

CALCIUM CURRENTS BURST BACK: A POSSIBLE ROLE FOR DENDRITES IN EPILEPTOGENESIS

Recruitment of Apical Dendritic T-type Ca^{2+} Channels by Backpropagating Spikes Underlies De Novo Intrinsic Bursting in Hippocampal Epileptogenesis. Yaari Y, Yue C, Su H. *J Physiol* 2007;580(Pt 2):435–450. A single episode of status epilepticus (SE) induced in rodents by the convulsant pilocarpine, produces, after a latent period of 2 weeks, a chronic epileptic condition. During the latent period of epileptogenesis, most CA1 pyramidal cells that normally fire in a regular pattern, acquire low-threshold bursting behaviour, generating high-frequency clusters of 3–5 spikes as their minimal response to depolarizing stimuli. Recruitment of a Ni^{2+} - and amiloride-sensitive T-type Ca^{2+} current (I_{CaT}), shown to be up-regulated after SE, plays a critical role in burst generation in most cases. Several lines of evidence suggest that I_{CaT} driving bursting is located in the apical dendrites. Thus, bursting was suppressed by focally applying Ni^{2+} to the apical dendrites, but not to the soma. It was also suppressed by applying either tetrodotoxin or the K_v7/M -type K^+ channel agonist retigabine to the apical dendrites. Severing the distal apical dendrites 150 μM from the pyramidal layer also abolished this activity. Intradendritic recordings indicated that evoked bursts are associated with local Ni^{2+} -sensitive slow spikes. Blocking persistent Na^+ current did not modify bursting in most cases. We conclude that SE-induced increase in I_{CaT} density in the apical dendrites facilitates their depolarization by the backpropagating somatic spike. The I_{CaT} -driven dendritic depolarization, in turn, spreads towards the soma, initiating another backpropagating spike, and so forth, thereby creating a spike burst. The early appearance and predominance of I_{CaT} -driven low-threshold bursting in CA1 pyramidal cells that experienced SE most probably contribute to the emergence of abnormal network discharges and may also play a role in the circuitry reorganization associated with epileptogenesis.

COMMENTARY

The hypothesis that calcium currents play an important role in epileptogenesis was proposed over two decades ago. The early studies supporting this hypothesis analyzed experimentally induced paroxysmal depolarization shifts (PDSs), which were widely viewed as the cellular correlate of the EEG interictal spike. Because an interictal spike has similarities to the spikes that occur during an electrographically recorded seizure, these PDSs also were thought to be an elementary component of seizures. The initial studies focused on PDSs that arise when GABA_A receptor-mediated inhibition is blocked pharmacologically, although numerous other treatments, including ionic manipulations and various chemoconvulsants other than GABA_A receptor antagonists, can create hyperexcitability and bursting in cortical brain slice preparations. One hypothesis was that intrinsic bursting mechanisms in neurons, mainly reliant on voltage-dependent calcium channels, were responsible for the epileptiform activity. Another hypothesis proposed that PDSs are giant glutamate-mediated synaptic potentials, and this view became better accepted than the intrinsic bursting mechanisms hypothesis. Although it was recognized that such synaptic potentials could activate intrinsic membrane currents (including calcium currents) that shaped the epileptiform events, it was thought that these intrinsic currents were not fundamentally involved in the generation of PDSs. In recent years, there has

been a resurgence of interest in the view that alterations in calcium currents and other intrinsic mechanisms lead to “epileptic neurons” that are fundamental to epileptogenesis. The present paper adds to data supporting the epileptic neuron hypothesis and proposes a conceptual hypothesis explaining how pathological overexpression of intrinsic ion channels results in bursting.

