CURRENT LITERATURE

THE EPILEPTIC NEURON REDUX

Upregulation of a T-Type Ca^{2+} Channel Causes a Long-Lasting Modification of Neuronal Firing Mode after Status Epilepticus

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A single episode of status epilepticus (SE) causes numerous structural and functional changes in the brain that can lead to the development of a chronic epileptic condition. Most studies of this plasticity have focused on changes in excitatory and inhibitory synaptic properties. However, the intrinsic firing properties that shape the output of the neuron to a given synaptic input also may be persistently affected by SE. Thus 54% of CA1 pyramidal cells, which normally fire in a regular mode, are persistently converted to a bursting mode after an episode of SE induced by the convulsant pilocarpine. In this model, intrinsic bursts evoked by threshold-straddling depolarizations, and their underlying spike after depolarizations (ADPs), were resistant to antagonists of N-, P/Q-, or L-type Ca^{2+} channels but were readily suppressed by low (30–100 μM) concentrations of Ni^{2+} known to block T- and R-type Ca^{2+} channels. The density of T-type Ca^{2+} currents, but not of other pharmacologically isolated Ca^{2+} current types, was upregulated in CA1 pyramidal neurons after SE. The augmented T-type currents were sensitive to Ni^{2+} in the same concentration range that blocked the novel intrinsic bursting in these neurons (IC_{50} = 27 μM). These data suggest that SE may persistently convert regular-firing cells to intrinsic bursters by selectively increasing the density of a Ni^{2+}-sensitive T-type Ca^{2+} current. This nonsynaptic plasticity considerably amplifies the output of CA1 pyramidal neurons to synaptic inputs and most probably contributes to the development and expression of an epileptic condition after SE.

COMMENTARY

The preponderance of research seeking to understand the basis of increased seizure susceptibility in animal models of injury-induced epilepsy has focused on alterations in neural connectivity and modifications in synaptic receptors, and comparatively fewer studies have explored possible changes in intrinsic voltage-dependent ionic conductances. In this article, Su et al. make the case that limbic epileptogenesis after pilocarpine-induced status epilepticus is due to changes in the fundamental excitability properties of hippocampal neurons. One to six weeks after experiencing status epilepticus from high-dose pilocarpine treatment, rats exhibit recurrent spontaneous limbic seizures. In corroboration of their earlier report (1), Su et al. found that CA1 hippocampal pyramidal cells in animals that have experienced pilocarpine-induced status epilepticus show an enhanced propensity to generate burst discharges in response to brief depolarizing pulses. In that previous study, 48% of CA1 pyramidal cells from rats that had experienced pilocarpine-induced status epilepticus fired intrinsic bursts compared with 3% in controls. The authors now show that the bursting is sensitive to low concentrations of Ni^{2+}, and they provide evidence that enhanced Ca^{2+} current could underlie the greater likelihood of bursting. On the basis of the high sensitivity to Ni^{2+}, insensitivity to other Ca^{2+}-channel blockers, and certain voltage-dependent properties, they conclude that the transformation to intrinsic bursting occurs as a result of an increase in the density of T-type Ca^{2+} channels. T channels are a type of voltage-dependent Ca^{2+} channel that activates at membrane potentials near the resting potential (approximately –60 mV) when the cell is depolarized from a more negative potential level (thus they are said to have a "low threshold"). In addition, T-type Ca^{2+} channels deactivate slowly (i.e., turn off gradually on repolarization) and have small single-channel conductances. Unlike other types of Ca^{2+} channels, which mainly regulate Ca^{2+} entry into neurons for cell signaling, T-type Ca^{2+} channels are believed to be involved in the generation of pacemaker activity and burst firing.

Plasticity of T-type Ca^{2+} channels represents a radical new concept in hippocampal epileptogenesis. However, caution is warranted. Although this is a careful quantitative analysis with statistical comparisons across large numbers of CA1 pyramidal cells, the authors have not completely characterized the Ca^{2+}

current by using biophysical techniques (particularly studies of steady-state inactivation) or with selective pharmacologic antagonists. It would have been interesting to know whether the current is sensitive to ethosuximide (ESM), which is believed to act, at least in part, through blockade of T-type Ca^{2+} channels (2). (Of course if ESM were to be effective, one would wonder why it does not protect against temporal lobe seizures!) It also would be important to know if the changes in Ca^{2+} current parallel the gradual increase in seizure susceptibility. Ultimately, full acceptance of this study will require confirmation with complementary approaches of increased expression or functional activity of molecularly defined T-type Ca^{2+} channel subunits (specifically the highly Ni^{2+}-sensitive α_{1H} subunit).

This article highlights some key challenges faced in attempts to study the cellular physiology of epileptogenesis. Prominent among these is the extensive loss of CA1 pyramidal cells, which has been well documented in the pilocarpine model and also observed in tissue obtained at surgery from people with intractable temporal lobe epilepsy. Could the results of Su et al. be due to selective dropout of nonbursting neurons rather than an increase in Ca^{2+} channel–rich bursting cells? The problem of understanding the basis of epileptogenesis also is made dramatically more difficult by the possibility that several different mechanisms may be operating together. Among the changes reported in the CA1 area in the pilocarpine model (and others) are decreased synaptic inhibition, increased *N*-methyl-D-aspartate (NMDA) receptor function and new recurrent excitatory circuits. Defining the importance of each is difficult, particularly because there are likely to be interactions among the various effects. Recognition of this complexity will certainly be a theme in future mechanistic studies in experimental epilepsy research.

Decades ago, epileptologists debated whether focal epilepsy is a disorder of neurons or a derangement of neural circuits (3). This article reminds us that the debate is still not settled. Whereas there has been a tendency to focus on circuit properties in recent years, the pendulum may be swinging back, and the "epileptic neuron" theorists may again be a large part of the discussion in the future.

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References

1. Sanabria ER, Su H, Yaari Y. Initiation of network bursts by Ca^{2+}-dependent intrinsic bursting in the rat pilocarpine model of temporal lobe epilepsy. J Physiol 2001;532:205–216.
2. Huguenard JR. Block of T-type Ca^{2+} channels is an important action of succinimide antiabsence drugs. Epilepsy Currents 2002;2:49–52.
3. Dichter M, Spencer WA. Hippocampal penicillin "spike" discharge: epileptic neuron or epileptic aggregate? Neurology 1968;18:282–283.