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Review

Losing the sugar coating: Potential impact of perineuronal net abnormalities on interneurons in schizophrenia

Sabina Berretta [a,b,c,*], Harry Pantazopoulos [a,b], Matej Markota [a,b], Christopher Brown [a], Eleni T. Batzianouli [a,b]

[a] Translational Neuroscience Laboratory, Mclean Hospital, 115 Mill St., Belmont, MA 02478, USA
[b] Dept. of Psychiatry, Harvard Medical School, 25 Shattuck St., Boston, MA 02115, USA
[c] Program in Neuroscience, Harvard Medical School, 25 Shattuck St., Boston, MA 02115, USA

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ABSTRACT

Perineuronal nets (PNNs) were shown to be markedly altered in subjects with schizophrenia. In particular, decreases of PNNs have been detected in the amygdala, entorhinal cortex and prefrontal cortex. The formation of these specialized extracellular matrix (ECM) aggregates during postnatal development, their functions, and association with distinct populations of GABAergic interneurons, bear great relevance to the pathophysiology of schizophrenia. PNNs gradually mature in an experience-dependent manner during late stages of postnatal development, overlapping with the prodromal period/age of onset of schizophrenia. Throughout adulthood, PNNs regulate neuronal properties, including synaptic remodeling, cell membrane compartmentalization and subsequent regulation of glutamate receptors and calcium channels, and susceptibility to oxidative stress. With the present paper, we discuss evidence for PNN abnormalities in schizophrenia, the potential functional impact of such abnormalities on inhibitory circuits and, in turn, cognitive and emotion processing. We integrate these considerations with results from recent genetic studies showing genetic susceptibility for schizophrenia associated with genes encoding for PNN components, matrix-regulating molecules and immune system factors. Notably, the composition of PNNs is regulated dynamically in response to factors such as fear, reward, stress, and immune response. This regulation occurs through families of matrix metalloproteinases that cleave ECM components, altering their functions and affecting plasticity. Several metalloproteinases have been proposed as vulnerability factors for schizophrenia. We speculate that the physiological process of PNN remodeling may be disrupted in schizophrenia as a result of interactions between matrix remodeling processes and immune system dysregulation. In turn, these mechanisms may contribute to the dysfunction of GABAergic neurons.

1. Introduction

Perineuronal nets (PNNs), first described by "Camillo Golgi" (1898), are specialized aggregates of extracellular matrix (ECM) molecules surrounding the somata, dendrites and proximal axon segment of distinct neuronal populations (Fig. 1) (Golgi, 1898; Brauer et al., 1993; Seeger et al., 1994; Celio et al., 1998; Vitellaro-Zuccarello et al., 1998; Spreafico et al., 1999; Kwok et al., 2011). Long believed to be responsible primarily for structural support, PNNs have in recent years come to the forefront of neuroscience research as critical elements regulating synaptic functions and plasticity during development and adulthood (Pizzorusso et al., 2002; Gogolla et al., 2009; Dityatev et al., 2010; Gundelfinger et al., 2010; Beurdeley et al., 2012; Yamada and Jinno, 2013; Xue et al., 2014). Emerging evidence from human postmortem studies highlights the involvement of PNNs in schizophrenia (SZ) (Pantazopoulos et al., 2010; Mauney et al., 2013; Pantazopolous et al., 2014). The relevance of PNN abnormalities to GABAergic neuron dysfunction in SZ is the main topic of this manuscript. We focus predominantly on evidence based on chondroitin sulfate proteoglycans (CSPGs), one of their main PNN components (Deepa et al., 2006; Carulli et al., 2007; Giamanco and Matthews, 2012). Importantly, other PNN elements, namely Reelin and semaphorin 3A, have been shown to be involved in the pathophysiology of SZ, although not directly as PNN components (Impagnatiello et al., 1998; Costa et al., 2001; Eastwood et al., 2003; Abdolmaleky et al., 2005a; Fatemi, 2005; Carulli et al., 2013a; Dick et al., 2013; Vo et al., 2013b). In particular, Reelin has been extensively investigated for its role in brain development, synaptic regulation during adulthood and involvement in several brain disorders, including SZ and bipolar disorder; although some of these aspects will be mentioned in this review, we refer to comprehensive publications by other groups for details (Curran and D'Arcangelo, 1998; Impagnatiello et al., 1998; Pesold et al., 1999; Guidotti et al., 2000, 2011; Costa et al., 2001; Fatemi, 2001; Abdolmaleky et al., 2005a; Chen et al., 2005; Sinagra et al., 2005; Akbarian and Huang, 2006; Dityatev et al., 2006; Eastwood and Harrison, 2006; Campo et al., 2009; Frotscher et al., 2009; Frotscher, 2010; Barros et al., 2011; Franco and Muller, 2011; Honda

* Corresponding author at: McLean Hospital, Mailstop 149, 115 Mill St., Belmont, MA 02478, USA. Tel.: +1 617 855 3484.
E-mail address: s.berretta@mclean.harvard.edu (S. Berretta).

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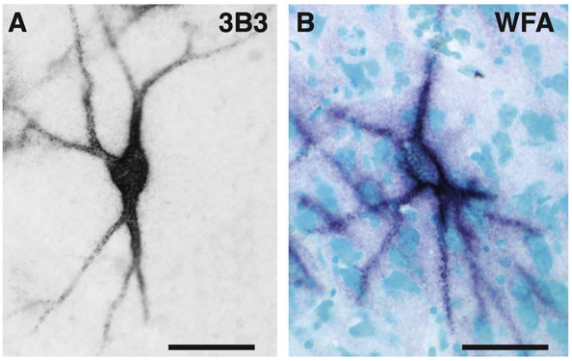

Fig. 1. PNNs in the human amygdala. Photomicrographs of PNNs labeled using the CS-6 antibody 3B3 (A), and the lectin WFA (B; counterstained with Nissl cresyl violet) in the lateral nucleus of the normal human amygdala. Scale bar = 50 μm.

et al., 2011; Lakatosova and Ostatnikova, 2012; Flashner et al., 2013; Folsom and Fatemi, 2013; Stranahan et al., 2013).

