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# Synaptic Sweet Talk: How Do Perineuronal Nets Contribute to Epileptogenesis and Neuroplasticity?

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## Synaptic Sweet Talk: How Do Perineuronal Nets Contribute to Epileptogenesis and Neuroplasticity?

### Perineuronal Net Degradation in Epilepsy.

Elyse K. Rankin-Gee, Paulette A. McRae, Esther Baranov, Stephanie Rogers, Luke Wandrey, and Brenda E. Porter. *Epilepsia* 2015 56(7):1124–1133. PMID: 26032766

**OBJECTIVE:** We previously reported loss of perineuronal net (PN) immunohistochemical staining around parvalbumin-positive interneurons in the hippocampus of rats after an episode of status epilepticus (SE). We hypothesized that the loss of the PN could alter seizure susceptibility and that matrix metalloproteinases (MMPs) were candidates for degradation of the PN following SE. **METHODS:** The pilocarpine chemoconvulsant rodent epilepsy model was used to characterize the degradation of the aggrecan component of the PN in the hippocampus following SE. Chondroitinase ABC (ChABC) was used to degrade the PN in mice. Onset, number, and duration of pentylenetetrazole (PTZ)-induced seizures were assessed. **RESULTS:** The loss of the PN in the hippocampus following SE is at least partially related to degradation of the aggrecan PN component by MMP activity. Forty-eight hours after SE, a neoepitope created by MMP cleavage of aggrecan was present and concentrated around parvalbumin-positive interneurons. The increase in aggrecan cleavage products was found at 48 h, 1 week, and 2 months after SE, with different fragments predominating over time. We demonstrate ongoing aggrecan proteolysis and fragment accumulation in the hippocampus of adult control rats, as well as in SE-treated animals. Degradation of the PN alters the seizure response to PTZ. ChABC treatment caused an increase in myoclonic seizures following PTZ administration, a delayed onset of Racine stage 4/5 seizure, and a decreased duration of Racine stage 4/5 seizure. **SIGNIFICANCE:** Status epilepticus increases MMP proteolysis of aggrecan, pointing to MMP activity as one mechanism of PN degradation post-SE. There is accumulation of aggrecan fragments in adult rat hippocampus of both control and SE-exposed animals. Loss of the PN was associated with increased numbers of myoclonic seizures; it also delayed and shortened the duration of Racine stage 4/5 seizures, suggesting a complex relationship between the PN and seizure susceptibility.

### Commentary

Epileptogenesis in acquired forms of temporal lobe epilepsy (TLE) involves changes in both the excitatory and inhibitory synaptic networks in the hippocampus. Recent findings suggest that alterations in the extracellular environment surrounding a hippocampal neuron may contribute to epileptogenesis. The extracellular space of the nervous system is a composite of several nets—an outer net of interlaced astrocyte processes is interposed with a second net of extracellular matrix molecules that hugs the neuronal surface. These lattice-like structures, called the “perineuronal nets” (PN), surround most, if not all, cortical and hippocampal neurons—as well as neurons in the spinal cord and other brain regions—and are mirrored by a third net, an intracellular net that is linked to the membrane and cytoskeleton (1).

Prominent PNs on cortical GABAergic interneurons were first depicted and described in detail in 1893 by Camillo

Golgi. In his view, PNs were a mantle or “corset of neurokeratin” that blocked the spread of current between cells (2). Further advances in understanding the structure of PNs surrounding neurons followed the discovery that they could be visualized by staining with lectins that bind to specific carbohydrate residues called N-acetylgalactosamines, or antibodies recognizing specific carbohydrate epitopes, including the monoclonal antibodies Cat-301, VC1.1, and HNK-1 (3). PNs were observed to ensheath the terminal boutons of synapses in contact with the cell bodies and proximal dendrites of GABAergic interneurons but were excluded from synaptic clefts. While especially prominent on parvalbumin-expressing basket cells in the hippocampus and cerebral cortex, PNs have been identified on multiple types of neurons, including spinal motor neurons (3). PNs are established during neuronal maturation and, once formed, may oppose synaptic plasticity, thereby strengthening and stabilizing the existing synapses on interneurons. The fact that PNs can be regulated by neuronal activity also suggests that they have an important role in opposing neuroplasticity; furthermore, many different studies have identified a role for PNs in closure of critical periods during development.

