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Review

The neuroplasticity marker PSA-NCAM: Insights into new therapeutic avenues for promoting neuroregeneration

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ABSTRACT

Neuroplastic alterations are the key processes involved in adaptation and rehabilitation after all neurological injuries and pathologies. Being the central contributor to the developmental and adult neuroplasticity, the polysialylated form of Neural Cell Adhesion Molecule (PSA-NCAM) may prove to be a potential target to facilitate repair/regeneration after CNS injury and disease. Over the years, several experimental approaches have been developed to exploit the therapeutic potential of PSA-NCAM. Broadly, the studies focused on cell-transplantation strategies to alter PSA-NCAM properties at the injury site, injection of peptide based as well as synthetic PSA mimetics directly into the injury site or the application of PSA containing hydrogels and scaffolds as biomaterials. A comprehensive understanding of the PSA-based experimental approaches, as well as their pros and cons, is urgently required for successful implementation of this molecule in therapeutics. The current review, therefore, has been designed to give the readers a thorough account of all the diverse roles of PSA in the adult nervous system and the recent progress that has been made in developing PSA-based therapeutic approaches for neuroregeneration.

1. Introduction

Polysialic acid (PSA) is a linear glycopolymer consisting of multiple α2,8-linked *N*-acetylneuraminic acid units that are attached to the neural cell adhesion molecule (NCAM) as a post-translational modification. The landmark report regarding the presence of large polysialosyl units in the developing rat brain was published 35 years ago [1]. Since then, a prodigious amount of research has been undertaken to explore the potential role of PSA-NCAM in regulating the nervous system functions. High degree of polymerization of sialic acid units in PSA-NCAM results in development of copious amounts of negative charge, which influences its hydration volume and subsequently affects the efficiency of binding between the cells or cell-glycomatrix [2,3]. Apart from mediating permissive and insulative regulations on the receptor

Abbreviations: 5-NOT, 5-nonyloxytryptamine oxalate; Akt, protein kinase B; Arc, activity-regulated cytoskeleton-associated protein; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; CREB, cAMP-response element binding protein; ELISA, enzyme-linked immunoassay; ERK, extracellular signal-regulated protein kinases; mTOR, mechanistic target of rapamycin; NCAM, neural cell adhesion molecule; NIH, national institutes of health; PNS, peripheral nervous system; PSA, polysialic acid; PST, polysialyltransferases; STX, siayltransferase; TSD, 50 % ethanolic extract of *Tinospora cordifolia* fed sleep deprived; VSD, vehicle-sleep deprived; VUD, vehicle-undisturbed sleep; WSD, ashwagandha water extract fed sleep deprived; WT, wild type.

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molecules present at the surface of cells [4–6], PSA also influences NCAM-mediated heterophilic interactions [7,8] as well as modulates the concentration of proximal soluble factors [9]. Thus, polysialylation imparts tremendous plasticity potential in the nervous system cells enabling them to undergo structural and synaptic remodeling under different physiological and pathological conditions [10–12,9].

Since PSA-NCAM, as a neuroplasticity marker, holds an immense therapeutic potential against a wide range of neuropathologies and neurological disorders, in the past years several experimental approaches have been developed to explore and exploit its therapeutic aspects. The purpose of this Review is to evaluate the recent progress in development of PSA-based therapies. The first part of the Review has been designed to give comprehensive information to the readers about the diverse roles of PSA-NCAM as a neuroplasticity marker in regulating the adult brain physiology and it also describes how PSA-NCAM has emerged as a risk factor for various neuropathologies. The second part of the Review gives a detailed account of the role of PSA-NCAM in facilitating regeneration after CNS and PNS injuries and describes the recent developments in identification and characterization of PSA mimetics and PSA-based biomaterials for neuroregeneration.

2. PSA-NCAM as a neuroplasticity marker in the adult nervous system

PSA-NCAM is known to be widely distributed throughout the nervous system during embryonic development [9]. However, in adults, it has been reported to be expressed in regions demonstrating the ability of neurogenesis, and structural and synaptic remodeling despite their stable structural, functional, and neurochemical specificities [13]. Such structural and synaptic transformations have been suggested to be incited due to heightened activity in the neurons in response to physiological conditions. This highlights the remarkable capacity of plasticity in the nervous system. Throughout adulthood, PSA-NCAM is expressed in the prime regions that are involved in persistent neurogenesis. The newly generated cells in the subventricular zone show PSA-NCAM immunoreactivity and presence of PSA-NCAM on these cells in adults has been suggested to be crucial for their migration to the olfactory bulb *via* corpus callosum and striatum [14] to form periglomerular and granular cells [15]. Enzymatic removal of PSA has been reported to interrupt the migration of subventricular zone-derived neural progenitor cells into the striatum lesioned by 6-hydroxydopamine [16]. Similar to the subventricular zone, the newly generated cells in dentate gyrus are also PSA-NCAM-positive and it is crucial for migration of these cells, their integration into new neuronal circuits and differentiation [17–19]. In addition, the olfactory receptor neurons and globose basal cells of the olfactory neuroepithelium also show continuous expression of PSA-NCAM where it facilitates their process outgrowth towards the olfactory bulb [20].

PSA-NCAM also plays an important role in the distinct structural modulations that occur in the neuronal and glial cells as well as synapses of the hypothalamo-neurohypophysial system in response to various physiological changes [4]. PSA-NCAM levels in the female rats correspond with different phases of the ovarian cycle. Higher levels of PSA-NCAM have been reported to occur in the GnRH neuron cell bodies in the pre-optic area and their terminals in median eminence-arcuate region of hypothalamus during the pro-oestrous phase as compared to the di-oestrous phase [21,22]. PSA-NCAM has been suggested to be involved in the regulation of synaptic changes and the position of ensheathing astrocytes in the arcuate nucleus in response to the levels of circulating estrogen [23,24]. Enzymatic removal of PSA-NCAM prevented gonadotrophin-releasing hormone axon terminal retraction and associated glial cell remodeling under both *in vitro* and *in vivo* conditions [25]. Also, treatment of cycling rats in the pro-oestrous phase with α-adrenergic receptor blocker phenoxybenzamine and γ-aminobutyric acid reduced the expression of gonadotrophin-releasing hormone and PSA-NCAM in the pre-optic area and the median eminence-arcuate region, thereby suggesting the potential involvement of PSA-NCAM in neuron-glial remodeling in reproductive cycles [25].

Interestingly, PSA-NCAM has also been suggested to be involved in the diet-induced structural remodeling of gonadotrophin-releasing hormone axons in the median eminence region [26]. Further, transient upregulation of PSA-NCAM by neuronal and glial cells of hypothalamic supraoptic and paraventricular nuclei and by magnocellular neurons was reported to regulate the number of synapses and glial coverage of the perivascular area during lactation and osmotic stimulation [27–29,4]. Recently, expression of PSA-NCAM and other neurotrophins in medial prefrontal cortex of dopamine transporter knockout rats have been observed to regulate sexual behavior [30].

Another hypothalamic region which depicts PSA-mediated structural plasticity in adults is suprachiasmatic nucleus, the seat for mammalian circadian rhythm. PSA-NCAM has been suggested to be critical for the stability of circadian rhythm under constant darkness and photic synchronization of circadian rhythm phase [31]. In the suprachiasmatic nucleus of Syrian hamster, PSA levels decreased during dark phase and increased after stimulation with light pulse [32]. Pretreating the rat brain slices with endoneuraminidase, which selectively removes PSA from NCAM, has been shown to abolish glutamate- and optic chiasm stimulation-induced phase delays of the suprachiasmatic nucleus circadian neuronal activity rhythm [33]. Enzymatic removal of PSA from suprachiasmatic nucleus disabled photic induction of cfos protein, which is the key molecule for clock resetting [34]. PSA removal also modulated intergeniculate leaflet and raphe nuclei-mediated non-photic shifts [35] of circadian rhythm.