Previous studies have reported that T-type calcium current, which is not normally prominent in CA1 hippocampal neurons, is increased after experimental status epilepticus (1–5). The present work by Yaari et al. provides evidence that T-type calcium current is increased specifically in apical dendrites. They hypothesize that this phenomenon sets up a situation in which fast sodium spikes in the soma back-propagate into the dendrites, where they detonate bursting. One important methodological concern is the use of relatively nonspecific pharmacological antagonists, including nickel and amiloride, to define T-type calcium current. The reliance on such agents makes it impossible to be certain that T-type calcium channels truly mediate the underlying events that generate the observed bursts. A second issue is the use of current-clamp recording with sharp intracellular electrodes. This technique is well suited for demonstrating differences in spike bursts between control and epileptic animals, but it provides only limited information on biophysical mechanisms and the spatial distribution of channels. Support for the dendritic localization of the relevant T-type calcium channels was provided in the present study by surgically cutting and disconnecting the apical dendrites, which eliminated bursting. However, a more reliable approach, which is now in common use, is dual whole-cell recording from the soma and dendrite. Such dual recording from a single neuron

requires visualized patch-clamp techniques, which are more feasibly applied to the immature brain and more difficult to use in older, damaged cortex. In the future, dual whole-cell recordings, in addition to on-cell or cell-attached recordings capable of isolating and analyzing single-channel activity, may further clarify the role of dendrites in epileptic activity and should allow a better definition of the contribution of calcium channels. Ultimately, these approaches may provide answers to the critical question of whether dendritic mechanisms involving voltage-gated calcium channels are responsible for interictal spikes and seizure activity in animal models and in humans with epilepsy.

In addition to intrinsic cellular mechanisms, it is well accepted that recurrent excitatory circuits also play an important role in synchronous bursting. Perhaps the best example is in the hippocampal CA3 area, where modeling and experimental studies have shown that all-or-none epileptiform bursts after blockade of GABA_A receptors involve recurrent excitation, although the intrinsic burst-generation properties of CA3 neurons also play a role (6). The relative lack of both intrinsic bursting and recurrent excitation in the normal CA1 area may explain why CA1 generates comparatively weaker bursts, which are graded with the intensity of afferent stimulation. However, CA1 pyramidal cells form recurrent excitatory circuits during epileptogenesis (e.g., after status epilepticus), and the present study further supports the hypothesis that CA1 neurons also undergo intrinsic changes that promote network bursting.

The concept that an increase in T-type calcium current in CA1 neurons is involved in the epileptic process in the status epilepticus model would be strengthened if it could be shown that there is a temporal correlation between the cellular electrophysiological changes and the development of electrographic and behavioral seizures. Yaari et al. made their measurements in the second and third week after pilocarpine-induced status epilepticus. This time window was chosen with the view that it represents the latent period prior to the onset of spontaneous seizures in this model. However, quantitative comparisons between changes in calcium current-mediated burst generation and both the development of interictal spikes and epileptic seizures are necessary to clarify the relevancy of the proposed alteration of T-type calcium current.

A critical question to be answered is whether dendritic bursting and changes in calcium current actually precede the onset of seizures (in which case, it could be argued that they are responsible for the epileptogenic process) or whether they coincide with the seizures (in which case, they may mediate the seizures but may not be responsible for the alterations in cellular

properties that occur in the latent period). A well-accepted pharmacological fact, which would appear to contradict the conclusions of this study, highlights the dichotomy. Ethosuximide is known to inhibit T-type calcium current, and this is the proposed mechanism by which it suppresses absence seizures. However, ethosuximide is not an effective treatment for partial seizures of the kind that occurs in the status epilepticus model. The differing efficacy suggests that T-type calcium current is not critical to the generation of these seizures. Perhaps this paradox would be resolved if the increase in dendritic T-type calcium current contributed not to spontaneous seizures, but rather to the generation of subclinical interictal activity during the latent period in the initial weeks after the epileptogenic insult. The T-type calcium current-dependent activity would then hypothetically trigger an epileptogenic process leading to a distinct type of mature interictal activity and also to spontaneous behavioral seizures, which, again hypothetically, would be dependent on a different set of channels (or even new circuit connections) for their expression. This concept provides a testable hypothesis: administration of T-type calcium current blockers, like ethosuximide (and more specific agents, which are being identified by pharmaceutical companies), would be predicted to prevent the development of spontaneous seizures, if administered during a critical period of epileptogenesis after an insult. It will be of interest to test this hypothesis, which could lead to disease-modifying epilepsy treatments.

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References

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