Review

Biological Psychiatry

Weaving a Net of Neurobiological Mechanisms in Schizophrenia and Unraveling the Underlying Pathophysiology

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ABSTRACT

Perineuronal nets (PNNs) are enigmatic structures composed of extracellular matrix molecules that encapsulate the soma, dendrites, and axon segments of neurons in a lattice-like fashion. Although most PNNs condense around parvalbumin-expressing gamma-aminobutyric acidergic interneurons, some glutamatergic pyramidal cells in the brain are also surrounded by PNNs. Experimental findings suggest pivotal roles of PNNs in the regulation of synaptic formation and function. Also, an increasing body of evidence links PNN abnormalities to schizophrenia. The number of PNNs progressively increases during postnatal development until plateauing around the period of late adolescence and early adulthood, which temporally coincides with the age of onset of schizophrenia. Given the established role of PNNs in modulating developmental plasticity, the PNN represents a possible candidate for altering the onset and progression of schizophrenia. Similarly, the reported function of PNNs in regulating the trafficking of glutamate receptors places them in a critical position to modulate synaptic pathology, considered a cardinal feature of schizophrenia. We discuss the physiologic role of PNNs in neural function, synaptic assembly, and plasticity as well as how they interface with circuit/system mechanisms of cognition. An integrated understanding of these neurobiological processes should provide a better basis to elucidate how PNN abnormalities influence brain function and contribute to the pathogenesis of neurodevelopmental disorders such as schizophrenia.

Keywords: Critical period, Neurodevelopment, Parvalbumin interneurons, Perineuronal nets, Schizophrenia, Synaptic plasticity

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Schizophrenia is a multifactorial disorder of neurodevelopmental origin (1–4) that is thought to arise from a complex interaction between genetic and environmental factors (5–11). The onset of schizophrenia occurs during late adolescence or early adulthood, when brain circuitry involving the prefrontal cortex and hippocampus, in addition to other limbic regions, undergoes maturation (2–4). The pathophysiologic features of schizophrenia stem from various aberrant neurobiological underpinnings that ultimately impinge on synaptic plasticity and synaptic connectivity (12–14), including anomalies in cortical myelogenesis (13) and synaptic pruning (12,15); altered glutamatergic signaling (16–18); and reduced neuropil (19) in conjunction with atypical development of cortical inhibitory circuits (14,20,21), dopaminergic pathways (22), and perineuronal nets (PNNs) (23–31).

The PNN is a reticular structure of the neural extracellular matrix (ECM) that is found surrounding many neurons in the central nervous system (CNS) (32–34). The developmental pattern of increasing PNN formation corresponds to the ending of the "critical period," a time window of postnatal life that is critical for experience-dependent formation of synaptic connections and wiring of functionally related neuronal pathways that underlie sensory, motor, cognitive, social, and language abilities (35), deficits in which have been linked to schizophrenia (36). Experimental disruption of PNNs in the adult brain can reopen critical periods, and therefore the PNN is generally considered to play a role in restricting synaptic plasticity (37). More recent work has expanded the list of functions attributed to PNNs within the CNS (Table 1), with potential significance to neuropathogenesis.

In this review, we focus on the neurobiological functions of PNNs and their putative basis in schizophrenia pathophysiology. In addition, we expound on the emerging hypothesis linking a dysfunctional orthodenticle homeobox 2 (OTX2)–PNN interaction to the cognitive and cortical plasticity deficits associated with schizophrenia. We conclude by touching on how these observations may provide a neurobiological framework for the conceptualization of a molecular targeted intervention against this extremely debilitating condition.

PNN CHARACTERISTICS: MOLECULAR HETEROGENEITY, DISTRIBUTION, AND DEVELOPMENTAL EXPRESSION

The PNNs are enriched in complex sugars called glycosaminoglycans and constitute a highly organized structure comprising hyaluronan, link proteins, tenascin-R, and chondroitin sulfate proteoglycans (CSPGs)—primarily the lectican family

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Table 1. Summary of Functions of PNNs in the Central Nervous System

Function Influenced by PNNs	References
Cognitive Functions	
Audition	(85,87)
Learning and memory	(41,51,52,54,80)
Motor coordination	(52)
Nociception	(86)
Olfaction	(38,76)
Vision	(71)
Vocal development	(49)
Neurophysiologic/Cell Biological Functions	
Critical period regulation	(37,61,62,67)
Glutamate receptor trafficking	(33,89)
Intercellular transport of molecules	(71)
Ion homeostasis	(145–147)
Neuroprotection	(148,149)
Membrane compartmentalization	(89)
Regulation of gamma oscillations	(25)
Synaptic stability and plasticity	(32,37,150)

PNN, perineuronal net.