Further, the mice vulnerable to diet-induced obesity have been shown to express low levels of PSA-NCAM in the hypothalamus region [36]. The reduction of hypothalamic PSA-NCAM levels has been reported to be sufficient to alter short-term homeostatic responses to dietary fat and increase body weight gain and promote fat storage under hypercaloric pressure for long term [37,38], thereby confirming that hypothalamic PSA-NCAM is critical for maintenance of energy homeostasis upon metabolic challenge. The inter-individual variability in hypothalamic PSA-NCAM levels may account for the difference in vulnerability to diet-induced obesity. Given the role of PSA-NCAM in brain plasticity, these data suggest that reduced plasticity in brain circuits that control appetite, metabolism as well as body weight may confer risk for developing eating disorders and obesity. Additionally, the factors controlling neural plasticity may also be the determinants of individual susceptibility to develop overweight with obesogenic foods [39–41].

Furthermore, PSA-NCAM functions broadly, serving to mediate synaptic plasticity, neurogenesis, signaling by neurotrophic factors and the inflammatory messengers throughout the brain; all of which are associated with the progression and treatment of depression. The expression of PSA-NCAM is known to be reduced by depression, and enhanced by antidepressant treatment, particularly within the hippocampus [42–44]. The selective cleaving of PSA moieties using endoneuraminidase N has been shown to inhibit the antidepressant efficacy of selective serotonin reuptake inhibitor fluoxetine in a chronic stress model of depression [45]. A corresponding attenuation of fluoxetine-induced hippocampal neuroplasticity, including decreased hippocampal neurogenesis, synaptic density, and neural activation has also been reported. These data suggest that PSA-NCAM-mediated neuroplasticity is necessary for antidepressant action.

3. Role of PSA-NCAM in learning and memory functions

In the adult brain, PSA-NCAM has been reported as a critical component that contributes to activity-induced synaptic plasticity and memory formation. It is important in the process of dendritic and synaptic remodeling, neurogenesis and plays crucial role in normal hippocampal function [46]. These phenomena enable synaptic morphogenesis in the hippocampal neurons; thereby, allowing them to adapt to new

situations or environmental changes. Experimental manipulations which alter the expression or function of PSA-NCAM affect the learning ability of animals; and learning may lead to the alterations in the expression of this molecule [9]. Polysialylation is a characteristic feature of widely interconnected, complex neural circuits, which also includes the olfactory system (comprising olfactory sheet, olfactory bulb and primary olfactory cortex) and the medial temporal lobe (comprising hippocampus, perirhinal and parahippocampal cortices) [47–49]. Most of these neuronal circuits are involved in learning and memory storage. In the olfactory bulb region, polysialylation is strictly associated with persistent neurogenic processes [9]. The medial temporal lobe confides a bidirectional link between hippocampal formation and cortical regions. Changes in the expression of PSA-NCAM and NCAM have been reported in relation to learning of olfactory discrimination tasks [50]. In a link to memory for odor-reward association, transient polysialylation has also been reported in the dentate gyrus region of hippocampus [51]. Structures of the medial temporal lobe including the hippocampus and adjoining cortical regions, *i.e.*, perirhinal, entorhinal and parahippocampal cortices, are involved in the process of memory consolidation, wherein, the memories are initially dependent upon medial temporal lobe but afterwards they gradually establish themselves as long-term memories in other regions of the brain. Further, the contextual and spatial learning and memory is also dependent on cortico-hippocampal circuitry [52].

Transient modulations in polysialylation have been reported following different regimens of spatial learning and memory [9,53]. Synaptic expression of PSA-NCAM and NCAM have shown enhanced expression in rats after 24 h of training session in the spatial version of Morris Water Maze [53]. However, the disruption of NCAM function by a synthetic peptide or treatment with endoneuraminidase (enzyme that cleaves PSA from NCAM) led to the impairment in spatial memory abilities, which supports the role of synaptic expression of PSA-NCAM and NCAM in spatial learning and memory. Recently, our lab has reported the impairment in memory function of rats (tested by novel object recognition test) fed with high-fat diet (30 % fat by weight) for the period of 12 weeks [54] as compared to the rats fed on low-fat diet. Cognitive impairment observed in the animals of the high-fat diet group has been attributed to the upregulation in expression of PSA-NCAM in the hippocampus and piriform cortex regions of the brain. This was also accompanied by reduction in NCAM expression in these brain regions. Chronic restraint stress has been reported to upregulate the expression of PSA-NCAM in the dentate gyrus and piriform cortex regions of brain while inhibiting neurogenesis [55,56]. The enhanced polysialylation in the high-fat diet group animals may be a neuroprotective mechanism in stress-vulnerable neuronal circuits. On the other hand, another group of rats received high-fat diet supplemented with dry leaf powder of *Withania somnifera* (Ashwagandha), at the dose of 1 mg/g body weight of the animal. The animals of this group showed more propensity towards novel object in novel object recognition test. Ashwagandha supplementation in high-fat diet led to near-control expression of PSA-NCAM and upregulation of NCAM expression. The poor recognition memory of the high-fat diet fed rats has been attributed to reduction in NCAM expression, which was reinstated with Ashwagandha supplementation, leading to improved performance in rats fed with high-fat diet supplemented with Ashwagandha in memory task [54].

In parallel studies, our lab investigated the effect of pre-administration of the water extract from leaves of Ashwagandha and the 50 % ethanolic extract of *Tinospora cordifolia* on memory and cognitive impairments induced by acute sleep deprivation [57,58]. The animals were divided into the following four groups- a) vehicle-undisturbed sleep (VUD) which included animals who were allowed to sleep regularly and were fed with water as vehicle for 15 days; b) vehicle-sleep deprived (VSD) which included water-fed animals who were sleep deprived on the 15th day in their light phase. Sleep deprivation was done for a period of 12 h by gentle handling method ; c) sleep deprived rats fed with water extract from the Ashwagandha leaves for 15 days (WSD) and d) sleep deprived rats fed with the ethanolic extract of *Tinospora cordifolia* for 15 days (TSD). Our experiments showed significant impairment in memory function of VSD group animals in the novel object recognition test following sleep deprivation. However, the animals of WSD and TSD groups showed improved memory functions after sleep deprivation regimen as compared to VSD group animals. Elucidation of underlying molecular mechanisms revealed enhanced expression of both PSA-NCAM and NCAM in the hippocampus and piriform cortex regions of VSD group animals, which may be the result of compensatory mechanisms under acute stress condition to retain the structural and functional integrity. On the other hand, administration of the Ashwagandha water extract as well as the ethanolic extract of *Tinospora cordifolia* led to reduction in anxiety and stress as observed from elevated plus maze test [57,59]. The reduction in stress inhibited the stress-induced synaptic remodeling in brain, thereby, maintaining the expression of both PSA-NCAM and NCAM to near-control levels in WSD and TSD group animals.

In another regimen involving intermittent fasting-dietary restriction for a period of 12 weeks, the animals were deprived of food on alternate days and were given *ad libitum* supply of food on the intervening day. The animals were tested for their motor coordination using rotarod performance test [13,60]. The dietary restricted-middle aged rats (15 months old) showed improved performance on the rotating rod as indicated by a smaller number of falls and more time spent on the rotating rod as compared to their age-matched counterparts fed *ad libitum*. These behavioral changes corresponded with enhanced expression of PSA-NCAM in the dentate gyrus, piriform cortex and median eminence regions of the brain in dietary restricted animals as compared to the animals that were fed *ad libitum*. These results suggested that enhanced PSA-NCAM expression may be the underlying mechanism for neuronal growth and synaptic remodeling, leading to improved motor coordination. Similar changes in expression of PSA-NCAM have been observed in 18 months old rats kept on *ad libitum* and dietary restricted regimen [61].

It is known that memory consolidation requires changes in gene transcription that is accompanied by synaptic remodeling [62]. It is attributable to the permissive action of PSA-NCAM in synaptic plasticity [9]. Adult neurogenesis in the dentate gyrus region is modulated during learning of hippocampus-dependent tasks, which involves the generation of new PSA-positive neurons. A large number of reports suggest the involvement of polysialylation in several aspects of cognitive functions of brain, which is exerted in synaptic plasticity at different levels of widely inter-connected neuronal circuits. The biosynthesis of PSA in the brain is catalyzed by two polysialyltransferases, which are differentially regulated during the lifespan. One of them, ST8SiaIV (PST), is predominantly expressed during adulthood, whereas, the other one, ST8SiaII (STX), dominates during embryonic and post-natal development. The knockout mice deleted for the enzyme ST8SiaIV have shown a drastic reduction in PSA-NCAM expression in the hippocampus and intact hippocampal adult neurogenesis during adulthood [63].

