CURRENT LITERATURE

HOW EPILEPSY CHANGES SODIUM CHANNELS

Induction of Neonatal Sodium Channel II and III α-Isoform mRNAs in Neurons and Microglia After Status Epilepticus in the Rat Hippocampus

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Sodium channels (NaChs) regulate neuronal excitability in both physiologic and pathological conditions, including epilepsy, and are therefore an important target for antiepileptic drugs (AEDs). In the present study, we examined the distribution of messenger RNAs (mRNAs) encoding neonatal NaChs II and III α-isoforms in control rat hippocampus and after electrically induced status epilepticus (SE), with nonradioactive in situ hybridization (ISH). Only weak expression of neonatal NaCh II and III mRNAs was observed in control hippocampus. By contrast, increased expression of neonatal NaCh II and III mRNAs was observed 4 hours after the induction of SE in neurons of CA1-CA3 and the dentate granule cell layer. These changes were detected only in rats in which SE was successfully induced and persisted, although less intensely, for up to 3 months, when rats display spontaneous seizures. Strong expression of neonatal NaCh α-isoforms was observed 1 week after SE in microglial cells, as confirmed by double labeling, combining ISH with immunocytochemistry for microglia markers. The increased expression of neonatal isoforms of the NaCh in both neurons and microglial cells may represent a critical mechanism for modulation of neuronal excitability, glial function, and pharmacologic response to AEDs in the course of epileptogenesis.

Sodium Currents in Isolated Rat Ca1 Pyramidal and Dentate Granule Neurones in the Post–Status Epilepticus Model of Epilepsy

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Status epilepticus (SE) was induced in the rat by long-lasting electrical stimulation of the hippocampus. After a latent period of 1 week, spontaneous seizures increased in frequency and severity in the following weeks, finally culminating after 3 months in a chronic epileptic state. In these animals, we determined the properties of voltage-dependent sodium currents in short-term isolated CA1 pyramidal neurons and dentate granule (DG) cells by using the whole-cell voltage-clamp technique. The conductance of the fast transient sodium current was larger in SE rats (84 ± 7 nS vs 56 ± 6 nS) but related to a difference in cell size, so that the neurons had a similar specific sodium conductance (control, 7.8 ± 0.8 nS/pF; SE, 6.7 ± 0.8 nS/pF). Current activation and inactivation were characterized by a Boltzmann function. After SE, the voltage dependence of activation was shifted to more negative potentials (control, -45.1 ± 1.4 mV; SE, -51.5 ± 2.9 mV; $P < 0.05$). In combination with a small shift in the voltage dependence of inactivation to more depolarized potentials (control, -68.8 ± 2.3 mV; SE, -66.3 ± 2.3 mV), it resulted in a window current that was much increased in the SE neurons (median, 64 pA in control; 217 pA in SE; $P < 0.05$). The peak of this window current shifted to more hyperpolarized potentials (control, -44 mV; SE, -50 mV; $P < 0.05$). No differences were found in the sodium currents analyzed in DG cells of control and SE animals. The changes observed in CA1 neurons after SE contribute to enhanced excitability, in particular, when membrane potential is near firing threshold. They can, at least partly, explain the lower threshold for epileptic activity in SE animals. The comparison of CA1 with DG neurons in the same rats demonstrates a differential response in the two cell types that participated in very similar seizure activity.

COMMENTARY

One of the questions of great interest in epilepsy is "What are the underlying changes, and what do they mean?" Much effort has been expended in defining these changes, and many have been identified. Although many changes have been uncovered in some common forms of epilepsy, the significance of the changes has been more difficult to determine. The greatest focus has been on the γ-aminobutyric acid subtype A ($GABA_A$) receptor, and multiple the changes found in it have significant physiological and pharmacologic implications. A common finding in some forms of epilepsy, especially in mesial temporal lobe epilepsy, has been changes that result in inhibitory activity that is less potent and less sensitive to some neuromodulatory compounds, endogenous or exogenous. Overall, these changes result in less effective inhibitory responses that are less sensitive to pharmacologic manipulation. This combination of effects may certainly contribute to therapy resistance by creating a situation in which the drugs that work at the GABA receptor are less effective in the epileptogenic regions, so that "normal" regions are more affected than the target zone, with the result that GABAergic side effects appear before the desired suppression of seizures.

Sodium channels have been of interest in epilepsy for many years, especially with the observation that many of the available medications work by blocking or attenuating the voltage-gated sodium currents. This family of ion channels has become of greater interest with the demonstration that a number of inherited epilepsy syndromes are associated with a mutation in the voltage-gated sodium channels, and some of these mutations result in a gain of function of the depolarizing sodium current, which in turn results in enhanced excitatory responses. Until recently, alterations in these channels have been confined to several relatively small and (usually, but not always) benign familial syndromes. With the combined reports by Ketelaars et al. (1) and Aronica et al. (2), there is now clear evidence for changes in the voltage-gated sodium channels in the post–status epilepticus rat model for limbic or temporal lobe epilepsy. Unlike the inherited epilepsies that are associated with specific mutations, these changes represent an enhanced expression of the messenger RNA (mRNA) for a sodium channel isoform that is normally present in the early phases of brain development. This return to an earlier state of development also has been hypothesized for the changes in subunit composition that are found in the $GABA_A$ receptor. These combined observations suggest that part of the process of epileptogenesis may involve the expression of receptors and channels that are developmentally more immature and perhaps more prone to support prolonged excitatory activity.

Are there any functional consequences to this observed change in the expressed sodium channel, in addition to the significant enhancement of the excitatory sodium currents? Although not addressed directly in these articles, this issue has been examined in several other studies. In earlier work, Vreugendenhil and Wadman (3) had shown that the median effective concentration (EC_{50}) for carbamazepine (CBZ) was significantly increased after limbic kindling. More recently, in a poster at the American Epilepsy Society, Remy et al. (4) presented evidence that the efficacy of CBZ in blocking the frequency-dependent firing was markedly reduced in dentate granule cells taken from rats and humans with epilepsy. These observations, also associated with changes in sodium channel–type expression, may provide some insight into the basis for widespread pharmacoresistance in epilepsy patients to drugs that were developed in naive animals with the normal pattern of sodium channel expression.

This combination of altered sodium channel expression with the associated alterations in physiology and pharmacosensitivity raise significant questions about the process of drug identification based on normal animals, and as the authors suggest, the findings support the concept of identifying compounds based on the receptors and channels that are found in the tissue from patients and from animals with appropriate forms of epilepsy.

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References

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