2. Perineuronal nets: composition and association with distinct neuronal populations

The brain ECM surrounds all cells, occupying approximately a volume fraction of 20% of the normal adult brain (Chvatal et al., 1999; Zuber et al., 2005; Thorne and Nicholson, 2006; Sykova and Nicholson, 2008). In addition to a loosely organized molecular lattice, the ECM forms highly structured aggregates, among which PNNs (Fig. 1) are the most extensively investigated. Their components include chondroitin sulfate proteoglycans (CSPGs), hyaluronan, tenascin-R, link proteins, Reelin and semaphorin 3A (Matthews et al., 2002; Deepa et al., 2006; Carulli et al., 2013b; Dick et al., 2013; Vo et al., 2013a). CSPGs, the organizers of the ECM, are highly represented in PNNs, with aggrecan, neurocan, brevican, versican and phosphacan among the most abundant (Yamaguchi, 2000; Deepa et al., 2006; Giamanco and Matthews, 2012). These macromolecules consist of core proteins with varying numbers of chondroitin sulfate (CS) glycosaminoglycan (GAG) chains (Fig. 2). The number and length of GAG chains, their sulfation patterns (e.g. CS-6, CS-4; see Fig. 2) and the position of sulfated residues within the chains are key factors in determining their functions, yielding enormous structural and functional diversity to these molecules (Wang et al., 2008; Maeda, 2010; Karus et al., 2012; Miyata et al., 2012).

The contribution of such diversity to PNN composition has been, to some extent, investigated using antibodies raised against core proteins and specific sulfation patterns (Bertolotto et al., 1996; Ojima et al., 1998; Hagihara et al., 1999; Haunso et al., 1999; Matthews et al., 2002; Yin et al., 2006; Hayashi et al., 2007; Saitoh et al., 2008; Nakamura et al., 2009; Caterson, 2012; Miyata et al., 2012; Madinier et al., 2014; Racz et al., 2014), as well as lectins such as *Wisteria floribunda* agglutinin (WFA). WFA, perhaps the most widely used in studies of PNNs, binds specifically to N-acetyl-D-galactosamine on the terminal end of CS chains, with a preference for beta glycosidic linkage (Kurokawa et al., 1976; Young and Williams, 1985). The specificity of WFA as a marker for CSPGs is supported by extensive literature, although the specific CSPGs and/or sulfation patterns detected by WFA are not currently known (Hartig et al., 1994; Dityatev et al., 2007; Galtrey and Fawcett, 2007; Pantazopoulos et al., 2010). Immunolabeling using antibodies against CSPG protein cores or sulfation patterns shows that PNNs are heterogeneous in composition, with only a subgroup labeled by WFA. For instance, PNNs containing brevican are broadly distributed across the brain in regions where few WFA-labeled PNNs are located (Ajmo et al., 2008). In the human amygdala, we recently investigated PNNs containing aggrecan, one of the main CSPGs in the brain, or a specific CS-6 pattern, detectable with antibody 3B3 (Fig. 2) (Caterson, 2012; Pantazopolous et al., 2014). Our results show that only approximately 54% of aggrecan-labeled PNNs were co-labeled with WFA. PNNs labeled with the CS-6 sulfation antibody 3B3 were substantially more numerous, and displayed a broader distribution in the human amygdala with respect to WFA-labeled PNNs. In the lateral nucleus, 49% of 3B3-IR PNNs are co-labeled with WFA; this percentage decreases drastically in the other amygdala nuclei where the large majority of PNNs were 3B3-positive but WFA-negative. Like WFA-labeled PNNs, 3B3-labeled PNNs show clear interneuron-like morphology, suggesting that a large population of interneurons in the amygdala is associated with 3B3-labeled PNNs (see also below). Furthermore, PNNs containing versican