PSA-NCAM has also been reported to be localized on both pre- and post-synaptic elements [64]. Since PSA-NCAM expression in the CNS is also regulated in an activity-dependent manner, it has been suggested to nurture experience-dependent excitatory synaptogenesis in neurons [65]. Synaptic activity-mediated shifts in PSA-NCAM localization from intracellular pools to the cell surface have also been reported [66,67]. PSA, along with heparin binding NCAM domain was demonstrated to be important for NCAM's synaptogenic activity mediated by the fibroblast growth factor and *N*-methyl-D-aspartate receptors [68]. Disruption of PSA-NCAM increased cell death in hippocampus due to formation of ectopic synapses and aberrant sprouting in the hippocampal mossy fibers [69–71]. Further, the balance between levels of PSA-NCAM and

NCAM has been suggested to be essential for glutamate-induced changes in synapses in the hippocampus [72]. Recent studies demonstrated the potential involvement of extrasynaptic glutamate receptor subunit epsilon-2 [73] and synaptic glutamate receptor subunit epsilon-1 [74] in PSA-NCAM-mediated synaptic plasticity. Furthermore, several reports suggested the potential role of PSA in induction of long-lasting changes in the synapses such as long-term potentiation and long-term depression. Constitutive ablation of PST diminished long-term potentiation and long-term depression at the Schaffer collateral synapses of the CA1 region of the hippocampus [75,76]. Similarly, enzymatic removal of PSA from hippocampal slices suppressed long-term potentiation induction after tetanic stimulation [77] as well as induction of long-term depression [64]. Application of soluble PSA and PSA-NCAM-Fc to CA1 region of NCAM-deficient hippocampal slices also restored long-term potentiation-induction ability [78]. Inhibition of neuraminidase in the hippocampal slices by 2-deoxy-2,3-dehydro-*N*-acetylneuraminic acid has also been reported to modulate the synaptic response [79].

The involvement of PSA-NCAM in hippocampal plasticity also indicates its potential role in regulating hippocampus-dependent spatial contextual learning and memory. In a paradigm of Pavlovian fear conditioning, mice lacking STX showcased higher investigative activity and decreased avoidance of the aversive stimulus [76]. Passive avoidance learning trail which includes testing of the avoidance of a fear-induced aversive stimulus in animals, also led to transient increase in hippocampal PSA-NCAM levels [80]. Enzymatic removal of PSA from dorsal dentate gyrus has been reported to reduce the freezing response in animals after contextual fear conditioning [81] indicating prime involvement of PSA-NCAM in unifying memories of fear related to context. PSA-NCAM removal also reduced the spatial learning and recalling ability of adult rats in Morris water maze [77]. Morris water maze training has been demonstrated to modulate NCAM polysialylation predominantly in the entorhinal cortex in a time-dependent manner [81]. Deletion of PST has been demonstrated to drastically reduce long-term memory in spatial and non-spatial tasks in mice and this behavioral change has been suggested to be reversed by environmental enrichment which results in generation of PSA-NCAM positive cells in dentate gyrus [63]. PSA-NCAM expression in piriform cortex and hippocampus regions also corresponds to olfactory discrimination-learning [50] as well as odor related memory formation [51]. Further, short-term dietary restriction regimen induced upregulation of PSA-NCAM in the dentate gyrus region of rats has also been suggested to have beneficial effects on learning and memory [13]. After 6½ months of social isolation, adult female *Octodon degus* have shown a normal auditory-cued fear memory, but a deficit in contextual fear memory, which is a hippocampus-dependent task [82]. A reduction in hippocampal synaptic levels of PSA-NCAM were found in isolated degus as compared to grouped-housed degus. No significant differences were found between the groups in hippocampal levels of the three main isoforms of NCAM (NCAM180, NCAM140, and NCAM120). The decrease in PSA-NCAM levels was accompanied by specific shrinkage of CA1 region, which might be related to the deficit in contextual fear memory observed in isolated female degus. Further, supplementation of sialic acids to rat pups during lactation in free form as *N*-acetylneuraminic acid or conjugated as 6′-sialyllactose has been shown to enhance long-term potentiation after one year [83]. 6′-sialyllactose supplemented rats showed better scores in cognitive outcomes as compared to *N*-acetylneuraminic acid supplemented rats as evident from novel object recognition test and Y-maze test. This was accompanied by enhanced expression of PSA-NCAM in frontal cortex of 6′-sialyllactose supplemented rats.

Aging is known to cause cognitive impairments, which is accompanied by decline in PSA-NCAM levels. Supplementation of 7-chloro-4-(phenylselanyl) quinoline in aged Wistar rats for 7 days has been shown to restore short-term and long-term memories in the object recognition tests [84]. Additionally, 7-chloro-4-(phenylselanyl) quinoline treatment was not shown to restore exploratory activity (rearing) but partially restore locomotor activity (crossings), otherwise reduced by aging, in the open-field test. Moreover, 7-chloro-4-(phenylselanyl) quinoline reinstated the reduced NCAM and PST levels, and acetylcholinestrase activity in cerebral structures. Hence, it was instrumental in restoring cognitive impairment caused by aging in rats by modulating synaptic plasticity as well as the cholinergic system.

The rising incidence as well as the prevalence of neurodegenerative diseases pose a dire need for a more comprehensive understanding of the effect of food components on the neural systems. Particularly, flavonoids have been recognized as promising agents capable of influencing different aspects of synaptic plasticity resulting in improvements in memory and learning [85]. A 3-week intervention with two dietary doses of flavonoids (Dose I: 8.7 mg/day and Dose II: 17.4 mg/day) has been shown to facilitate spatial memory acquisition and consolidation in young healthy rats [86]. The behavioral improvements in rats were linked to upregulation of PSA-NCAM expression in the dentate gyrus region of hippocampus. A parallel increase was observed in hippocampal *N*-methyl-D-aspartate receptors containing the *N*-methyl-D-aspartate receptor subtype 2B for both doses, which is suggestive of enhancement in glutamate signaling. A simultaneous modulation in hippocampal ERK/CREB/BDNF signaling and the activation of Akt/mTOR/Arc pathway was also observed. Collectively, the data suggests PSA-NCAM and the *N*-methyl-D-aspartate receptor subtype 2B as underlying factors for flavonoid-induced improvements in learning and memory.

Macrophage migration inhibitory factor, which is a multifunctional cytokine, is well known for its role in inflammation enhancement. A growing body of evidence suggests its role in energy metabolism in insulin sensitive tissues such as hippocampus [87]. To elucidate the role of macrophage migration inhibitory factor in brain in regulating systemic insulin sensitivity by possible changes in the hippocampal synaptic plasticity, Mif gene-deficient ($MIF^{-}/^{-}$) and wild type C57BL/6 J mice (WT) were tested for memory, exploratory behavior and anxiety [88]. $MIF^{-}/^{-}$ mice exhibited enhanced anxiety-like behavior and impaired recognition memory. This behavioral phenotype was associated with impaired systemic insulin sensitivity and attenuated hippocampal insulin sensitivity. $MIF^{-}/^{-}$ mice exhibited decreased hippocampal PSA-NCAM levels as compared to WT mice and unchanged BDNF, neurotrophin-3, neurotrophin-4 and insulin-like growth factor-1 mRNA levels. The results suggest that the lack of macrophage migration inhibitory factor may lead to disturbances in systemic and hippocampal insulin sensitivity, which may be responsible for memory deficits and anxiety, attributable to decreased PSA-NCAM-mediated neuroplasticity rather than through neurotrophic factors.

