SiaII, ST8SiaIV	Fn1, glycan on Ig5	Mendiratta et al. (2006) J Biol Chem 281:36052–9; Wuhrer et al. (2003) Biochimie 85:207–18; Angata et al. (2002) J Biol Chem 277:36808–17; Close et al. (2003) J Biol Chem 278:30796–805
PrP	Ig5, Fn1	Santuccione et al. (2005) J Cell Biol 169:341–54
ADAM17, ADAM10	ED	Kalus et al. (2006) J Neurochem 98:78–88; Hinkle et al. (2006) J Neurobiol 66:1378–95
β1 spectrin	ID	Leshchyns'ka et al. (2003) J Cell Biol 161:625–39; Sytnyk et al. (2006) J Cell Biol 174:1071–85
Calmodulin	ID	Kleene et al. (2010) J Neurosci 30:10784–98
Kir3	ID	Kleene et al. (2010) J Biol Chem 285:28968–79; Delling et al. (2002) J Neurosci 22:7154–64
TrkB	ID	Cassens et al. (2010) J Biol Chem 285:28959–67
DHHC3, DHHC7	ID	Ponimaskin et al. (2008) J Neurosci 28:8897–907
RPTP	ID	Bodrikov et al. (2005) J Cell Biol. 168:127–39; Ditlevsen et al. (2008) J Neurosci Res. 86:727–43
PDGF	PSA	Zhang et al. (2004) J Cell Sci 117:93–103.
BDNF, NGF, NT-3, NT-4	PSA	Muller et al. (2000) PNAS 97:4315–20; Kanato et al. (2008) Glycobiology 18:1044–53
FGF2	PSA	Ono et al. (2011) J Biol Chem, in press
GluN2B	PSA	Hammond et al. (2006) J Biol Chem 281:34859–69; Kochlamazashvili et al. (2010) 30:4171–83.
GluA	PSA	Vaithianathan et al. (2004) J Biol Chem 279:47975–84; Potschka et al. (2008) Neuroscience 152(4):1093–8
Siglec-11	PSA	Wang and Neumann (2010) J Neurosci 30:3482–8
Histone H1	PSA	Mishra et al. (2010) J Neurosci 30:12400–13

NCAM/PSA-related medical applications

Molecular fingerprint	CNS dysfunction	References
ST8SiaII, ST8SiaIV SNPs	Autism	Anney et al. (2010) Hum Mol Genet 19:4072–82
↓ ST8SiaII, ST8SiaIV	↓ Social, ↑ aggressive, ↓ anxiety-related behaviors	Calandreau et al. (2010) Genes Brain Behav 9:958–67
ST8SiaII SNPs	Schizophrenia	Tao et al. (2007) Schizophr Res. 90:108–14; Arai et al. (2006) Biol Psychiatry 59:652–9; Isomura et al. (2011) J Biol Chem 286:21535–45
NCAM SNPs	Schizophrenia bipolar disorder	Sullivan et al. (2007) Biol Psychiatry 261:902–10; Arai et al. (2004) Biol Psychiatry 55:804–10; Atz et al. (2007) Psychiatr Genet. 17:55–67
↑ PSA–NCAM	Heroin addiction	Weber et al. (2006) Neuroscience 138:1215–23
↑ VASE in CSF	Schizophrenia aging	Vawter et al. (2000) J Psychiatr Res 34:25–34; Qin et al. (2005) J Neurosci Res 80:838–44
↑ VASE in hippocampus	Bipolar disorder	Vawter et xal. (1998) Exp Neurol 154:1–11
↓ SEC/MSD1c	Bipolar disorder	Atz et al. (2007) Psychiatr Genet 17:55–67
↑ Soluble NCAM	Alzheimer's disease	Strekalova et al. (2006) Neurobiol Aging 27:1–9; Todaro et al. (2004) Neurobiol Dis 15:387–93
↑ Soluble NCAM	Schizophrenia	Lyons et al. (1998) Biol Psychiatry 23:769–75; Poltorak et al. (1995) Exp Neurol 131:266–72; van Kammen et al. (1998) Biol Psychiatry 43:680–86; Vawter et al. (1998) Exp Neurol 149:424–32; Vawter et al. (2001) Exp Neurol 172:29–46
↓ NCAM, NCAM180 ↓ PSA	↓ Hyperalgesia, ↑ hyperalgesia after injury	Maarouf et al. (2011) Exp Neurol, in press
↓ ST8SiaIV	↑ Epilepsy	Pekcec et al. (2010) Neuroreport 21:549–53
↓ PSA–NCAM	Epilepsy	Mathern et al. (2002) Epilepsia 43:68–73