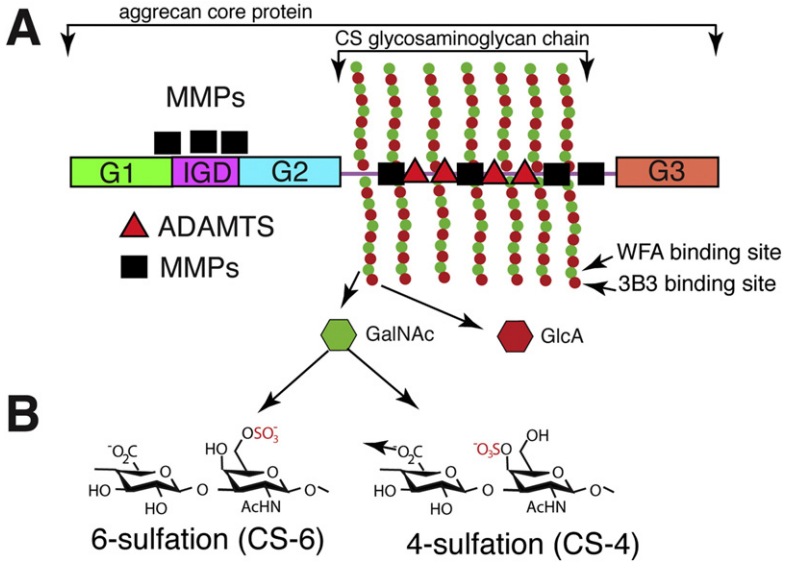

Fig. 2. CSPG structure and cleavage sites. Schematic diagram depicting the structure of CSPGs, aggrecan in this specific example. CSPGs are composed by a protein core protein that includes distinct domains (e.g. G1, G2). Attached to the protein core are numerous chondroitin sulfated glycosaminoglycan chains, creating a CS rich region (A). Each glycosaminoglycan chain consists of repeated pairs of glucuronic acid (GlcA) and N-acetyl-galactosamine (GalNAc). This latter can be sulfated in position 6 (CS-6) or 4 (CS-4) (B). The antibody 3B3 detects a non-reducing terminal end saturated CS disaccharide consisting of glucuronic acid N-acetyl-galactosamine-6-sulfate (CS-6; in A) (Sorrell et al., 1988; Caterson, 2012), whereas the lectin WFA detects N-actetyl-D-galactosamine on the terminal ends of CS chains, with a preference for beta glycosidic linkage (A) (Kurokawa et al., 1976; Young and Williams, 1985). CSPGs are cleaved by several metalloproteases, including ADAMTS (triangles) and MMPs (squares) on various sites of the protein core; indicated in A are those known for aggrecan (Nakamura et al., 2000; Porter et al., 2005).

(v0/v1 isoform) were detected selectively in the central nucleus (Fig. 3), but not in other amygdala nuclei, and represented a clearly distinct population with respect to those containing WFA (unpublished observations).

The questions of which neuronal populations bear PNNs and whether the molecular composition of PNNs is neuron-specific are critical to the understanding of their functional role, and the implications of their pathology in several brain disorders. Several studies in rodent, human and non-human primates have shown that a large population of WFA-labeled PNNs ensheaths fast-firing inhibitory interneurons expressing the calcium binding protein parvalbumin (PVB) and Kv3.1b, a subunit of voltage gated potassium channels typically expressed in fast-firing neurons (Brauer et al., 1993; Hartig et al., 1995; Morris and Henderson, 2000; Pantazopoulos et al., 2006). More recent evidence indicates that WFA-labeled PNNs are associated with more heterogeneous neuronal phenotypes than previously thought, including several subgroups of interneurons, a small subset of cortico-cortical pyramidal cells, spinal cord motor neurons and cerebellum Purkinje cells (Bruckner et al., 1993; Seeger et al., 1994; Brauer et al., 1995; Hartig et al., 1995; Wegner et al., 2003; Pantazopoulos et al., 2006; Ajmo et al., 2008; Gati and Lendvai, 2013). Among these, GABAergic neurons undoubtedly represent one of the largest populations in several brain regions, including several cortical areas, striatum, hippocampus, inferior colliculus, septum and amygdala (Hartig et al., 1994; Seeger et al., 1996; Pantazopoulos et al., 2006; Lee et al., 2012; Shah and Lodge, 2013; Foster et al., 2014). As an example, in the amygdala of rhesus monkey, the overwhelming majority of WFA-positive PNNs ensheath neurons expressing glutamic acid decarboxylase (GAD), a typical marker for GABAergic neurons, with many of these neurons also expressing PVB and/or calbindin (Hartig et al., 1995). In the human amygdala, 68% of WFA-labeled PNNs envelop PVB-positive neurons, a small percentage of which also express calbindin (Pantazopoulos et al., 2006). This result confirms the association of WFA-labeled PNNs with PVB-positive neurons, yet indicates that about a third of these PNNs ensheath other neuronal populations. Among these are interneurons expressing somatostatin (Fig. 4; unpublished data), a particularly interesting neuronal population in light of their expression of the voltage-gated potassium channel subunit Kv3, which may confer them high frequency firing properties, and their involvement in psychiatric disorders including schizophrenia (McDonald and Mascagni, 2006; Volk et al., 2012; Lin and Sibille, 2013; Fung et al., 2014; Volk and Lewis, 2014).

3. Perineuronal net abnormalities in schizophrenia

Our group has shown marked decreases of PNNs in several brain regions of subjects diagnosed with SZ (Pantazopoulos et al., 2010; Mauney et al., 2013; Pantazopolous et al., 2014). Lower numbers of WFA-labeled PNNs were detected in the amygdala, entorhinal and prefrontal cortex (Pantazopoulos et al., 2010; Mauney et al., 2013). Within each brain structure examined, WFA-labeled PNN reductions were selective for distinct subregions, i.e. the lateral nucleus of the amygdala, superficial layers of the entorhinal cortex and layers III and V of the prefrontal cortex. The distribution of these changes matches closely not only the normal distribution of WFA-labeled PNNs, but also that of GABAergic interneurons expressing PVB (Pantazopoulos et al., 2010). Notably, numbers of these neurons were normal in the amygdala and entorhinal cortex, and densities of WFA-labeled PNNs were unchanged in the central nucleus of the amygdala and visual cortex of subjects with SZ (Pantazopoulos et al., 2010; Mauney et al., 2013) (Fig. 3, unpublished data). Together, these findings suggest that reductions of WFA-labeled PNNs in SZ do not simply reflect loss of PVB-expressing neurons, and impact selective populations of these neurons in a region-selective manner.