4. PSA-NCAM as a risk-factor for neurological disorders

Decline in brain plasticity and changes in cell connectivity are considered as one of the prime causes of several neurological disorders [89]. Therefore, PSA-NCAM may play an important role in the course of development of these diseases. Alteration in the levels of PSA-NCAM has been observed in Alzheimer's disease [90], epilepsy [91], schizophrenia [92,93], meningococcal diseases, and infections by influenza virus [94]. The dentate gyrus and entorhinal cortex of Alzheimer's patients showed massive remodeling of neurons and disorganization of PSA-NCAM-positive fibers [95,96]. PSA-NCAM expression has been shown to undergo alteration in all those regions of hippocampus which are implicated in formation of neurofibrillary tangles and amyloid plaques and the regions undergoing remodeling and loss of synaptic inputs [65]. Acute injection of Aβ in the hippocampus of rats increased PSA-NCAM expression in the CA1 and dentate gyrus regions [97]. PSA-NCAM-associated massive neural reconstruction and neurogenesis has also been reported in the substantia nigra of patients with

Parkinson's disease [98]. Depletion of dopamine in the substantia nigra of rats and monkeys led to upregulation of PSA-NCAM [98]. Expression of PSA-NCAM in hippocampus [92], prefrontal cortex [93] and serum [99] has also been correlated with schizophrenia. In Chinese Han population, the gene encoding STX (*SIAT8B*) has been reported to be located in the susceptibility region for schizophrenia [100]. Further, the PSA-NCAM levels in the inner molecular layer of dentate gyrus and entorhinal cortex in patients with temporal lobe epilepsy correlated with duration and severity of epilepsy as well as glial reactivity and mossy fiber sprouting [91]. PST deficient mice demonstrated a reduced latency of seizure and higher mortality after kianate-mediated induction of seizure [101]. Decreased PSA-NCAM level in the retinal ganglion cells by matrix metallopeptidase-9 resulted in enhanced kainite induced excitotoxicity [102]. PSA-NCAM has also been implicated in anxiety response after status epilepticus [101].

Further, PSA-NCAM is well reported to play a neuroprotective role in several neurodegenerative diseases. Apart from promoting neurite outgrowth and migration *via* modulation of cell-cell interactions, PSA-NCAM reduced the sensitivity of α-amino-3-hydroxy-5methyl-4isoxazolepropionic acid and *N*-methyl-D-aspartate receptors to glutamate and protected the cells from excitotoxicty [89]. Sialic acid has been reported to serve as ligand for the sialic acid-binding immunoglobulin-like lectin receptor family that are crucial for regulating the immune defense and thus suggested to be the targets in several diseases [103,89]. Interaction of ectopically expressed sialic acid-binding immunoglobulin-like lectin -11 on murine microglia with neuronal PSA reduced lipopolysaccharide-mediated pro-inflammatory response, diminished phagocytosis and attenuated microglial toxicity [104]. Several other putative PSA binding molecules have been identified such as BDNF [105] and fibroblast growth factor-2 [106] with noticeable neuroprotective properties. Using a model of kainic acid-mediated mesial temporal lobe epilepsy, Duveau and Fritschy [107] observed severe degeneration in hippocampal formation and early onset of seizures after contralateral infusion of endosialidase. The observed effects were reversed after injection of antibodies against glial cell-derived neurotrophic factor suggesting the potential role of PSA-NCAM-mediated glial cell-derived neurotrophic factor signaling in restraining neurodegeneration due to status epilepticus.

PSA-NCAM has also been suggested to play an important role in chronic stress and subsequent psychological conditions such as depression. Chronic stress-mediated hippocampal shrivel and learning impairments in rodents induced changes in the expression of cell adhesion molecules [108]. Levels of PSA-NCAM in piriform cortex, amygdala and hippocampus have been suggested to correspond with chronic stress administration [109,56,110,111]. Chronic, but not acute restraint, stress led to biphasic changes in expression of PSA-NCAM in the dentate gyrus region [109]. Hippocampal PSA-NCAM levels were reduced in the animal models of chronic mild unpredictable stress [44] and in case of chronic immobilization stress, PSA-NCAM was implicated in dendritic plasticity at CA3 region [70]. Chronic stress-mediated alterations in PSA-NCAM have also been evident in prefrontal cortex, amygdala and hippocampal CA1 region [112,71,113]. Further, it has been suggested that a cross-talk exists between depression and mode of action of PSA-NCAM [71]. PSA-NCAM has been reported to affect the hippocampal neurogenesis which occurs in depression by mediating the sensitization of neurons to neurotrophins [71]. The co-localization of PSA-NCAM with cholecystokinin in CA1 region of hippocampus plays a pivotal role in regulating its antidepressant efficacy [114]. Patients with depression-related disorders demonstrated altered levels of PSA-NCAM expression in amygdaloid and prefrontal cortex [115,71]. The depression-related changes in PSA-NCAM expression in medial prefrontal cortex, hippocampus and amygdala were also reported to be reverted by antidepressant administration [42,43,116,45]. PSA-NCAM was also associated with the alteration in excitatory and inhibitory circuits in amygdala in the patients with depression and bipolar disorders [117]. Furthermore, variation in *ST8SIA2* gene has also been reported to be associated with bipolar disorder and autism spectrum [118–120].

5. PSA-NCAM and repair/regeneration after injury

Adult neuroregeneration is an intricate concept which relies on the crosstalk between several processes ranging from neuroplasticity to neuroprotection. Since PSA-NCAM aids in cell migration and pathfinding to form correct neural circuitries and it also has a global impact on the nervous system remodeling, it has emerged as a potential candidate for promoting repair after nervous system injuries in the recent years. Substantial evidence indicates that PSA-NCAM has been implicated in modulating the plasticity of preserved neuronal structures after nervous system injuries. PSA-NCAM has been implicated in sprouting of Purkinje cell axons in the events of reactive gliosis after axotomy [121], axonal sprouting in dentate gyrus after entorhinal cortex injury [122] and post-lesional morphological remodeling in the mediobasal hypothalamus [123]. The animal model of fimbria-fornix injury, regenerating septohippocampal, choline acetyltransferase-positive axons exhibited modulation of PSA-NCAM levels. In these axons, PSA expression was upregulated during elongation and downregulated upon reaching hippocampal formation [124]. Additionally, increased PSA expression by reactive astrocytes after fimbria-fornix injury generated permissive conditions for axonal regrowth across this area [124]. Alteration in PSA-NCAM levels was also observed in the cerebral cortex immediately after controlled cortical impact injury [125]. Similarly, consistent increase in PSA-NCAM expression by reactive astrocytes and increase in the number of PSA-positive cells in subventricular zone of rodents has been observed after CNS injuries [9].

Using an *in vitro* model of hippocampal injury-induced reactive synaptogenesis, Muller et al. [126] demonstrated that PSA-NCAM was essential for neuritogenesis and regeneration of synapses following injury. Regenerating axons of the sensory pathway show upregulated PSA-NCAM expression while crossing the lesion site after transection of femoral nerve in mice [127]. Further, enzymatic removal of PSA interfered with preferential targeting by motor axons and modulated the number of collateral sprouts as well as arborisation area in the regenerating femoral nerve after transection [127]. Similarly, alteration in the cellular localization and expression of PSA-NCAM was observed to fine-tune the regenerating axons after sciatic nerve crush injury and suggested to be imported for their regeneration [128]. In mice expressing PST under control of a glial-specific promoter, the fraction of successfully mono-reinnervated motor endplates in the muscles of the foot pad was significantly increased after sciatic nerve crush injury [129].

PSA-NCAM has also been reported to facilitate repair after spinal cord injury and is rapidly re-expressed in the neurons of the adult rat spinal cord after unilateral dorsal rhizotomy [130] and lysolecithin-induced demyelination [131]. Upregulation of PSA-NCAM expression was also observed in reactive astrocytes at the lesion site after dorsal hemisection in mice [132]. It was also correlated with the synaptic remodeling in the sensorimotor cortex after spinal cord injury [133]. Further, sialic acids have also been suggested to play a protective role against chronic neuropathic pain after CNS injuries. Enzymatic removal of PSA-NCAM from the spinal cord led to retention of nociceptive C terminals in the spinal lamina II which aggravated hyperalgesia [134].

6. PSA-based approaches in promoting neuroregeneration

Over the years, several strategies to exploit the regenerative potential of PSA-NCAM have been developed. Broadly, the PSA-based

Table 1
PSA-based approaches in promoting neuroregeneration.