ADAM10 and ADAM17, a disintegrin and metalloproteinases 10 and 17; ATP, adenosine triphosphate; BDNF, brain-derived neurotrophic factor; CSF, cerebrospinal fluid; CSPG, chondroitin sulfate proteoglycan; DHHC3 and DHHC7, palmitoyltransferases of the DHHC family; FGF2, fibroblast growth factor-2; FGFR, fibroblast growth factor receptor; Fn, fibronectin type-III module; GDNF, glial-derived neurotrophic factor; GFRα1, GDNF receptor; GluA, AMPA glutamate receptor; GluN2B, a subunit of NMDA glutamate receptors; HSPG, heparan sulfate proteoglycan; Ig, immunoglobulin domain; Kir3, inwardly rectifying K^+ channel; NGF, nerve growth factor; NT-3 and NT-4, neurotrophin-3 and -4; PDGF, platelet-derived growth factor; PrP, prion protein; RPTP, protein tyrosine phosphatase-α; Siglec-11, sialic acid binding Ig-like lectin 11; SNPs, single-nucleotide polymorphism; ST8SiaII, ST8SiaIV, polysialyltransferases; TrkB, tyrosine kinase receptor B.

located between exons 12th and 13th. The others are produced by shedding and proteolytic cleavage of the extracellular part of NCAM. There are more alternatively spliced insertions: the so-called VASE exon located between 7th and 8th major exons encodes a 10 aa-long sequence. Besides the SEC exon, four additional small exons can be inserted between 12th and 13th exons; three of these exons encode muscle specific domain 1 (MSD1: MSD1a, MSD1b and MSD1c), the fourth exon AAG consists of only a single nucleotide triplet (Walmod et al., 2004; see additional Refs. in Table 1).

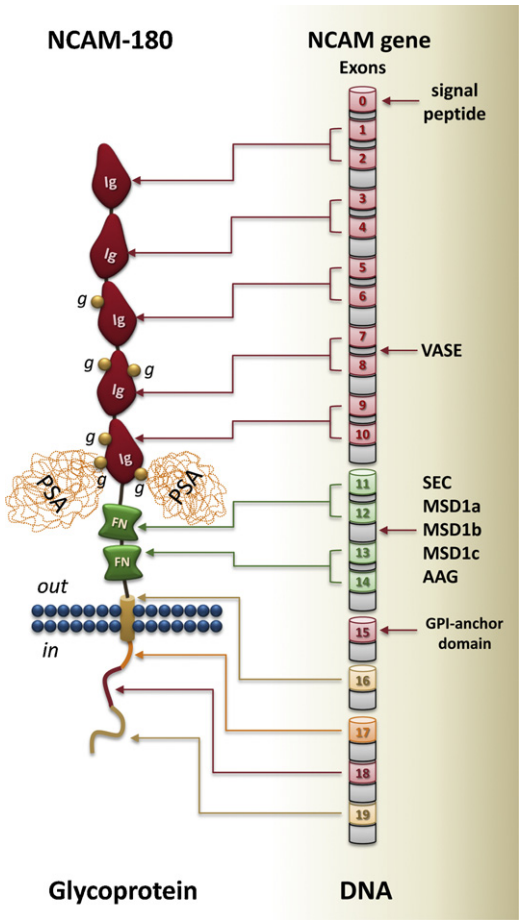

Fig. 1. Structure of NCAM depicted as a largest NCAM-180 isoform (from the left) and a scheme of its gene Ncam1 (from the right). NCAM-180 consists of 5 Ig-like domains (red) and 2 fibronectin-type III (Fn, green) modules, a transmembrane domain and an intracellular tail. NCAM protein backbone contains 6 potential N-glycosylation sites (yellow globules), last two of them can be polysialylated, carrying a carbohydrate with an unusual α2,8 linkage of sialic acids in its chains (marked as PSA). The scheme of NCAM gene shows a sequence of 20 main exons and small inserts like VASE, SEC, MDS1a,b,c and AAG.

