

INTRINSIC BURSTING ALONE DOES NOT BEGET SEIZURES

Long-Lasting Modification of Intrinsic Discharge Properties in Subicular Neurons Following Status Epilepticus

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A single episode of status epilepticus (SE) induces neuropathologic changes in the brain that may lead to the development of a permanent epileptic condition. Most studies of this plasticity have focused on the hippocampus, where both synaptic function and intrinsic neuronal excitability have been shown to be persistently modified by SE. However, many other brain structures are activated during SE and also may be involved in the subsequent epileptogenic process. Here we investigated whether SE, induced in rats with pilocarpine and terminated after 40 minutes with diazepam (DZP), persistently modifies the intrinsic excitability of pyramidal neurons in the subiculum. Subicular slices were prepared from control and SE-experienced rats (2 to 5 weeks after SE). In the control group, only 4% of the neurons fired bursts in response to intrasomatic, threshold-straddling depolarizing current pulses (low-threshold bursters). The remaining neurons either fired bursts in response to strong (3 times threshold) depolarizations (35%; high-threshold bursters) or fired in a completely regular mode (61%; nonbursters). In the SE-experienced group, the fractions of low- and high-threshold bursters markedly increased to 29% and 53%, respectively. This change in firing behavior was associated with a marked increase in the size of the spike afterdepolarization, particularly in low-threshold bursters. Experimental suppression of Ca^{2+} currents selectively blocked low-threshold bursting but did not affect high-threshold bursting, suggesting that a dual Ca^{2+} -dependent and Ca^{2+} -independent mechanism controls bursting in these neurons. The persistent upregulation of intrinsic bursting in the subiculum, in concert with similar changes in the hippocampus, undoubtedly contributes to epileptogenesis after pilocarpine-induced SE.

COMMENTARY

As in an article from the same group (1), recently reviewed in these pages by Drs. Dudek and Rogawski (2), we are presented with a long-lasting “upregulation” of calcium currents after pilocarpine-induced status epilepticus, albeit this time in subiculum. This article is less specific with regard to the exact types of calcium currents involved and is more heuristic than quantitative and comprehensive in its approach. Suffice it to say that the firing properties of pyramidal neurons of the subiculum are not dissimilar from those in CA1 in the hippocampus, or even those of layer V in the neocortex, in that a range of intrinsic excitabilities among cells can be elicited by a long intracellular current pulse under normal conditions. This range can be grouped as regular spike firing, burst firing with higher current intensities, or burst firing at low current intensities.

In animals with SE after pilocarpine administration, rat subicular pyramidal cells show a long-lasting shift toward hyperexcitability. This alteration consists of a decrease in regular spiking cells, and an increase in low- and high-threshold burst-firing neurons. The hyperexcitability is mediated through calcium channels, as evidenced by the enhancement of the related calcium-dependent afterdepolarization in these cells, and the tendency toward suppression by calcium-free and nickel-containing solutions. Alterations in input resistance and time constant also were seen (i.e., decreased and increased, respectively).

These findings are not novel, being quite similar to those found in hippocampus. However, this article provides an opportunity to focus some attention on the subiculum, a structure that is largely ignored in the experimental epilepsy literature, certainly as compared with the hippocampus. The subiculum is known to be a gating structure for outputs originating from the hippocampus proper to the neocortex. As such, under normal conditions, it plays a pivotal role in cognitive function, especially learning and memory. Under abnormal conditions characterized by mesial temporal sclerosis, it is likely a key player in the limbic epilepsy that results.

In mesial temporal sclerosis, CA1 and CA3 are often devasted, whereas the contiguous subiculum remains more intact. The work of David Prince’s laboratory on the chronic injury model of epilepsy has shown that it is not the damaged region of neocortex that becomes epileptogenic, but rather the surrounding, less anatomically deranged areas that develop

into epileptic foci. Accordingly, in mesial temporal sclerosis, the subiculum is the likely locus of hyperexcitability that may well comprise human epileptic foci. Evidence in support of this can be found in the recent report of Cohen et al. (3), as discussed later.

The basic finding of enhanced calcium electrogenesis recalls the work of Wong and Prince in the late seventies in hippocampus (5–8). These investigators examined the nature of bursting in CA3 pyramidal neurons and established that bursting was sustained by calcium currents and was related to the spike afterdepolarization (5,6). Furthermore, burst behavior was a property of CA1 and CA3 dendrites in pyramidal cells (7). Although bursting was not seen in response to extracellular stimulation, it did occur under epileptic conditions when fast-GABA inhibition had been blocked (8). The point was that GABA inhibitory postsynaptic potentials (IPSPs) were perfectly timed to shunt the bursts triggered in dendrites under normal conditions, but when inhibition was depressed, this activity invaded the soma, resulting in a somatic burst, which is then projected via cell axons. When such activity occurs in synchrony, a seizure is generated; thus intrinsic bursting by itself does not beget seizures.

Faced with similar findings in hippocampus with the pilocarpine model, Dudek and Rogawski (2) reminded us of the decades-old debate as to whether epilepsy is due to abnormal single neurons or aberrant circuits. The corollary to this was the question of whether the paroxysmal depolarization shift (“PDS”)—the fundamental epileptic event of neurons—is an intrinsic burst or a giant excitatory postsynaptic potential. This controversy seemed settled for practical purposes two decades ago when we agreed, almost collectively, that whereas intrinsic properties, passive and active, changed or unchanged, could contribute to hyperexcitability, focal epilepsy remains a disorder mediated through and by neuronal circuits. This perspective has continued to be reinforced by computational work, an earlier example of which was alluded to by the

present authors to explain how heightened intrinsic excitability can lead to epileptic activity (i.e., by overwhelming inhibition; see ref. 4). Despite alterations in intrinsic properties that enhance individual cell excitability, the transfer or spread of this excitability to a neuronal network, manifested as electrographic and clinical seizures, occurs via synaptic transmission.

In sum, regardless of the presence of intrinsic bursting properties, some other alteration must ensue to allow synchronous firing. This is because synaptic inhibition must be overcome to permit synchronization, even when a neuron’s intrinsic properties are markedly abnormal. Indeed, as is illustrated by Cohen et al. (3), disinhibition among a group of subicular neurons in human epileptic brain, via a shift in IPSP reversal potential in the depolarizing direction, is one such mechanism by which a group of cells (bursting or not) are synchronized.

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References

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