Approach I	Cell-based approaches to engineer PSA-NCAM functions at injury site				Strengths	Limitations
	A. Using PSA-NCAM$^+$ precursors					
	Author	**Year**	**Strategy**	**Outcome**		
	Keirstead et al. [135]	1999	Grafting of PSA-NCAM$^+$ newborn rat CNS precursors (expanded as clusters with fibroblast growth factor 2) into a focal demyelinating lesion in adult rat spinal cord.	The neural precursors generated oligodendrocytes, astrocytes and Schwann cells *in vivo* and completely remyelinated the lesion.	Embryonic stem cells have high differentiation potential and better survival rate as compared to adult stem cells or other somatic cells.	The same precursor cells can generate different cell types when implanted into different areas of the developing nervous system. Long-term studies are required to thoroughly assess the potential tumorigenicity and immunogenicity of PSA-NCAM$^+$ precursors. Lacks cell specificity as immature cells could be still be detected *in vivo*; therefore, requires robust cell differentiation strategies. Combinatorial approaches including co-application of neurotrophic factors might be necessary for complete functional restoration. Most injected cells do not survive the traumatic injection procedure and the transition to a hostile environment.
	Glaser et al. [136]	2007	Overexpression of PSA-NCAM in embryonic stem cell-derived glial precursors.	PSA-overexpressing cells displayed targeted migration toward the subventricular zone when transplanted into adult straitum.		
	Butenschön et al. [137]	2016	Injection of purified PSA-NCAM$^+$ progenitor cells overexpressing BDNF into the lesion core after contusion spinal cord injury in mice.	The combinatorial therapy approach improved motor function in mice following the injury.		
	Kim et al. [138]	2014	Transplantation of PSA-NCAM$^+$ neural precursor cells into the brain in rats with ischemic stroke.	The transplanted cells successfully integrated and differentiated in the host brain and improved functional outcome.		
	Czepiel et al. [139]	2014	Overexpression of PSA-NCAM in induced-pluripotent stem cell-derived oligodendrocyte progenitor cells *via* lentiviral transduction of STX and their transplantation into demyelinated corpus callosum of cuprizone-fed mice.	The PSA overexpressing cells showed a normal differentiation and maturation pattern. The cells were able to downregulate PSA during differentiation into oligodendrocytes. PSA overexpressing cells showed enhanced migration along the axons following implantation in the demyelinated corpus callosum of cuprizone-fed mice.		
	B. Transplantation of PSA-NCAM expressing Schwann cells					
	Author	**Year**	**Strategy**	**Outcome**		
	Gravvanis et al. [140]	2005	*In vitro* transduction of Schwann cells with STX encoding reovirus.	The expression of PSA-NCAM promoted Schwann cell motility *in vitro*.	Schwann cells have been acknowledged to be involved in the key processes for neuroregeneration for over a century. Harvesting and expansion of human Schwann cells *in vitro* can be exploited for autologous transplantation in the clinic set ups. PSA on transduced Schwann cells has been shown to redistribute and downregulate during differentiation process. STX containing Schwann cells showed better integration within the CNS as compared to non-transduced Schwann cells.	Extensive early cell death of transplanted Schwann cells cannot be prevented by STX or PST transduction.
	Lavdas et al. [141]	2006	Schwann cells were transduced with a retrovirus encoding STX, and migration of wild type and transduced cells was examined using a gap bridging assay in dissociated cells and by grafting cells in slice cultures of postnatal brain.	PSA expressing Schwann cells showed enhanced migration in a gap bridging assay and after grafting in postnatal forebrain slice cultures. Transduced Schwann cells were able to myelinate CNS axons in cerebellar slices. PSA was redistributed on the cell membrane and the PSA expression reduced during differentiation in pure Schwann cell cultures and slice co-cultures.		
	Papastefanaki et al. [142]	2007	Transplantation of engineered STX-green fluorescent protein Schwann cells with sustained PSA expression in a mouse model of spinal cord injury.	Grafts of STX-Schwann cells resulted in improved locomotor recovery, enhanced remyelination as well as sprouting of regenerating serotonergic nerve fibres into and across the injury site.		
	Bachelin et al. [143]	2010	Transplantation of PSA-overexpressing adult macaque Schwann cells in mice with focally induced demyelination.	Accelerated recruitment of Schwann cells towards the lesion site as well as enhanced migration along the dorsal midline.		

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Table 1 (*continued*)

Approach I	Cell-based approaches to engineer PSA-NCAM functions at injury site					
	Luo et al. [144]	2011	Transplantation of Schwann cells, which had been genetically modified to overexpress PSA by lentiviral delivery of PST, into mouse spinal cord following crush injury.	More interaction with existing reactive astrocytes. More PSA-expressing Schwann cells survived than green fluorescent protein-expressing Schwann cells after transplantation. Increased number of PST-Schwann cells migrated to the injury site and integrated with the host cells and did not initiate stress response in the resident astrocytes.		
	Ghosh et al. [145]	2012	Transplantation of PST expressing Schwann cells in spinal cord injury contusion mice model to evaluate the migration, supraspinal axon growth support, and functional recovery.	PST containing Schwann cells migrated up to 4.4 mm across the lesion-host cord interface. Extensive serotonergic and corticospinal axon growth was observed in PST-Schwann cell transplanted cords leading to improved locomotor outcome in mice.		
	C. Overexpression of PSA in the cells at injury site					
	Authors	**Year**	**Strategy**	**Outcome**		
	El Maarouf et al. [146]	2006	PSA expression was induced in astrocytes present at the injury site using lentiviral PST injection following corticospinal tract transection in mice.	Sustained expression of PSA was observed in scar astrocytes and this overexpression of PSA significantly promoted the growth of severed corticospinal tract axon processes through the injury site.	Taken together, the results from these studies suggest the ability of PSA in overcoming the inhibitory environment in the glial scar to promote axonal regeneration.	These studies are an initial proof-of-principle rather than a demonstrable clinical therapy. In general, the studies demonstrated that overexpression of PSA at the injury site is not in itself sufficient to achieve successful axonal regeneration and needs an additional conditioning lesion. Not easily amenable to therapeutic application.
	Zhang et al. [147]	2007 a	Inducing expression of PSA in the spinal cord of mice following dorsal rhizotomy by lentiviral vector delivery of PST.	Overexpression of PSA in the dorsal root entry zone in combination with a conditioning lesion promoted the growth of sensory axons across the dorsal root entry zone into spinal cord.		
	Zhang et al. [148]	2007 b	PSA expression was induced in the glial scar by lentiviral vector-mediated expression of PST following dorsal column transection in mice.	PSA expression led to increased astrocyte infiltration and penetration of regenerating axons into the lesion cavity. In animals that got a peripheral nerve-conditioning lesion along with PSA induction, more axons grew into the lesion cavity than the controls.		

Approach II	PSA mimetics					
	A. PSA mimicking peptides					
	Author	**Year**	**Strategy**	**Outcome**		
	Torregrossa et al. [149]	2004	Screening of phage display library using PSA-specific monoclonal antibody to identify cyclic PSA mimicking peptides and evaluating their bioactivity *in vitro* and *in vivo*.	The PSA mimicking peptides promoted axon growth, defasciculation, and migration of neural progenitors *in vitro* and modified the trajectory of retinal ganglion cell axons in developing chick retina. PSA mimicking peptides enhanced migration of grafted neuroblasts in mouse brain. Acute administration of PR-21 to the injury site improved bladder function recovery and enhanced sensorimotor control and hindlimb coordination, increased serotonergic axon density at and caudal to the injury site, and decreased reactive gliosis in mice.	PSA mimicking peptide-based approach has been suggested to be a more direct, clinically and practically feasible approach than gene- and cell-based strategies as the peptides mimicking polysaccharides can be readily produced and are easier to manufacture and modify. The peptide mimetics are non-toxic, non-immunogenic and biocompatible as compared to native glycans.	Though the peptide mimetics are more stable than native glycans, they can display a short half-life *in vivo* due to enzymatic degradation mediated by proteases and rapid clearance through the renal system and therefore, may be required in higher doses as compared to the pharmaceutical drugs. These glycomimetics have been used successfully in small gap repair in PNS and CNS injury when presented in soluble form in mice; however, their use in more challenging injury models would require increase in retention time in the tissue.
	Marino et al. [150]	2009	Acute administration of PSA mimicking peptide PR-21 after spinal cord dorsal hemisection in mice.			