3. Expression, activation and turnover

PSA–NCAM is abundant in the developing brain, but its expression is gradually decreasing after birth, remaining only in brain areas with high degree of plasticity and renewal, e.g. hippocampus, subventricular zone, thalamus, prefrontal cortex and amygdala (Rutishauser, 2008). Attachment of PSA to NCAM at two glycosylation sites on the 5th Ig-like domain of NCAM is performed by two independently regulated but synergetic polysialyltransferases, ST8SiaII/STX and ST8SiaIV/PST (Table 1). The former is predominantly expressed during prenatal and early postnatal development, the expression of the latter persists in adulthood. Expression of PSA–NCAM is synaptic activity-, learning- and brain subregion-dependent. Massive polysialylation of NCAM expressed on granular neurons of the dentate gyrus occurs after spatial or passive avoidance tasks at 12–16 h post-training time-window (Murphy and Regan, 1999), 24 h after contextual fear conditioning in the dorsal, but not ventral, hippocampus (Lopez-Fernandez et al., 2007) and in the amygdala following the extinction, but not after acquisition of auditory fear conditioning memory (Markram et al., 2007). In vivo induction of LTP in adult rat dentate gyrus is followed by a rapid and sustained (up to 4 h) NCAM polysialylation by activation of ST8SiaII and ST8SiaIV gene expression (Guiraudie-Capraz et al., 2011). NCAM is synthesized in the endoplasmatic reticulum, and within an hour can be expressed on a cell surface. Polysialylation of NCAM is a rapid process (~10 min) that takes place in Golgi compartments. Another important posttranslational modification of NCAM is palmitoylation, mediated by DHHC3 and DHHC7 (Table 1), which is necessary for targeting of NCAM to lipid rafts and NCAM signaling in lipid rafts via the tyrosine kinase fyn and the focal adhesion kinase. Co-signaling via this pathway and FGF receptors is required for NCAM-mediated neurite outgrowth (Niethammer et al., 2002). Degradation of transmembane isoforms of NCAM occurs via enzymatic cleavage by metalloproteases ADAM10 and ADAM17/TACE, whereas GPI-anchored NCAM-120 is cleaved by a phosphatidylinositol-specific phospholipase C (PI-PLC). NCAM biosynthesis rate and turnover is high in embryonic and early postnatal periods, whereas biosynthesis rate decreases with age by factor 100 in neurons from E17 to P25 and turnover declines by factor 350 during this time period (Berezin, 2010).

4. Biological functions of PSA–NCAM

Early experiments using endoneuraminidase to digest PSA revealed its importance for cell migration, synaptic plasticity, neuronal repair and learning and memory (Rutishauser, 2008). More recent genetic studies demonstrated that ablation of ST8SiaIV gene results in impaired long-term potentiation (LTP) and depression (LTD) in CA3-CA1 synapses, whereas LTP at perforant path-DG and mossy fiber-CA3 synapses is undisturbed (Eckhardt et al., 2000). Deletion of either ST8SiaII or ST8SiaIV impaired fear conditioning (Angata et al., 2004; Senkov et al., 2006). Ablation of both enzymes leads to gross brain-wiring abnormalities due to a gain of NCAM-mediated adhesion (Hildebrandt et al., 2009).

4.1. PSA–NCAM and proteoglycans

Apart from interactions with cell adhesion molecules, NCAM may also interact with ECM molecules (Table 1). For example, heparan sulfate and chondroitin sulfate proteoglycans (HSPG and CSPG, respectively), including agrin, neurocan and phosphacan, directly bind to a region on the second Ig-like domain of NCAM (Reyes et al., 1990; Kulahin et al., 2005). The binding sites of HSPGs and CSPGs partially overlap with the homophilic binding site of NCAM and interaction between NCAM and these proteoglycans may alter NCAM-mediated neurite outgrowth (Kulahin et al., 2005). Importantly, PSA promotes binding of HSPGs to NCAM (Storms and Rutishauser, 1998), suggesting that PSA can function as a switch between cell–cell and cell-ECM adhesion. Enzymatic removal of PSA or heparan sulfates from cultured neurons, or a mutation in the heparin-binding domain of NCAM diminishes synaptogenic activity of postsynaptically expressed PSA–NCAM. This activity is NMDA and FGF receptor-dependent. These data suggest that interaction between PSA–NCAM and HSPGs incorporated in the ECM may support FGF receptor-mediated signaling and promote synaptogenesis (Dityatev et al., 2004; Fig. 2a). This mechanism may nicely complement the direct interaction between NCAM and FGF receptors. The latter can be mimicked by application of NCAM-derived FGL peptides, which have been shown to stimulate FGF receptors and promote synaptogenesis and memory consolidation (Cambon et al., 2004).

