

DOES PRESERVATION OF PERISOMATIC INHIBITION IN EPILEPTIC HIPPOCAMPUS CONTRIBUTE TO SEIZURES?

Surviving CA1 Pyramidal Cells Receive Intact Perisomatic Inhibitory Input in the Human Epileptic Hippocampus

Wittner L, Eross L, Czirjak S, Halasz P, Freund TF, Maglóczy Z

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Temporal lobe epilepsy (TLE) is known to be linked to an impaired balance of excitation and inhibition. Whether inhibition is decreased or preserved in the human epileptic hippocampus, beside the excess excitation, is still a debated question. In the present study, quantitative light and electron microscopy has been performed to analyze the distribution, morphology, and input–output connections of parvalbumin (PV)-immunopositive interneurons, together with the entire perisomatic input of pyramidal cells, in the human control and epileptic CA1 region. Based on the degree of cell loss, the patients with therapy-resistant TLE formed four pathologic groups. In the nonsclerotic CA1 region of TLE patients, where large numbers of pyramidal cells are preserved, the number of PV-immunopositive cell bodies decreased, whereas axon terminal staining and the distribution of their postsynaptic targets was not altered. The synaptic coverage of CA1 pyramidal cell axon initial segments (AISs) remained unchanged in the epilep-

tic tissue. The somatic inhibitory input also is preserved; it has been decreased only in the cases with patchy pyramidal cell loss in the CA1 region (control, 0.637; epileptic with mild cell loss, 0.642; epileptic with patchy cell loss, 0.424- μm synaptic length/100- μm soma perimeter). The strongly sclerotic epileptic CA1 region, where pyramidal cells can hardly be seen, contains a very small number of PV-immunopositive elements. Our results suggest that perisomatic inhibitory input is preserved in the epileptic CA1 region as long as pyramidal cells are present. Basket and axoaxonic cells survive in epilepsy if their original targets are present, although many of them lose their PV content or PV immunoreactivity. An efficient perisomatic inhibition is likely to take part in the generation of abnormal synchrony in the nonsclerotic epileptic CA1 region, and thus participate in the maintenance of epileptic seizures driven, for example, by hyperactive afferent input.

COMMENTARY

Any attempt to explain mechanisms of epilepsy inevitably leads to investigation of the balance between neuronal excitation and inhibition. In temporal lobe epilepsy (TLE), this principle applies to the interaction between principal excitatory neurons and inhibitory interneurons in the hippocampus. A shift in the balance between inhibition and excitation to favor of the latter occurs in different hippocampal fields, including the dentate gyrus, a gateway in the spread of seizure activity; CA3, which receives projections from dentate gyrus neurons and sends axons to CA1; and CA1, which represents a cortical output of the hippocampus. Alterations in the dentate gyrus, such as interneuron loss in the polymorphic cell layer and mossy fiber sprouting, have been extensively discussed as factors contributing to TLE. However, similar modifications

appear in other hippocampal subfields and may play a role in the enhanced excitability and epileptogenesis.

A variety of changes in both morphology and physiology of the CA1 neuronal network have been reported in TLE. For example, loss of excitatory pyramidal neurons is accompanied by the formation of new excitatory pathways, including sprouting of CA1 pyramidal cell axons (1) and enhanced excitatory input from CA3 (2). From the physiologic standpoint, such changes in neuronal excitability and connectivity might represent compensatory responses to CA1 pyramidal cell loss, possibly to balance the deficit of the excitatory drive. At the same time, the alterations of pyramidal cell properties result in the hyperexcitability of neuronal populations that have been spared in epileptic hippocampus.