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Table 1 (*continued*)

Approach II			PSA mimetics	Strengths	Limitations
	Mehanna et al. [151]	2009	Acute administration of PSA mimicking peptide after femoral nerve injury in mice using polyethylene cuff.	Better functional outcome was observed in PSA mimicking peptide treated animals over a period of 3 months after injury. PSA mimetic promoted remyelination of regenerated axons distal to the injury site and promoted Schwann cell proliferation in both motor and sensory branches of femoral nerve.	
	Mehanna et al. [152]	2010	Acute administration of PSA mimicking peptide in mice *via* subdural infusion through osmotic pump following thoracic spinal cord injury.	Acute PSA mimicking peptide administration resulted in improved locomotor recovery in mice over a 6-week observation period. Higher numbers of cholinergic and glutamatergic terminals and monaminergic axons were observed in the lumbar spinal cord of PSA mimicking peptide treated mice. PSA mimicking peptide promoted axonal myelination proximal to the injury site. PSA mimetic peptide treatment was not effective when started 3 weeks after injury.	
	Podestá et al. [71]	2014	Exposing cultured hippocampal neurons, after they have reached a synaptogenic peak to glutamate, resulting in a reduction of the area of the dendritic tree and subsequent treatment with PSA mimicking peptide.	The PSA mimicking peptide prevented dendritic atrophy and subsequent synaptic changes following 6 h of treatment.	
	B. PSA mimicking synthetic compounds				
	Authors	**Year**	**Strategy**	**Outcome**	Drug repurposing has the potential to rapidly introduce new therapies using existing drugs for novel applications and hence, has increased translational potential.
	Bushman et al. [153]	2014	Screening of the NIH Clinical Collection 1 Library using PSA-specific monoclonal antibody and the identification of 5-hydroxytryptamine 4 receptor agonist tegaserod as a PSA mimetic.	Tegaserod depicted PSA mimicking activity in the cultures of CNS and PNS cells of the mouse. The PSA mimicking activities of tegaserod were found to be independent of its described function as a serotonin (5-hydroxytryptamine 4) receptor agonist. Tegaserod administration at the site of injury in an *in vivo* model for peripheral nerve regeneration in mice promoted functional recovery.	The PSA mimicking compounds have been demonstrated to be effective at lower doses as compared to peptide mimetic and the glycan itself.
	Loers et al. [154]	2014	Screening of the NIH Clinical Collection 1 Library using PSA-specific monoclonal antibody and the identification of 5-nonyloxytryptamine oxalate (5-NOT), described as a selective 5-hydroxytryptamine receptor 1B agonist as a PSA mimetic.	5-NOT promoted neurite outgrowth of primary neurons and process formation of Schwann cells, promoted myelination, promoted endogenous PSA-NCAM expression and protected neurons from oxidative stress *in vitro*.	These glycomimetic compounds have been used successfully in small gap repair in PNS and CNS injury when presented in soluble form in mice; however, their use in more challenging injury models would require increase in retention time in the tissue.
	Pan et al. [155]	2014	Acute administration of PSA mimicking compound tegaserod in mice *via* subdural infusion through osmotic pump following thoracic spinal cord injury.	Tegaserod administration promoted hindlimb motor function and increased density of tyrosine hydroxylase and serotonin-positive axons rostral and caudal to the injury site following 6 weeks of spinal cord injury.	
	Loers et al. [156]	2016	Screening of the NIH Clinical Collection 1 Library using PSA-specific monoclonal antibody and the identification of vinorelbine, a semi-synthetic third generation vinca alkaloid, and epirubicin, an anthracycline and 4′-epimer of doxorubicin, as PSA mimetics.	Vinorelbine and epirubicin stimulated neurite outgrowth and migration in cerebellar neurons, enhanced process formation of Schwann cells and reduced migration of astrocytes after injury. Vinorelbine and epirubicin regulated axonal growth *via* the neural cell adhesion molecule (NCAM), myristoylated alanine-rich C kinase	

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Table 1 (*continued*)

Approach II			PSA mimetics	Strengths	Limitations
	Saini et al. [157]	2016	Acute, one-time administration of PSA mimicking compounds 5-NOT and vinorelbine in mice through small capillaries following thoracic spinal cord injury.	substrate, and fibroblast growth factor receptor, signalling through Erk pathways. 5-NOT and vinorelbine promoted regain of motor functions, axonal regrowth, motor neuron survival and remyelination following 8 weeks of injury.	
	Loers et al [158].	2017	Screening of the NIH Clinical Collection 1 Library using PSA-specific monoclonal antibody and the identification of idarubicin, an antineoplastic anthracycline, and irinotecan, an antineoplastic agent of the topoisomerase I inhibitor class as PSA mimetics.	Idarubicin as well as irinotecan promoted neuritogenesis and survival of cerebellar neurons *in vitro* following oxidative stress. The effect of Idarubicin and irinotecan on neurons was mediated *via* Fyn, casein kinase II and the phosphatase and tensin homolog.	

Approach III			PSA-based biomaterials		Strengths	Limitations
	Authors	**Year**	**Strategy**	**Outcome**	PSA or PSA mimetic containing biomaterials have been demonstrated to be stable under *in vitro* and *in vivo* conditions with no negative effect on cells. Incorporating PSA mimicking peptides or compound molecules into a biomaterial may lead to improvements in stability and presentation for clinical translation of these mimetics to regenerative therapies and they may also be beneficial for promoting regeneration across large gaps. As PSA mimicking peptides as well as compounds have high phenotypic specificity, incorporating them into a biomaterial maybe particularly important for encouraging preferential motor reinnervation in the PNS and targeting regeneration in the CNS.	Combination of PSA mimetics with different biomaterial scaffolds using different cross-linking chemistries to promote their controlled and continuous delivery under the *in vivo* model systems still needs to be evaluated.
	Gravvanis et al. [140]	2005	Use of silicone tubes lined with STX-transduced Schwann cells following peripheral nerve injury (10 mm) in Wistar rats.	Following 3 months of injury, the STX-transduced Schwann cells promoted nerve regeneration through silicone tubes, increased fiber diameter and myelin thickness and promoted functional recovery in rats.		
	Haile et al. [159]	2007	Neonatal and adult Schwann cells, neural progenitor cells, spinal ganglionic neurons and motor neurons were cultured on PSA coated cell culture dishes.	PSA was stable under *in vitro* conditions and had no negative effects on cell cultures.		
	Stark et al. [160]	2008	Use of PSA as a scaffold material was tested in its soluble form as coating material.	No toxic effect of the PSA coating on different cell lines was observed. PSA as a coating material was comparable to other well-established coating materials e.g. collagen I, hyaluronic acid, and poly-L-lysine. This PSA hydrogel was not toxic to PC12 cells and was completely stable under physiological conditions.		
	Berski et al. [161]	2008	The design, synthesis and evaluation of PSA-based hydrogel for tissue engineering.	Endosialidase treatment resulted in degradation of PSA hydrogel within 2 to 11 days, depending on the amount of cross-linker used. The study demonstrated the use of an additional coating of collagen I, poly-L-lysine or Matrigel to improve regenerative properties of the hydrogel.		
	Mehanna et al. [151]	2009	Acute administration of PSA mimicking peptide after femoral nerve injury in mice using polyethylene cuff.	Better functional outcome was observed in PSA mimicking peptide treated animals over a period of 3 months of injury.		