4.2. PSA–NCAM and glutamate receptors

In addition to its positive influence on interactions with proteoglycans, PSA promotes signaling via the brain derived neurotrophic factor (BDNF) and platelet-derived growth factor (PDGF)

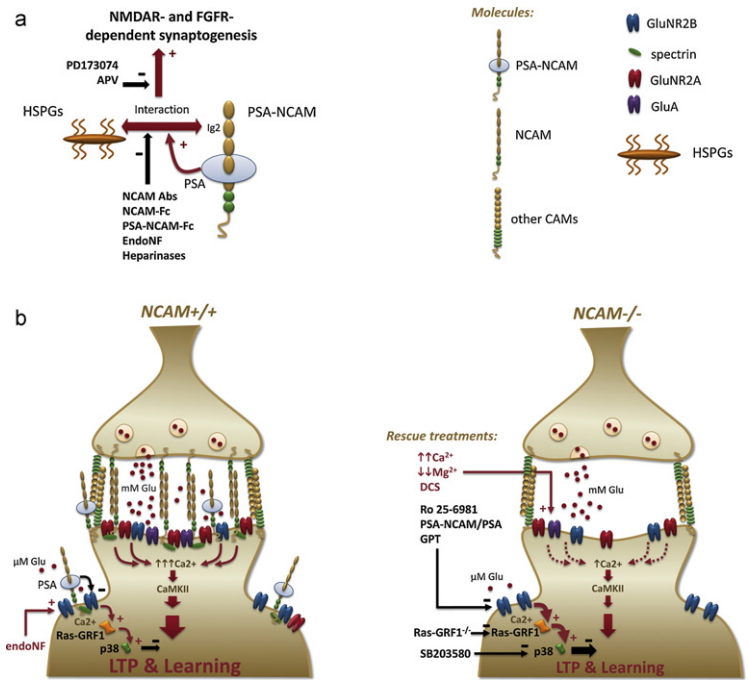

Fig. 2. (a) A scheme showing a cooperative action of HSPGs and PSA–NCAM in synaptogenesis. *Abbreviations*: APV, NMDAR blocker; PD173074, FGFR inhibitor. (b) A scheme, depicting a possible causal link between PSA–NCAM deficiency and unbalanced signaling through extrasynaptic GluNR2B- versus synaptic GluN2A-containing NMDA-Rs. The absence of PSA–NCAM at synapses can cause disinhibition of a subset of extrasynaptic GluN2B-containing glutamate receptors, resulting in activation of Ras-GRF1-p38 MAPK signaling cascade and leading to impaired synaptic plasticity and cognitive functions. This mechanism might be operant in schizophrenia, in brain regions where PSA–NCAM function is disturbed. *Abbreviations*: CaMKII, calmodulin-dependent protein kinase II; DCS, D-cycloserine; endoNF, endoneuraminidase that cleaves PSA from the NCAM backbone; GPT, glutamate scavenger; Glu, glutamate; Ras-GRF1, guanine nucleotide exchange factor 1; Ro 25-6981, specific blocker of GluN2B receptors; SB203580, inhibitor of a mitogen-activated protein kinase p38.