(aggrecan, brevican, neurocan, and versican) and phosphocan (38–40). The possibility of simultaneously costaining for various markers of the PNN has revealed a molecular heterogeneity of PNNs in distinct interneuronal subpopulations as indicated by different staining intensities of these markers in the cerebral cortex, subcortical forebrain, and brainstem (41,42). Because PNNs exhibit a high degree of constitutive heterogeneity, the alteration of a single marker during development or in disease states may not necessarily reflect the alteration or loss of the entire structure.

Previous research conducted across various animal species [i.e., rhesus monkey (43,44), bison (45), dog (46), gerbil (47), guinea pig (48), zebra finch (49), rat (38), and mouse (25,50–56)] has shown PNNs to be widely distributed in the brain. Similarly, in humans, PNNs have been found to be present in various brain regions, including entorhinal cortex (28), amygdala (28,29,57), hippocampus (58), motor and somatosensory cortex (59), visual cortex (27), and prefrontal cortex (27), all regions (except the visual cortex) that have been reported to be affected in schizophrenia (60).

Experimental evidence from animal studies suggests a progressive increase in PNN expression to be associated with the postnatal maturation of the CNS (35,51,61–63). Consistent with the animal findings, a study using human postmortem brain tissue revealed that the number of PNNs in the prefrontal cortex also increases through the peripubertal period until late adolescence and early adulthood (27), which is considered the peak period of risk for onset of schizophrenia (2,64). Notable findings from the visual cortex (65), motor cortex (66), and somatosensory system (67) in animals as well as in the pallial (cortical) song nuclei (49) in songbirds suggest that PNN expression is dependent on neuronal activity during the critical period.

Although most PNNs condense around the fast-spiking parvalbumin-expressing gamma-aminobutyric acid (GABA)ergic interneurons, some pyramidal cells are also surrounded by PNNs (68,69). The presence of PNNs around parvalbumin interneurons is of particular significance in the context of critical period plasticity. This period of plasticity seems to be triggered by a shift in the excitatory/inhibitory balance associated with the maturation of parvalbumin interneurons (35,70), whose functional disturbances have been strongly linked to schizophrenia (25). Parvalbumin interneurons control the initiation and termination of the developmental critical periods, with termination being dependent on the formation of PNNs (35,37,71). In this context, evidence showing the PNN to play a role in the "capture" of the homeodomain transcription factor OTX2 is of particular interest (71,72). The presence of a short motif within the OTX2 sequence (RKQRRERTTFTRAQL), which partially overlaps with the first helix of the homeodomain, possesses consensus traits of a glycosaminoglycan-binding domain (73) and is a requisite for the specific recognition of OTX2 by parvalbumin interneurons that are surrounded by PNNs (71). The sulfation pattern of PNNs represents another important factor in OTX2 binding (61). Secretion of OTX2 from choroid plexus epithelial cells has been shown to signal the maturation of the parvalbumin interneurons and the subsequent regulation of critical period plasticity (71,74). Therefore, PNNs serve not only as "molecular brakes" that limit morphologic and physiologic plasticity but also as "receptors," which function to control the availability of molecular factors (e.g., OTX2) that regulate plasticity and modulate parvalbumin cell function to influence the opening and possibly also the closure of the critical period (61,71,72,74,75).

ROLE OF PNNs IN THE MODULATION OF COGNITIVE FUNCTION

Given that PNN-encapsulated neurons are prevalent throughout the limbic system (28,29,76) and PNNs are capable of modulating receptors (i.e., alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid [AMPA] receptors) known to be integral for learning and memory (77), these structures have been considered to play an important role in memory formation (54), which may include emotional memory (51,55) in addition to reward-related memory (50,78). It has been reported that PNNs are involved in long-term potentiation and long-term depression in hippocampal slices, as these physiologic events are impaired after enzymatic degradation of CSPGs, or removal of tenascin-R (79,80). Moreover, PNNs seem to be important for the maturation and stabilization of synapses (65,81), key developmental processes that are altered in schizophrenia (12–14), suggesting that PNNs also serve a specialized role for normal neurophysiologic development.

The presence of PNNs in the striatum (52), olfactory pathway (38,76), basal ganglia (82), cerebellum (83), thalamus (56), visual cortex (27), insular cortex (50), high vocal center (49), orbital cortex (53), central auditory pathway (43,84,85), and spinal cord (86) suggests that the regulatory effects of PNNs are involved in a wide range of brain functions. These functions include motor coordination; olfaction; procedural learning; voluntary motor movement; arousal state; vision; integration of cognitive, affective, sensory, and autonomic information; vocal development; mediating decision making; processing of auditory stimuli; and nociception. Depletion or