We recently tested the hypothesis that PNN decreases in SZ may be broader than those detected with WFA, affecting several PNN

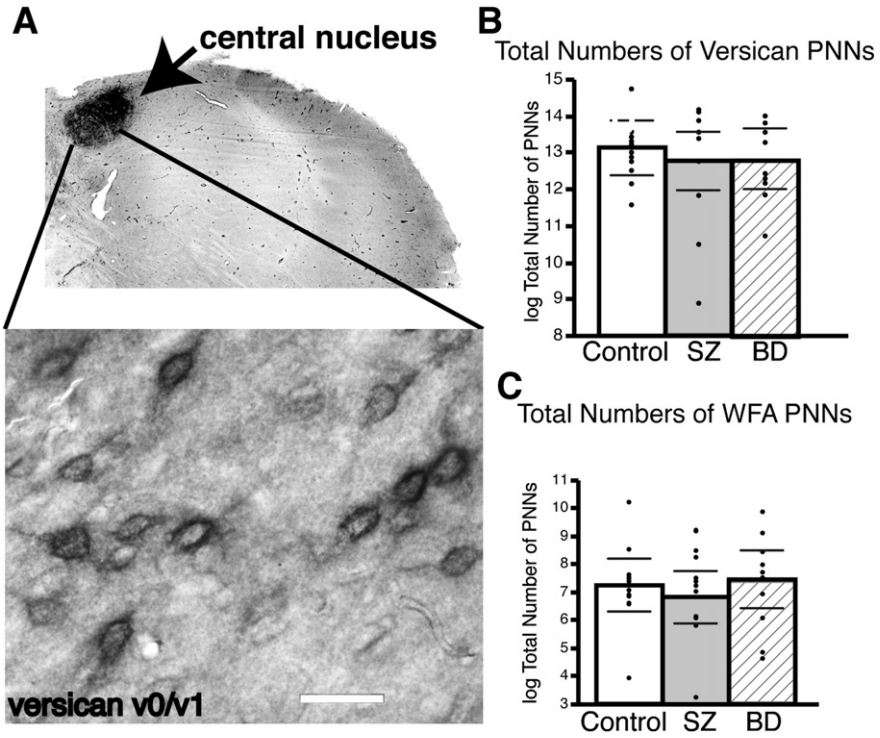

Fig. 3. PNN numbers in the central nucleus of the amygdala: region specificity of PNN abnormalities in SZ. (A) In the normal human amygdala, PNNs immunolabeled with an antibody against the v0/v1 isoform of the CSPG versican were exclusively found in the central nucleus (A). Inset in A shows numerous versican-immunolabeled PNNs in this nucleus. Scale bars = 50 μm. (B) Numbers of PNN containing versican v0/v1 in the central nucleus were normal in subjects with (SZ) or bipolar disorder (BD). Similarly, numbers of WFA-labeled PNNs were not altered in this nucleus in either disorder. Black circles indicate values for each subject, black lines indicate 95% confidence intervals (unpublished data).