(Table 1), presumably by capturing and improving presentation of these factors to their cognate receptors. One of the first clue that PSA–NCAM itself might function as an extracellular ligand/modulator of some receptors was a study (Senkov et al., 2006) in which (1) hippocampus-dependent contextual memory in wild-type mice could be disrupted via intrahippocampal injection of either the extracellular domain of PSA–NCAM or PSA alone; (2) impaired contextual memory in NCAM mutants could be normalized via injection of PSA-NCAM, but not NCAM; (3) impaired CA1 LTP in hippocampal slices was rescued via application of PSA or PSA–NCAM, but not NCAM. A parallel in vitro study (Hammond et al., 2006) reported that PSA alone or attached to NCAM inhibited activation of GluN2B-containing NMDA receptors by low micromolar concentrations of glutamate (Fig. 2b), which are characteristic for extrasynaptic space but much lower than synaptic concentration of glutamate following transmitter release. In the absence of PSA–NCAM, GluN2B-containing receptors become disinhibited, resulting in activation of Ras-GRF1-p38 MAPK signaling cascade and leading to impaired LTP (Kochlamazashvili et al., 2010). Indeed, the level of phosphorylated p38 MAPK is upregulated in NCAM mutants and in endoneuraminidase-treated slices (Kochlamazashvili et al., 2010), while it is reduced in Ras-GRF1 knockout mice (Li et al., 2006). Inhibition of GluN2B-containing receptors by Ro25-6981 restores not only LTP in NCAM- or PSA-deficient slices, but also contextual fear conditioning in NCAM deficient mice (Kochlamazashvili et al., 2010). Consistently with these reports, mice deficient in the glial glutamate transporter GLT-1 have increased extracellular concentration of glutamate and impaired LTP (Katagiri et al., 2001) and contextual fear conditioning (Kiryk et al., 2008). Corroborating these findings, a decrease of extrasynaptic glutamate concentration by glutamate scavenger GTP restores LTP in NCAM deficient mice (Kochlamazashvili et al., 2010). The following experiments support the view that PSA–NCAM is involved in regulation of Ras-GRF1-p38 MAPK signaling: inhibition of p38 rescues LTP in PSA/NCAM-deficient slices and PSA deficiency does not cause impaired LTP in Ras-GRF1 knockout mice (Fig. 2b). Increased signaling via extrasynaptic GluN2B in NCAM deficient mice is associated with impaired signaling through synaptic GluN2A receptors. The latter can be compensated by the agonist of NMDA receptor D-cycloserine, which restores CA1 LTP and fear conditioning in NCAM deficient mice (Kochlamazashvili et al., 2012). In addition to NMDA receptors, PSA and PSA–NCAM can potentiate α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) subtype of glutamate receptors in astrocytes and immature pyramidal neurons isolated from CA1 region of the hippocampus (Vaithianathan et al., 2004). The functional importance of this regulation is currently unknown.

4.3. Possible medical applications

Impairment in NCAM and/or PSA function in humans have strong association with major neuropsychiatric and neurodegenerative disorders such as schizophrenia, bipolar disorder, depression, anxiety and Alzheimer's disease (Brennaman and Maness, 2010; Table 1). Expression of PSA–NCAM is decreased in hippocampi of schizophrenic patients, whereas soluble NCAM fragments (105–115 kDa) are increased in the cerebrospinal fluid and in the brain. Majority of single nucleotide polymorphisms (SNPs) in NCAM gene are located in intronic regions and may interfere with splicing or NCAM expression. SNP rs58447 is a modification in exon 12 encoding the first fibronectin domain that is a binding site for the polysialyltransferases and it is a susceptibility locus for schizophrenia. Additionally, SEC exon has inhibitory effect on neurite outgrowth and its abnormal expression might play a role in schizophrenia and bipolar disorder. Elevated VASE exon expression of NCAM is found in CSF of schizophrenia patients, in the hippocampus of senescence-accelerated mice

(SAM), and in the hippocampus of patients with bipolar disorder (Table 1). It is noteworthy that unbalanced glutamatergic signaling due to aforementioned PSA/NCAM deficit in animal models bears some similarity to glutamatergic system impairment in schizophrenic patients. For example, expression of glutamate transporter VGlut1, glutamate uptake sites, GluN1 subunit of NMDA-Rs, and AMPA-Rs are decreased in the hippocampus and prefrontal cortex in schizophrenia and D-cycloserine ameliorates negative symptoms in schizophrenia (Heresco-Levy et al., 1998). It also normalizes impaired CA1 LTP/LTD and learning in NCAM deficient mice (Kochlamazashvili et al., 2012). Systemic treatment with the FGL peptide (mimicking NCAM interaction with FGF receptors) reverses depression-like behavior in NCAM deficient mice, reduces neuroinflammation and neuroglial activation within the aged rat hippocampus and the age-related loss of synaptophysin immunoreactivity within CA3 and hilus, and attenuates beta amyloid-induced neuropathology and cognitive impairment that are hallmarks of Alzheimer's disease (Berezin and Bock, 2010).

5. Conclusion

PSA–NCAM has "many faces" and regulates synaptic functions by modulation of signaling through BDNF, FGF and NMDA receptors. Genetic and/or environmentally triggered disturbances in NCAM/PSA function in the human brain may lead to unbalanced glutamatergic signaling via GluN2B-, GluN2A-contaning NMDA and AMPA receptors, which may contribute to cognitive dysfunctions. Synaptic and cognitive abnormalities in NCAM deficient mice can be pharmacologically compensated by modulators of NMDA-Rs. As FGL and several other NCAM mimetic and binding peptides can promote neurite outgrowth and exhibit neuroprotective, synaptogenic and plasticizing properties, NCAM is an attractive target for drug development, in particular for the treatment of neurodegenerative and cognitive disorders.

Acknowledgments

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