Concurrent loss of inhibitory interneurons, which control the excitability of pyramidal cells, is another factor that might contribute to TLE. However, interneurons in the hippocampus are a heterogeneous group of cells, with regard to their location, morphology, and immunochemical profiles. Some interneurons innervate distal dendrites of pyramidal cells (that is, they provide dendritic inhibition). Other interneurons

provide perisomatic inhibition and innervate proximal dendrites, somata, and a part of the axon adjacent to the somata of pyramidal cells (3). Although both types of interneurons use GABA as a neurotransmitter, their respective roles in controlling hippocampal output are different. Dendritic inhibition regulates input plasticity, limits excitatory input from CA3, and consequently, mitigates the strength of CA1 output. Perisomatic inhibition appears to be critical in synchronizing the activity of ensembles of pyramidal cells (4). The electrophysiologic correlate of such synchronization is gamma oscillations (30–80 Hz). Under physiologic conditions, such synchronized activity of the pyramidal cell populations is instrumental in basic cortical processing and in such activities as attention, cognition, and sleep (5).

Along with functional differences between the subpopulations of hippocampal interneurons, it is conceivable that alterations in dendritic and perisomatic inhibition in epileptic hippocampus might have different outcomes. On the one hand, dendritic inhibition, if preserved, would restrict hyperexcitation of CA1 pyramidal cells. On the other hand, hypersynchrony of neuronal activity afforded by preserved perisomatic inhibition might strengthen epileptiform neuronal firing. Therefore, when analyzing the inhibition in epileptic hippocampus, it is critical to specify which type of inhibition is compromised.

The study by Wittner and collaborators examines morphologic correlates of perisomatic inhibition in hippocampal tissue that was surgically removed from patients with refractory TLE. The authors used a marker of perisomatic interneurons, parvalbumin, to characterize perisomatic inhibitory input of pyramidal cells in CA1. An important methodologic aspect of the study was that the authors did not just compare normal and epileptic tissue, but rather correlated morphologic and immunochemical characteristics of perisomatic interneurons with the extent of the loss of CA1 pyramidal cells—both among the patients and among different CA1 regions within each sample. Such an approach allowed analysis of perisomatic inhibition of surviving pyramidal cell populations, which represent a substrate of TLE.

The major finding of the study was that the loss of perisomatic parvalbumin-immunopositive interneurons in the CA1 occurred only in the areas in which pyramidal cell loss was observed. At the same time, surviving pyramidal cells received fully preserved perisomatic inhibitory input. Whereas several other studies found that perisomatic inhibition was preserved in TLE (6,7), impaired perisomatic inhibition also was reported (8). The work by Wittner and collaborators resolves, at least to some extent, this controversy by pointing out the importance of correlating the preservation or loss of perisomatic interneurons with the preservation or loss of target pyramidal cells.

What is the consequence of the preservation of perisomatic inhibition in TLE? This question should be addressed

in light of the other changes that occur in the hippocampus. First, the excitability of the CA1 pyramidal cells is increased as a result of reorganization of excitatory pathways (1,2). Second, interneurons that provide dendritic inhibition appear to be lost in epileptic hippocampus (8), which leads to the disinhibition of pyramidal cells and further promotes their hyperexcitability. Finally, preserved perisomatic inhibition may facilitate hypersynchronous firing of surviving pyramidal neurons and, thus, strengthen CA1 output. Each of these three components contributes to the enhanced hippocampal excitability and might be a mechanistic factor in TLE.

The reported preservation of perisomatic inhibition of pyramidal cells may explain the lack of efficacy of GABAergic antiepileptic drugs in some TLE patients. Indeed, antiepileptic drugs that enhance GABA neurotransmission do not discriminate between the two targets—perisomatic and dendritic interneurons. Furthermore, if dendritic inhibition is selectively compromised, GABAergic therapy, in some instances, may worsen the course of TLE, as it will enhance CA1 pyramidal cell synchrony without limiting excitation within the CA3–CA1 projection. In this regard, it is important to emphasize that all the patients enrolled in the study had refractory epilepsy, although the authors did not specify what kind of antiepileptic therapy the patients had undergone before surgery.

by *Andrey M. Mazarati, MD, PhD*

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