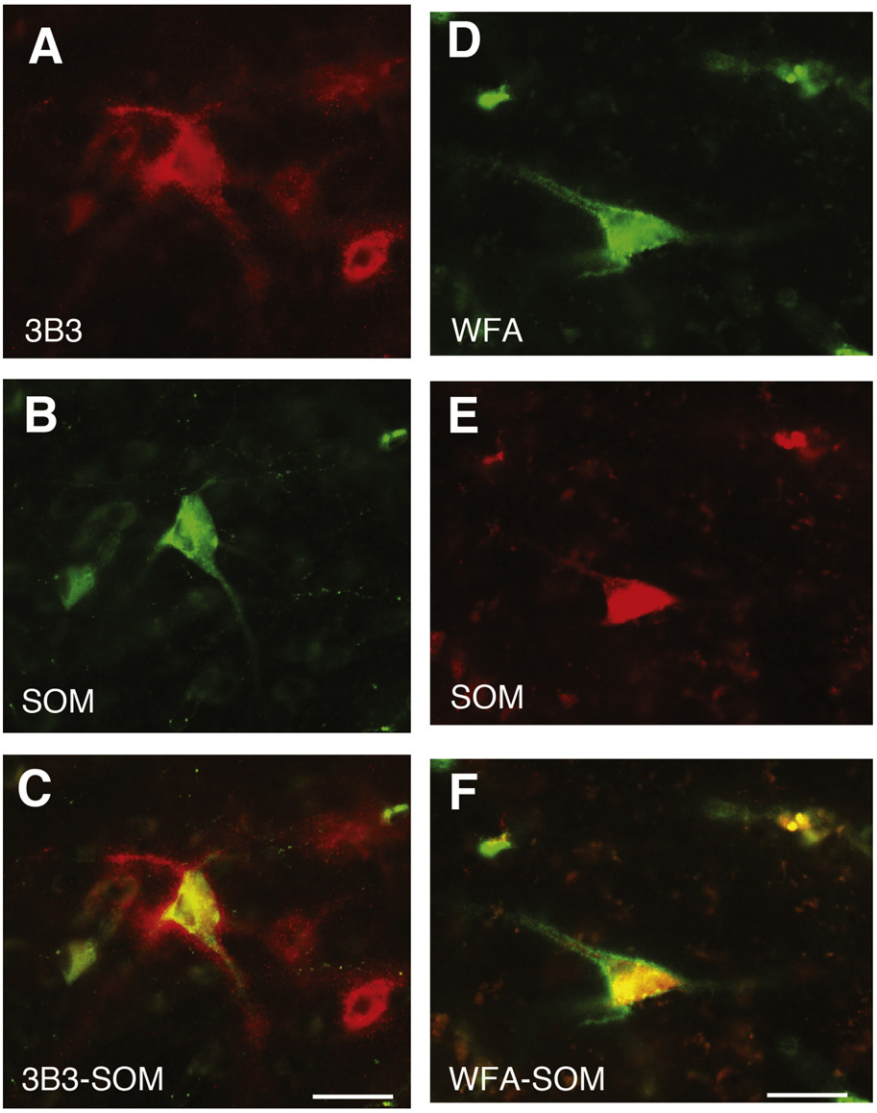

Fig. 4. Neurons expressing somatostatin are ensheathed by PNNs. Dual antigen immunofluorescence shows that a subgroup of neurons expressing somatostatin bears PNNs. Similar to neurons expressing parvalbumin, to a large extent associated with PNNs, somatostatin-positive neurons express voltage-gated potassium channel subunit Kv3 and have been shown to be altered in psychiatric disorders (McDonald and Mascagni, 2006; Volk et al., 2012; Lin and Sibille, 2013; Fung et al., 2014; Volk and Lewis, 2014). Photomicrographs in A–C show a neuron expressing somatostatin (green) ensheathed by a PNN containing CSPG CS-6 (3B3). In D–F, a neuron expressing somatostatin (red) is ensheathed by a WFA-labeled PNN. Scale bars = 50 μm.

populations. For these studies, we chose to investigate aggrecan, a major component of at least a subgroup of PNNs, and GAG chains containing CS-6, using the antibodies cat 301 and 3B3, respectively (Pantazopolous et al., 2014) (Fig. 2C). Our results show marked reductions of aggrecan- and CS6-positive PNNs in the amygdala of SZ subjects (effect size, aggrecan $g = -0.82$; 3B3 $g = -1.71$) (Fig. 5). Decreases of aggrecan-immunoreactive PNNs were selective for the lateral nucleus of the amygdala, similar to previous observations using WFA. However, only one-third (30%) of WFA-positive PNNs also express aggrecan, raising the possibility that neuronal populations affected by WFA- and aggrecan-positive PNN loss only partially overlap. In contrast, decreases of CS-6 immunoreactive PNNs were detected broadly across several amygdala nuclei, including the lateral, basal, accessory basal, cortical, and medial nuclei. These findings show that PNN abnormalities in SZ impact several distinct PNN phenotypes and neuronal populations, many likely to correspond to interneurons. Remarkably, the central nucleus of the amygdala appears to be spared by these abnormalities in SZ. Numbers of PNN immunolabeled for CS-6 (Pantazopolous et al., 2014), WFA, and v0/v1 isoforms of the CSPG versican were normal in this nucleus (Fig. 3; unpublished data).

In summary, our findings show consistent reductions of PNNs in subjects with SZ, affecting molecularly distinct PNN subgroups in several brain regions. These abnormalities are large in magnitude, robust to confounding factors and shared by several brain regions involved in SZ (Pantazopoulos et al., 2010; Mauney et al., 2013; Pantazopolous et al., 2014). Yet, they are restricted in their distribution to specific cortical layers and amygdala nuclei, suggesting specialized mechanisms affecting distinct neuronal populations.

4. Functional implications of PNN abnormalities in schizophrenia

What aspects of the pathophysiology of SZ may be related to PNN abnormalities? Below, we discuss synaptic functions, including regulation of glutamatergic transmission in GABAergic neurons, plasticity and learning and protection from oxidative stress as examples.

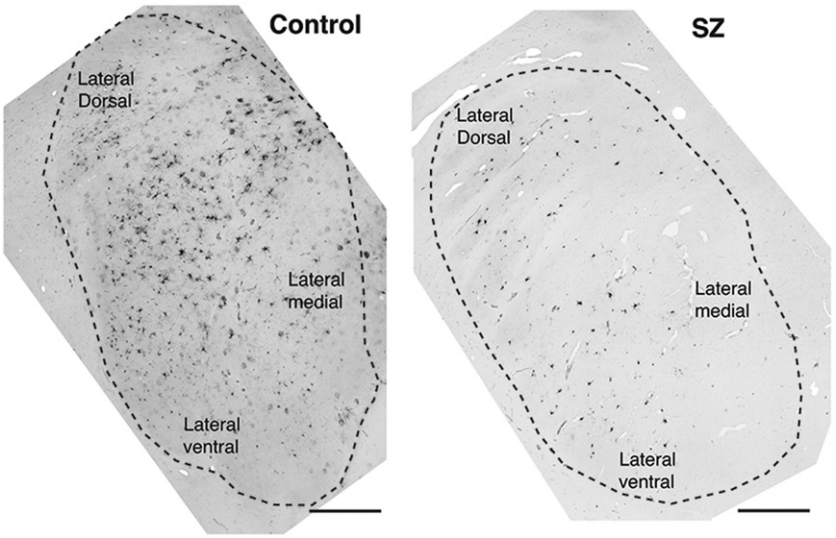

Fig. 5. Numbers of PNNs containing CS-6 (3B3) are decreased in the amygdala of subjects with SZ. Low magnification photomicrographs showing PNNs containing CS-6 (antibody 3B3) in the lateral nucleus of the human amygdala. Note the heterogeneous distribution within the dorsal medial and ventral portions of this nucleus, perhaps reflecting topographic association with distinct inputs. In healthy control subjects, 3B3-immunoreactive PNNs are particularly numerous in the lateral nucleus (A). In subjects with SZ, 3B3-immunoreactive PNNs were sharply decreased (B) (Pantazopolous et al., 2014). Scale bar = 1000 μm.