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Table 1 (*continued*)

Approach III			PSA-based biomaterials	Strengths	Limitations
	Steinhaus et al. [162]	2010	To study the effect of PSA, immobilized on glass surfaces *via* an epoxysilane linker, on immortalized Schwann cells.	PSA mimetic promoted remyelination of regenerated axons distal to the injury site and promoted Schwann cell proliferation in both motor and sensory branches of femoral nerve. PSA could be immobilized on glass surfaces *via* the epoxysilane linker and this surface-bound PSA had no toxic effects on Schwann cells.	
	Assmann et al. [163]	2010	Fiber scaffolds of bioactive PSA were prepared by electrospinning for peripheral nerve regeneration and their effect was studied on immortalized Schwann cells.	The PSA fiber scaffolds were optimized in this study for good cell viability. The fiber scaffolds directed the proliferation of immortalized Schwann cells along their lengths.	
	Hasstert-Talini et al. [164]	2010	*In vivo* administration of cell-free and Schwann cell-containing synthetic peripheral nerve grafts supplemented with soluble exogenous K1-PSA following peripheral nerve injury in rats.	K1-PSA nerve grafts improved structural nerve regeneration across 10 mm gaps. Though structural nerve regeneration was also observed in 13 mm nerve gaps, auto transplantation was still more successful.	
	Masand et al. [165]	2012 a	Studied the neural cell type specific response following functionalization of type I collagen with PSA mimicking peptide.	PSA mimicking peptide retained its bioactivity following functionalization to the collagen backbone. PSA functionalized collagen promoted sensory and motor neuron outgrowth and Schwann cell proliferation and process extension *in vitro*.	
	Masand et al. [166]	2012 b	Evaluation of the use of collagen hydrogels functionalized with PSA mimicking compound in bridging 5 mm gap in a mouse model of femoral nerve injury.	PSA mimicking peptide-coupled collagen hydrogels promoted functional recovery in mice. Animals receiving PSA mimicking peptide-coupled collagen hydrogels had more myelinated axons as compared to controls.	
	Williams et al. [167]	2015	A report on different silane-based functionalization strategies to bind PSA onto nanoporous silica nanoparticles.	PSA could be immobilized on the surface of nanoporous silica nanoparticles using different strategies involving succinic anhydride-based linker system and copper-catalyzed click chemistry and the kind of surface immobilization had a strong influence on the cytotoxicity of the material.	
	Zhang et al. [168]	2018	Administration of a polycaprolactone-PSA hybrid nanofiber scaffolds encapsulating glucocorticoid methylprednisolone in rats following spinal cord transection.	The polycaprolactone-PSA hybrid nanofiber scaffolds reduced inflammation, apoptosis and promoted axonal regrowth and functional recovery in rats following 7 weeks of spinal cord transection.	
	Kalotra et al. [169]	2019	Development and evaluation of PSA mimicking compound 5-NOT containing collagen-laminin hydrogels for neuroregenerative potential *in vitro* and to study the effect of acute, one-time administration of these PSA mimicking compound 5-NOT containing collagen-laminin hydrogels in mice following thoracic spinal cord injury.	5-NOT containing collagen-laminin hydrogels promoted neurite outgrowth, migration, and fasciculation in cerebellar neurons *in vitro*. Acute administration of 5-NOT containing collagen-laminin hydrogels in mice following spinal cord injury resulted in ~75 % of motor recovery after 14 days of injury. This effect was shown to be dependent on the ERK–MAPK pathway and augmentation of cell survival.	

therapeutic strategies for promoting neuroregeneration can be classified into the following three types (summarized in Table 1):

6.1. Cell-based approaches to engineer PSA-NCAM functions at the injury site

Using PSA-NCAM expressing cells into injury microenvironment is one of the earliest approaches reported in literature. The aim of these cell-based studies was to introduce more cellular PSA-NCAM into the injury niche either through transplantation of cells enriched in PSA-NCAM or through induced overexpression of PSA-NCAM in resident cells. PSA-NCAM enrichment in the injured tissue has been shown to promote cell-cell interactions [143] thus resulting in enhanced recruitment of the transplanted as well as resident cells to the injury site [143,144], re-myelination and growth of severed axons [141,142,146–148] in the injury niche leading to improved functional outcome in the experimental animal models [138]. Following are the predominant cell-based approaches that have been reported over the years:

6.1.1. Using PSA-NCAM-positive precursor cells

Keirstead et al. [135] reported that grafting of the PSA-NCAM-positive precursor cells, from mixed glial cultures into focal demyelinating lesion in adult rat spinal cord could completely remyelinate the lesions. Though the study provided preliminary insights and proof-of-concept of PSA-based cell therapy, most of the later studies used embryonic stem cells enriched with PSA-NCAM for such purpose. Embryonic stem cells are known to have limitless self-renewal capacity and the ability to generate many different cell types. In all of the following studies, these PSA-NCAM transduced embryonic stem cell-derived glial progenitors have been shown to differentiate into different cell types. They underwent enhanced migration and directional chemotaxis upon exposure to defined conditions in brain or chemo attractants *in vivo*. ESGPs overexpressing PSA-NCAM displayed targeted migration towards subventricular zone when transplanted into adult rat straitum [136]. Kim et al. [138] demonstrated that transplantation of PSA-NCAM-positive neural precursor cells into the rat brain after ischemic stroke led to improvement in behavioral performance and reduction in microglial and astroglial response. The transplanted cells successfully integrated and differentiated in the host brain and also depicted pro-angiogenic activity. Similarly, Czepiel et al. [139] reported that overexpression of PSA-NCAM in induced-pluripotent stem cell-derived oligodendrocyte progenitor cells and their transplantation into demyelinated corpus callosum of cuprizone-fed mice promoted cell differentiation and migration along the axons.

Further, in order to get enhanced functional restoration, Butenschön et al. [137] suggested a combinatorial approach involving PSA-NCAM-positive cells enriched with neurotrophic factors. Injection of purified PSA-NCAM-positive progenitor cells expressing BDNF promoted functional recovery after spinal cord contusion injury in mice. BDNF overexpression led to better differentiation of the progenitors into neurons and oligodendrocytes as well as enhanced the numbers of corticospinal tract fibers caudal to the lesion site, which is indicative of axonal re-growth and regeneration.

6.1.2. Transplantation of PSA-NCAM expressing Schwann cells

Reovirus- or lentivirus-mediated transduction of Schwann cells to express PSA-NCAM have been reported to target two goals. Firstly, the Schwann cells act as a carrier for PSA-NCAM in the CNS following insult and secondly, PSA-NCAM expression facilitates migration of Schwann cells and their integration with the host cells [170]. Sustained expression of PSA-NCAM in Schwann cells by retrovirus-mediated transduction of gene encoding STX promoted their migration *in vitro* after scratch injury. Similarly, grafting of these PSA overexpressing Schwann cells into neonate cerebellar slices resulted in myelination of Purkinje cell axons [141]. Furthermore, STX transduction enhanced the motility and transplantation of Schwann cells to lesioned peripheral nerve [140] and spinal cord [142] of mice promoted functional recovery. Grafting of these Schwann cells in mice accelerated the remyelination process and rendered the lesion site permissive to host cells after spinal cord compression injury [142]. Similarly, grafting of PST transduced Schwann cells into the injured spinal cord in mice promoted cell migration, regeneration of axons, axonal remyelination as well as functional recovery [144,145]. In addition to the spinal cord injury models, transplantation of PSA-overexpressing Schwann cells in mice with focally induced demyelination has also been demonstrated to accelerate their recruitment towards the lesion site, enhanced interaction with existing reactive astrocytes and enhanced migration along the dorsal midline [143].

Furthermore, the above studies also demonstrated that transduction of STX or PST in Schwann cells does not interfere with their myelinating capacity or differentiation process, which is an added advantage. However, STX or PST transduction has not been demonstrated to prevent the Schwann cells from undergoing early, extensive cell death following injection into the injury site, which still persists as a major limitation of using Schwann cell-based therapies to facilitate neuroregeneration.

6.1.3. Overexpression of PSA-NCAM in the cells at injury site

Virus vector mediated persistent expression of PSA-NCAM in astrocytes at the corticospinal injury site has been shown to promote axonal growth and recruitment of precursor cells across the lesion [146]. Further, lentiviral-mediated injection of PST into the superficial dorsal horn of rats after conditioned injury in the dorsal root has also been demonstrated to facilitate migration of Schwann cells and regeneration of sensory axons across the dorsal root entry zone into the spinal cord [147]. Similarly, lentiviral-induced overexpression of PSA also promoted axonal regeneration and infiltration of the astrocytes after transection of dorsal column [148].

Though these studies provide a good proof-of-concept that PSA helps in overcoming inhibitory environment at the injury niche, they are not amenable to clinical therapy. Furthermore, as demonstrated by Zhang et al. [147,148] lentivirus-mediated overexpression of PSA is not sufficient to achieve successful axonal regeneration and needs to be combined with additional conditioned lesion; this makes this approach even more impracticable to clinical therapy.

