That’s a Wrap: Could Controlling Activity-Regulated Myelination Prevent Absence Seizures?

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Maladaptive Myelination Promotes Generalized Epilepsy Progression
Knowles JK, Xu H, Soane C, Batra A, Saucedo T, Frost E, Tam LT, Fraga D, Ni L, Villar K, Talmi S, Huguenard JR, Monje M. Nat Neurosci. 2022;25(5):596-606. doi:10.1038/s41593-022-01052-2

Activity-dependent myelination can fine-tune neural network dynamics. Conversely, aberrant neuronal activity, as occurs in disorders of recurrent seizures (epilepsy), could promote maladaptive myelination, contributing to pathogenesis. In this study, we tested the hypothesis that activity-dependent myelination resulting from absence seizures, which manifest as frequent behavioral arrests with generalized electroencephalography (EEG) spike-wave discharges, promote thalamocortical network hypersynchrony and contribute to epilepsy progression. We found increased oligodendrogenesis and myelination specifically within the seizure network in two models of generalized epilepsy with absence seizures (Wag/Rij rats and Scn8a⁺/mut mice), evident only after epilepsy onset. Aberrant myelination was prevented by pharmacological seizure inhibition in Wag/Rij rats. Blocking activity-dependent myelination decreased seizure burden over time and reduced ictal synchrony as assessed by EEG coherence. These findings indicate that activity-dependent myelination driven by absence seizures contributes to epilepsy progression; maladaptive myelination may be pathogenic in some forms of epilepsy and other neurological diseases.

Commentary
Seizures are associated with highly synchronous neural activity, and as such, when studying epilepsy it is critical to think about the mechanisms by which neural synchrony is achieved. Activity-dependent oligodendrogenesis and subsequent myelination help facilitate neural synchrony by altering the saltatory conduction velocities of axons and fine-tuning and expediting neuronal communication in a healthy brain. Myelin abnormalities have been reported previously in epilepsy patients and seizures have often been observed in demyelinating diseases such as multiple sclerosis,¹ indicating a potential role for myelination in facilitating seizures. Although these abnormalities have been identified, the precise role of irregular myelin in epilepsy progression is still largely unknown.

Knowles and colleagues² examined myelination within the context of 2 rodent models of epilepsy, Wag/Rij rats, a well-characterized model of absence epilepsy, and Scn8a⁺/mut mice, a model harboring a loss-of-function SCN8A mutation that leads to generalized epilepsy with absence seizures.³ First, using immunohistochemistry and flow cytometry, the authors investigated the numbers of myelinating oligodendrocytes and their precursors (OPCs) before seizure onset and at a time point at which seizures were fully established. The results were similar in both rodent models: the number of both proliferating OPCs and mature oligodendrocytes were higher following the onset of absence seizures compared to controls. Myelin was then assessed directly using transmission electron microscopy, with g-ratio, the ratio of axon diameter relative to the myelin sheath thickness, as the primary quantifiable measurement. Following seizure onset, the g-ratio of axons in both rodent epilepsy models was decreased, meaning that these axons showed more myelination relative to the axon size. Differences in g-ratio were not detected prior to seizure onset. Thus, in both models, the onset of absence seizures was followed by an increase in myelinating glia and subsequent myelination. Interestingly, the changes in myelin structure and increases in

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oligodendrocyte/OPC numbers were localized specifically within networks involved in absence seizure generation and synchronization, namely the mid region of the corpus callosum, and not in networks less involved with seizure activity, further supporting a very focused anatomical pattern of increased myelination.

To further explore whether absence seizure activity is a requirement for this increased myelination, the authors treated Wag/Rij rats with the anti-seizure medicine ethosuximide. Treatment was initiated before the onset of seizures and continued for 5 months, a time point at which seizures are fully developed. As expected, ethosuximide either reduced seizure frequency or prevented seizures altogether. Importantly, treatment also prevented the increases in relative myelin sheath thickness, signifying that seizure activity, rather than some other phenomenon occurring pre- or post-seizure onset, was instrumental in establishing the aberrant myelination observed.

If seizure activity leads to increased myelination of axons, then would a reduction in myelination prevent seizures? To address this question, the authors crossed their Scn8a+/mut absence seizure mice with a conditional mouse model where TrkB, a receptor important for signaling in OPCs and their activity-dependent maturation into myelinating oligodendrocytes, could be deleted specifically from OPCs. This blockade of activity-dependent myelination led to a profound decrease in seizure activity in Scn8a+/mut mice as well as a decrease in ictal coherence between the somatosensory cortices, demonstrating the potential role that activity-dependent myelination plays in ictal synchronization. Similar results were seen when the authors blocked activity-dependent myelination pharmacologically using Trichostatin A, a histone deacetylase inhibitor that prevents OPCs from maturing into oligodendrocytes. Treatment resulted in a decrease in mature oligodendrocytes in Scn8a+/mut mice and a decrease in seizure frequency, whereas seizure duration was unaffected. The reduction in seizure frequency associated with a decrease in activity-dependent myelination indicates a role for this process in establishing absence seizure burden.

This study is highly relevant to the epilepsy field and opens the door to further evaluating the role of myelinating glia and other non-excitable cells in epilepsy. The models used were particularly shown in the context of absence seizures, but how might these findings apply to models representing other types of seizures? Absence seizures often occur more frequently than tonic seizures, up to 100 times in a single day, and this disparity in seizure frequency could suggest differing roles for activity-dependent myelination in absence epilepsy and generalized epilepsy. Some previous studies, particularly clinical studies, show a decrease in myelination in epilepsy patients and models, however, others show an increase in myelination and decrease in g-ratio, similar to the results seen by Knowles and colleagues.

Proper myelination is integral to the organization of neural networks, and cortical disorganization has been suggested previously in models of epilepsy. Perhaps maladaptive myelination in some epilepsies could translate to alterations in white matter that may contribute to epilepsy progression, as many forms of epilepsy involve an increase in seizure frequency and severity over time. Additionally, the connection shown between activity-dependent myelination and the progression of epilepsy naturally provokes questions about how we may use this information to better understand and treat the progression of seizures. On the other hand, the well-described epilepsy syndrome, childhood absence epilepsy, usually undergoes spontaneous remission, not progression. In these cases, activity-dependent myelination may primarily function as a mechanism of synchronization, particularly between both hemispheres in generating generalized seizures.

With respect to the maladaptive myelination seen in this study, it may also be important to look at the interactions of OPCs and myelinating oligodendrocytes with other cell types. For instance, excess myelin is typically phagocytosed by microglia. When microglia are unable to phagocytose, seizure susceptibility is heightened, which could provide a target to further examine the relationship between myelination and epilepsy highlighted in this study.

Altogether, the authors initially identify maladaptive myelination within rodent models of absence epilepsy, but then offer further evidence for a link between activity-dependent myelination and incidence of seizures by subsequently modulating each part of the equation. In the absence of seizures, activity-dependent myelination in Wag/Rij rats appears normal, and in the absence of activity-dependent myelination, seizure frequency is decreased in Scn8a+/mut mice. Increased understanding of how this relationship can be fine-tuned could possibly have clinical implications in interrupting the spread of generalized seizures or slowing the progression of not only absence epilepsy but other types of epilepsies where activity-dependent increases in myelination is evident.

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