4.1. PNN regulation of synaptic functions

Compelling evidence supports a key role of PNNs in the regulation of synaptic functions (Dityatev and Schachner, 2006; Frischknecht and Gundelfinger, 2012). PNNs form perisynaptic condensations of organized ECM, which become an integral component of the functional synaptic complex. The term 'tetrapartite synapse' has been proposed for this complex, adding ECM perisynaptic condensations to the classic tripartite synapse formed by pre- and post-synaptic neuronal elements and glial processes surrounding them (John et al., 2006; Dityatev et al., 2010; Faissner et al., 2010). The role played by PNNs in synaptic regulation has been extensively discussed by other authors (e.g. Gundelfinger et al., 2010; Dityatev and Rusakov, 2011; Frischknecht and Gundelfinger, 2012), and only briefly summarized here. First, perisynaptic ECM components bind and sequestrate neurotrophins and transcription factors, making them available to cell surface receptors and/or allowing them to penetrate the cell membrane (Celio and Blumcke, 1994; Galtrey and Fawcett, 2007; Fawcett, 2009; Beurdeley et al., 2012). Second, PNNs divide the neuronal surface into multiple compartments, which control the diffusion of neurotransmitter receptors laterally within the plasma membrane (Fawcett, 2009; Frischknecht et al., 2009). For instance, during high frequency firing, desensitized synaptic glutamate AMPA receptors are exchanged for naive ones, which emerge extrasynaptically and diffuse laterally into the postsynaptic membrane (Heine et al., 2008). This process, proposed to represent a fundamental mechanism for the maintenance of synaptic receptor pools, has been shown to be controlled by PNNs, which restricted the lateral diffusion of AMPA receptors and thus allow synaptic desensitization (Heine et al., 2008; Frischknecht et al., 2009; Frischknecht and Gundelfinger, 2012). Consistently, PNN enzymatic digestion results in increased excitability of interneurons (Dityatev et al., 2007). Third, ECM components have been shown to interact actively with surface molecules to modify synaptic functions (Gundelfinger et al., 2010; Frischknecht and Gundelfinger, 2012). Notable examples are interactions of ECM molecules with 'neuronal activity-regulated pentraxin' (Narp) complexes and integrins, shown to regulate AMPA and NMDA receptor subunit composition, synaptic clustering and homeostatic synaptic scaling in GABAergic neurons (Cingolani et al., 2008; Campo et al., 2009; Chang et al., 2010; Dityatev et al., 2010; Frischknecht and Gundelfinger, 2012). Relevant to the pathophysiology of several psychiatric disorders, Reelin plays a key role in these latter mechanisms, interacting with integrins to regulate NMDA receptor subunit composition (Campo et al., 2009).

The considerations above highlight the effects of PNNs on synaptic functions and support the idea that PNN disruption in SZ may result in synaptic dysregulation and altered firing properties of PNN-bearing neurons. As discussed, these are predominantly represented by GABAergic neurons, including, but not restricted to, those expressing PVB and somatostatin (Brauer et al., 1993; Bruckner et al., 1993; Hartig et al., 1995, 2001; Wintergerst et al., 1996; Haunso et al., 1999; Morris and Henderson, 2000; Adams et al., 2001; Pantazopoulos et al., 2006; Pantazopoulos et al., unpublished observations, Fig. 4). Thus, PNN disruption may impact the activity of intrinsic circuitry and consequent information outflow. A recent study in a rodent model is consistent with this possibility. In this study, PNN enzymatic degradation in the ventral hippocampus resulted in increased activity of pyramidal neurons, postulated to result from disruption of GABAergic neuronal activity following PNN loss (Shah and Lodge, 2013). The discrepancy between this and previous findings of increased firing in vitro (Dityatev et al., 2007) is potentially explained by preparation and time course differences. We suggest that a similar disruption of inhibitory activity may occur in subjects with SZ in brain regions affected by PNN abnormalities, such as the amygdala, entorhinal cortex and prefrontal cortex (Pantazopoulos et al., 2010; Mauney et al., 2013; Pantazopolous et al., 2014). Such disruption may contribute to increased amygdala activity, consistent with the observation in SZ subjects tonically and during the processing of emotional stimuli (Taylor et al., 2005; Holt et al., 2006; Rauch et al., 2010; Suslow et al., 2013). In animal models, increased activity from the amygdala has been shown to result in decreased GABA neurons in sector CA2/3 of the hippocampus, thus potentially contributing to hippocampal abnormalities in this region in SZ (Benes and Berretta, 2000, 2001; Berretta et al., 2004; Heckers and Benes, 2005; Konradi et al., 2011; Wang et al., 2011). In the prefrontal cortex, PNN degradation may affect gamma oscillatory activity originating from interneurons expressing parvalbumin (Carter et al., 1998; Manoach et al., 1999; Lewis and Gonzalez-Burgos, 2008; Spencer, 2008; Kim and Webster, 2010; Uhlhaas and Singer, 2010; Woo et al., 2010). Furthermore, given the role of PNNs in regulating the trafficking of glutamate receptors (Sinagra et al., 2005; Frischknecht et al., 2009), it is possible

that PNN loss may contribute to a decrease of NMDA receptors on PVB-expressing neurons reported in the prefrontal cortex of subjects with SZ (Bitanihirwe et al., 2009).