6.2. PSA mimetics

Although carbohydrates play an important role in vast array of physiological processes, only a limited number of carbohydrate-based drugs are available for use as therapeutic agents [171]. Previous studies have demonstrated several drawbacks of using native glycans as drugs because of the limitations owing to their pharmacodynamics and pharmacokinetic properties. Also, despite tremendous methodological advancements in synthesis of oligosaccharides, carbohydrate-based therapies often require complicated, multi-step synthesis [172]. Recently, the advancements in the X-ray crystallography, nuclear magnetic resonance spectroscopy and bioinformatics tools to model the structure of these carbohydrates have contributed significantly towards identification of the structural and functional mimetics of carbohydrates. These glycomimetics can be derived from either proteins or from other smaller compounds and may provide a potential alternative for modulating the carbohydrate-receptor interactions [171–173].

6.2.1. PSA mimicking peptides

The first report for identification and characterization of PSA mimicking peptides came in the year 2004. Torregrossa et al. [149] reported the identification of PSA mimicking peptides by screening of phage display libraries using PSA-specific monoclonal antibody. *In vitro* application of PSA mimicking peptides was shown to promote growth and defasciculation of dorsal root ganglion axons and migration of progenitor cells from subventricular zone explants. Similarly, the

peptides were also demonstrated to enhance the migration of neuroblasts grafted in the mouse anterior subventricular zone towards olfactory bulb [149]. In several subsequent studies, PSA mimicking peptides have been reported to foster functional recovery and plasticity after peripheral nerve injury and spinal cord injury in mice [150–152]. Reconnection of the severed stumps of femoral nerve with PSA mimicking peptide containing polyethylene cuff promoted remyelination of axons and Schwann cell proliferation in the motor and sensory branches [151]. Functional recovery after spinal cord injury in peptide treated mice was associated with modulation of glutamatergic and cholinergic synapses and monoaminergic innervation in the lumber region. Further PSA mimicking peptides also ameliorated axon myelination in the vicinity of the lesion. Moreover, the PSA mimicking peptide-mediated treatment for injured spinal cord was found to be effective when the peptides were applied at the acute stages of injury [152]. In another study, Florian et al. [174] demonstrated that injection of PSA mimicking cyclic peptide PR2 into the dorsal hippocampus of mice promoted memory retention and improved their spatial performance. Podestá et al. [72] further reported that application of functional PSA mimicking peptide to hippocampal neurons prevents glutamate-induced remodeling of synapses.

6.2.2. PSA mimicking synthetic compounds

Though the peptide mimetics were suggested to be more stable than native glycans, they still display a short half-life *in vivo* due to enzymatic degradation by proteases and therefore, required in higher doses as compared to pharmaceutical drugs. Therefore, in the pursuit of developing efficient PSA-based therapies, several studies used the drug-repurposing approach and reported the identification and characterization of PSA mimicking small organic compounds from ELISA-based screening of NIH Clinical Collection 1Library [153,154,156,158]. The NIH Clinical Collection 1 Library consists of small molecules that have a history of use in human clinical trials and have known pharmacokinetic profile and pharmacodynamics. So, identification of PSA mimetics among them further adds an advantage towards clinical implementation of PSA-based therapies. Among the 446 molecules from the NIH Clinical Collection 1 Library that have been screened, six PSA mimicking molecules namely, tegaserod, 5-nonyloxytryptamine oxalate, vinorelbine, epirubicin, idarubicin and irinotecan have been identified [153–158]. Irrespective of their role as 5-hydroxytryptamine 4 and 5-hydroxytryptamine 1B receptor agonists, tegaserod and 5-nonyloxytryptamine depicted an ability to bind with anti-PSA antibody and promoted neurite outgrowth, neuronal migration and myelination *in vitro* [153,154]. Pan et al. [155] further demonstrated the beneficial effect of implantation of tegaserod-containing osmotic pump after spinal cord injury in mice in restoring the lost hindlimb motor functions. Further, in our study, we used the paradigm of single, immediate intraoperational application of PSA mimicking compounds directly into the injury site after thoracic spinal cord injury in mice [157]. In this study, the application of PSA mimicking compound 5-nonyloxytryptamine resulted in improvement of locomotor function, augmentation of structural and synaptic plasticity and enhancement of remyelination caudal to the injury site. Similarly, the cytostatic drugs epirubicin and vinorelbine as well as antineoplastic agents idarubicin and irinotecan demonstrated PSA mimicking properties *in vitro* and promoted neuritogenesis as well as cell migration [156,158] comparable to the bacterial analogue of PSA.

6.3. PSA-based biomaterials

Despite significant progress in encouraging axonal regrowth after CNS injuries, misrouted reinnervation of emanating neurites still pose a major limitation towards complete functional recovery after injury. Since PSA had been implicated in preferential reinnervation of motor axons and formation of correct circuitries [175], this led to the idea of inclusion of PSA or its mimetics as guiding cues into appropriate scaffolding material as a biomaterial-based strategy for promoting regeneration across large gaps. In recent years, several studies [159,160] have demonstrated the compatibility between different cell types derived from the embryonic and adult rat brain and non-neuronal cell lines cultured on the dishes coated with soluble PSA. The potential use of PSA-NCAM containing hydrogels modified with poly-L-lysine, laminin or collagen in nervous system repair has also been suggested [161]. Initial PSA-based biomaterials developed for facilitating regeneration after nervous system injury consisted of PSA-NCAM immobilized on glass surface by epoxysilane linker [162]. Synthetic peripheral nerve grafts containing Schwann cells complemented with exogenous, soluble PSA (isolated from *Escherichia coli* K1) promoted regeneration of transected sciatic nerve stumps in rats [164]. Further, Williams et al. [167] have shown the formation of PSA-based nanomaterials by conjugating it with silica nanoparticles. Zhang et al. [168] reported the transplantation of PSA multifunctional nanofiber scaffold in combination with polycaprolactone and glucocorticoid in recovery of spinal cord injury in rat. These PSA nanofiber scaffold reduced inflammation, apoptosis and promoted axonal regrowth in animal model of spinal cord injury.

Several groups have further studied the effect of PSA mimetics plus biomaterial-based combinatory approaches for neuroregeneration. Assmann et al. [163] reported the utility of PSA or PSA mimetic-coupled collagen fibrils that were electrospun in fiber scaffolds with the help of photochemical crosslinking in nerve regeneration. These fiber scaffolds promoted proliferation of immortalized Schwann cells along the fiber lengths. Grafting of collagen, functionalized with PSA mimicking peptide, stimulated the outgrowth from sensory and motor neurons and promoted proliferation and process extension from Schwann cells *in vitro* [165]. It also promoted functional recovery and axon myelination after femoral nerve injury in mice [166]. A recent study from our lab reported that intraoperational administration of 5-NOT impregnated collagen-laminin hydrogels following spinal cord injury in mice resulted in ~75 % of locomotor recovery after 14 days of injury [169]. Further this effect was shown to be dependent on the ERK–MAPK pathway and augmentation of cell survival. 5-NOT containing hydrogel also promoted the axonal re-growth and reduced astrogliosis at the injury site as compared to sham group, injured mice receiving collagen-laminin scaffold alone as well as injured mice without hydrogel. Moreover, re-innervation of monoaminergic and glutamatergic neurons caudal to injury site as well as reduced γ-aminobutyric acid innervations was also observed after 14 days of spinal cord injury [169].

7. Conclusion

PSA-NCAM, as a neuroplasticity marker holds immense neurotherapeutic potential. As discussed in the preceding sections, polysialylated form of NCAM is a promising candidate for modulating neuroplasticity, cell migration, and neuroregeneration in CNS injuries and diseases. Successful implementation of PSA into therapeutics needs designing and development of robust techniques. The available scientific data suggests that identification of novel proteins, synthetic or natural compounds, as PSA mimetics may offer a new therapeutic approach in the management of neurological impairments. PSA mimetics have been reported to regulate synaptic plasticity, axon pathfinding, neurite outgrowth, cell migration and cell survival in both *in vitro* and *in vivo* model systems. However, the current scientific evidence on PSA based therapies is only limited to CNS and PNS injury, whereas, applications of PSA mimetics in the animal model of neurological diseases such as Alzheimer's disease, Parkinson's disease, schizophrenia, and multiple sclerosis still needs to be explored. Further, combination of PSA mimetics with different biomaterial-based scaffolds using different cross-linking chemistries may be evaluated to promote their controlled and continuous delivery under the *in vivo* conditions using appropriate model system.

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Declaration of Competing Interest

The authors report no declarations of interest.

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