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Some of the classes of extracellular matrix molecules that make up PNs have been identified, including hyaluronan, glycoproteins, and chondroitin sulfate proteoglycans. Lecticans are chondroitin sulfate proteoglycans characterized by hyaluronan binding domains and C-type lectin domains. The lectican group includes several family members. One member of considerable interest is aggrecan, a molecule almost exclusively found associated with PN in the brain. Aggrecan has a protein core that supports extensive carbohydrate side chains, giving the molecule a bottlebrush-like structure that enables it to bind other molecular components of the extracellular matrix.

Because of their prominence on parvalbumin-expressing GABAergic interneurons called “basket cells,” investigating the functions of PNs in these cells is of considerable interest for understanding TLE. Many studies have now demonstrated the loss or dysfunction of GABAergic interneurons in TLE, and deficits in inhibition may be partially responsible for causing the dentate gyrus to become hyperexcitable. Studies in the pilocarpine model of TLE in rodents suggest that while some types of GABAergic interneurons are particularly vulnerable and die following status epilepticus (SE), the parvalbumin basket cells are resistant. Although they survive SE, this type of GABAergic inhibitory interneuron may develop reduced synaptic input and output and become hypofunctional (4). A long-standing question has been whether losing the excitatory drive to the parvalbumin-expressing neurons can explain their hypofunctionality.

Recently, a study conducted by Rankin-Gee and colleagues approached this question by determining whether seizure activity compromises PNs on the parvalbumin-expressing interneurons. The investigators experimentally manipulated PNs in two ways— first, with chemoconvulsant-induced SE and, second, by direct enzymatic injections into the hippocampus of naïve mice. To examine whether seizures triggered PN degradation, they made systemic injections of the cholinergic agonist pilocarpine in rats to induce severe SE. Western blot studies of hippocampal tissue from rats subjected to 1 hour of SE showed that this period of seizure activity was sufficient to degrade aggrecan. The resulting cleavage products corresponded to the extracellular matrix breakdown products produced by increased enzymatic activity of matrix metalloproteinases (MMPs). This study also showed that SE-induced cleavage of PN by MMPs exposed a novel epitope on aggrecan that could be detected by immunohistochemical staining. Using antibodies specific for epitopes in the aggrecan molecule, the researchers found that SE triggered aggrecan degradation specifically on parvalbumin interneurons throughout the hip-

pocampus. Seizures apparently increase the enzymatic activity or expression of MMPs, triggering the enzymatic breakdown of the PNs that prominently surround the parvalbumin-expressing basket cells.

In another set of experiments described by Rankin-Gee and colleagues, the aggrecan component of PNs was degraded in naïve mice by making intrahippocampal stereotaxic injections of the chondroitinase ABC enzyme. They then examined whether this treatment altered pentylenetetrazole-induced seizures. The chondroitinase ABC-treated mice had significantly more severe seizures than controls, suggesting a link between the integrity of the PNs on the parvalbumin-expressing basket cells and seizure thresholds.

The gradual disintegration of the PN on basket cells caused by SE suggests a molecular scenario to explain why basket cells lose functionality in TLE; when seizures elevate MMP enzymatic activity, PNs on basket cell somas and dendrites gradually degrade, resulting in a decrease in excitatory synapses onto these interneurons and an overall increase in network excitability. While these findings are compelling, additional experiments are required to directly demonstrate that PN disruption by MMPs reduces spontaneous firing rates in parvalbumin-expressing basket cells. Understanding how interneuron dysfunction contributes to epileptogenesis is a long-standing puzzle in the field, and perhaps these approaches could be used in future studies to solve this puzzle. The specific MMPs or other enzymes, such as aggrecanases, that degrade PN after SE are not yet known. Identifying these MMPs and how they are regulated by seizures or other events, such as traumatic brain injury, might also facilitate the discovery of drugs to protect or rebuild perineuronal nets on GABAergic interneurons.

by Janice R. Naegele, PhD

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