4.2. PNN regulation of synaptic plasticity and learning

In the mammalian brain, the composition and properties of the ECM undergo a profound transformation during late postnatal development (Lander et al., 1997; Fawcett, 2009; Gundelfinger et al., 2010). A juvenile form of ECM, supportive of neurogenesis, cell migration, axonal outgrowth and synaptogenesis, is substituted by an adult form, which predominantly restricts plasticity (Bandtlow and Zimmermann, 2000; Galtrey and Fawcett, 2007; Fawcett, 2009; Faissner et al., 2010). The implementation of this adult form of ECM coincides with the closure of critical periods of postnatal development, during which neuronal circuits are shaped by experience, and culminates with the maturation of PNNs and PNN-like perisynaptic ECM aggregates (Pizzorusso et al., 2002; Yin et al., 2006; McRae et al., 2007; Balmer et al., 2009; Gogolla et al., 2009; Nowicka et al., 2009; Gundelfinger et al., 2010; Takesian and Hensch, 2013; Ye and Miao, 2013; Xue et al., 2014). Relevant to the pathophysiology of SZ, in human and non-human primates these events span across adolescence and early adulthood, potentially coinciding with the prodromal period and onset of SZ (Penn, 2001; Hensch, 2004; Sturman and Moghaddam, 2011). Consistently, in the human PFC, numbers of PNNs gradually increase from childhood through early adulthood, consistent with their role in regulating human prefrontal cortex circuit refinement (Mauney et al., 2013).

PNN gradual maturation around the somata and dendrites stabilizes successful synapses, restricting plasticity, regulating synaptogenesis and maintaining mature forms of learning (Bukalo et al., 2001; Dityatev et al., 2007; Faissner et al., 2010; Gundelfinger et al., 2010; Pyka et al., 2011; McRae and Porter, 2012; Carulli et al., 2013b). In the visual cortex, where this process has been most extensively studied, PNN maturation around PVB-expressing neurons closes the critical period for ocular dominance (Pizzorusso et al., 2002). Similarly, and particularly relevant to findings in SZ, PNN maturation in the amygdala determines the transition from juvenile to adult forms of emotion-related plasticity (Gogolla et al., 2009; Xue et al., 2014). Specifically, Gogolla and coworkers demonstrated that PNNs in the amygdala are necessary to protect fear-related memories from full erasure following extinction (Gogolla et al., 2009). Localized enzymatic CSPG digestion in adult animals caused a reversal to a juvenile form of fear conditioning, one that can be fully erased by extinction (Kim and Richardson, 2007; Gogolla et al., 2009). Notably, this mechanism was shown to depend on GABAergic transmission, pointing at the interactions between inhibitory interneurons and PNNs in plastic mechanisms. Xue et al. used a drug-related memory paradigm to demonstrate that PNN control over extinction memory in the amygdala is not limited to fear learning (Xue et al., 2014). In their experiments, CSPG/PNN degradation in the amygdala in combination with extinction training resulted in erasure of drug (cocaine, morphine)-related memories, facilitated the extinction of drug-seeking behavior and prevented the spontaneous recovery and drug-induced reinstatement of drug-seeking behavior (Xue et al., 2014). Together, this evidence suggests that PNN abnormalities in SZ may profoundly impact emotion processing and plasticity. Consistent with this possibility, altered fear learning, and related activity of the PFC and amygdala, has been reported in subjects with SZ (Holt et al., 2009, 2012).

4.3. Oxidative stress

Emerging evidence shows that PNNs may play a key role in protecting neurons from oxidative stress, such as it may be caused by a decrease of glutathione, a key brain antioxidant found to be decreased in SZ (Gawryluk et al., 2011; Cabungcal et al., 2013; Suttkus et al., 2014). In particular, PNN components such as aggrecan, tenascin-R, and link proteins are essential for this protection (Suttkus et al., 2014). However, PNNs may in turn be vulnerable to oxidative stress, as shown in mice with a genetic redox dysregulation (Cabungcal et al., 2013). As proposed by Do and coworkers, the protection afforded to GABAergic neurons by PNNs might reflect a balance between the oxidative burden on these ECM structures and the capacity of the system to maintain them (Cabungcal et al., 2013). Further support for the neuroprotective properties of PNNs comes from postmortem findings on older subjects, showing that neurons enveloped by PNNs contain less of the lysosomal pigment lipofucsin, which accumulates as a consequence of oxidative processes (Morawski et al., 2004).

5. Potential causes of PNN abnormalities

In subjects with SZ, decreases of PNNs in multiple brain regions were robust to confounding variables, including exposure to pharmacological agents, and did not correlate with age at onset of the disease or duration of illness (Pantazopoulos et al., 2010; Mauney et al., 2013; Pantazopolous et al., 2014). These observations are consistent with the idea that PNN abnormalities in SZ may be inherent to this disorder and, perhaps, present at its onset. Two main mechanisms, not reciprocally exclusive, may be postulated. First, PNNs may fail to mature, or form correctly, during late postnatal development, coinciding with the prodromal period and age of onset of SZ. Second, during adulthood, PNNs may undergo degradation, and/or lack stability, as a consequence of dysregulation of ECM remodeling processes. Our findings, together with recent findings from genetic studies showing that several vulnerability genes for SZ encode PNN components and enzymes involved in ECM remodeling, support these hypotheses (Buxbaum et al., 2008; Rybakowski et al., 2009; Cichon et al., 2011; Dow et al., 2011; Groszewska et al., 2011; Ripke et al., 2011, 2013; Ripke and Schizophrenia Working Group of the Psychiatric Genomics, 2014).

5.1. Decreased CSPG availability may contribute to PNN decreases in SZ

Recent findings from our group show that decreases of PNNs in the amygdala of subjects with SZ are accompanied by marked reductions of glial cells expressing aggrecan and CS-6 sulfation (Pantazopoulos et al., in press). Glial cells are a main source of chondroitin sulfate proteoglycans (abbreviated here as CSPGs), and have been shown to critically contribute to the formation and maintenance of PNNs (John et al., 2006; Faissner et al., 2010; Klausmeyer et al., 2011; Wiese et al., 2012). Thus, these findings raise the possibility that decreased CSPG synthesis in glial cells may contribute PNN reductions in SZ. Speculatively, altered expression of transforming growth factor, and other growth factors known to powerfully regulate astroglial CSPG synthesis, may play a role in this mechanism (Smith and Strunz, 2005; Benes et al., 2007; Markota et al., 2013). In addition, recently reported genetic vulnerabilities for CSPG genes, including PTPRZ1 and neurocan (Buxbaum et al., 2008; Muhleisen et al., 2012; Ripke and Schizophrenia Working Group of the Psychiatric Genomics, 2014), may contribute to decrease CSPG synthesis in SZ. These considerations suggest that reduced availability of CSPGs, perhaps in part due to genetic factors, may lead to a failure to form PNNs during late development, potentially disrupting the maturation of inhibitory neural circuits in SZ.

5.2. Disruption of ECM remodeling may contribute to PNN decreases in SZ

Until recently, mature PNNs were considered to be highly stable over time, and to permanently restrict neuronal plasticity (e.g. Corvetti and Rossi, 2005; Galtrey and Fawcett, 2007). Emerging evidence supports the intriguing idea that the ECM, both in its developmental and adult forms, is constantly remodeled in response to a broad variety of stimuli, which in adulthood include learning and memory, stress, and immune system activation (Frischknecht and Gundelfinger, 2012). The main agents of this remodeling process are three families of metalloproteases

collectively known as metzincin family, i.e. 'matrix metalloproteases' (MMPs), 'a disintegrin and matrix metalloproteases' (ADAMS), and 'ADAMS with a thrombospondin domain' (ADAMTS), which cleave ECM molecules, including those that compose PNNs (Fig. 2) (Muir et al., 2002; Medina-Flores et al., 2004; Abdolmaleky et al., 2005b; Hobohm et al., 2005; Rivera et al., 2010). For instance, ADAMTSs are known to cleave multiple PNN components including the CSPGs aggrecan, brevican, neurocan, versican, and phosphacan (Fig. 2) (Porter et al., 2005; Tauchi et al., 2012). Notably, metalloproteases play a key role in synaptic plasticity and memory, creating windows of opportunity for learning by temporarily releasing neurons from the ECM clamping effects on plasticity and increasing synaptogenesis (Wright and Harding, 2009; Rivera et al., 2010; Frischknecht and Gundelfinger, 2012; Van Hove et al., 2012). For instance, expression of MMP9 was shown to increase in the amygdala, prefrontal cortex, and hippocampus during contextual fear learning, while pharmacological disruption of MMP activity results in disruption of reconsolidation of fear memory (Brown et al., 2009; Ganguly et al., 2013). Similar disruption of MMP3 and MMP9 activity in the hippocampus results in disruption of spatial memory and avoidance learning (Nagy et al., 2007; Wright et al., 2007). Notably, altered expression of MMPs and ADAMTS was found to be associated with PNN reduction (Gray et al., 2008).

We suggest that altered expression of members of the metzincin family of metalloproteases may contribute to a disruption of PNNs in SZ. Altered metalloproteases expression, during development and/or adulthood, would result in dysregulation of ECM remodeling with consequent failure of PNN maturation and impaired PNN stability. Consistent with this hypothesis, a recent gene expression profiling study of the superior temporal gyrus in subjects with SZ showed altered mRNA expression of MMPs and ADAMTSs, including MMP16 (Pietersen et al., 2014). At least two, potentially linked, factors may lead to a disruption of metalloprotease expression. First, converging results from several recent genetic association and genome-wide association studies indicate that genes encoding for a number of metzincin metalloproteases may represent vulnerability factors for SZ. These include ADAMTSL3, ADAMTS12, ADAMTS-16, ADAM22, and MMP16 (Dow et al., 2011; Ripke et al., 2011; Bespalova et al., 2012; McGrath et al., 2013; Ripke and Schizophrenia Working Group of the Psychiatric Genomics, 2014). Thus, expression of several metalloproteases may be altered in subjects with SZ as a result of genetic predisposition. Second, PNN integrity and expression of metalloproteases are markedly affected by stress and immune responses (Medina-Flores et al., 2004; Franklin et al., 2008; Gray et al., 2008; Fillman et al., 2014). These responses have been linked to the pathogenesis of SZ, with a very recent study pointing to a genetic contribution to immune factor involvement (Arion et al., 2007; Saetre et al., 2007; Smith et al., 2007; Fillman et al., 2013; Horvath and Mirnics, 2014; Ripke and Schizophrenia Working Group of the Psychiatric Genomics, 2014). Thus, interactions between dysregulated stress response and immune systems in subjects with SZ may impact the expression of metalloproteases, resulting in degradation of PNNs.

6. Conclusions

PNN abnormalities may represent an important factor in the pathophysiology of SZ, contributing to a disruption of GABAergic circuits observed in this disorder. These abnormalities may result from complex interactions of genetic vulnerabilities of genes encoding for CSPGs, metalloproteases and immune system molecules with environmental factors leading to stress and immune system activation, and in turn impact postnatal neuronal maturation, protection from oxidative stress, synaptic regulation and plasticity of distinct interneuronal populations, potentially accounting for molecular and functional anomalies in intrinsic inhibitory circuits. In turn, these may result in a disruption of cognitive and emotional processing.

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Contributors

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Conflict of interest

The authors of this manuscript do not have any actual or potential conflict of interest to disclose.

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