

# THE EPILEPTIC HIPPOCAMPUS REVISITED: BACK TO THE FUTURE

**Massive and Specific Dysregulation of Direct Cortical Input to the Hippocampus in Temporal Lobe Epilepsy.** Ang CW, Carlson GC, Coulter DA. *J Neurosci* 2006;26(46):11850–11856. Epilepsy affects 1–2% of the population, with temporal lobe epilepsy (TLE) the most common variant in adults. Clinical and experimental studies have demonstrated hippocampal involvement in the seizures underlying TLE. However, identification of specific functional deficits in hippocampal circuits associated with possible roles in seizure generation remains controversial. Significant attention has focused on anatomic and cellular alterations in the dentate gyrus. The dentate gyrus is a primary gateway regulating cortical input to the hippocampus and, thus, a possible contributor to the aberrant cortical-hippocampal interactions underlying the seizures of TLE. Alternate cortical pathways innervating the hippocampus might also contribute to seizure initiation. Despite this potential importance in TLE, these pathways have received little study. Using simultaneous voltage-sensitive dye imaging and patch-clamp recordings in slices from animals with epilepsy, we assessed the relative degree of synaptic excitation activated by multiple cortical inputs to the hippocampus. Surprisingly, dentate gyrus-mediated regulation of the relay of cortical input to the hippocampus is unchanged in epileptic animals, and input via the Schaffer collaterals is actually decreased despite reduction in Schaffer-evoked inhibition. In contrast, a normally weak direct cortical input to area CA1 of hippocampus, the temporoammonic pathway, exhibits a TLE-associated transformation from a spatially restricted, highly regulated pathway to an excitatory projection with >10-fold increased effectiveness. This dysregulated temporoammonic pathway is critically positioned to mediate generation and/or propagation of seizure activity in the hippocampus.

## COMMENTARY

The hippocampus is considered by many to be the generator of temporal lobe epilepsy (TLE). This view largely is due to the frequent observation of the histopathology of sclerosis in the Sommer's sector and in the endfolium of the hippocampus of TLE patients. In addition, surgical removal of the sclerotic hippocampus often improves this epileptic condition (1). However, several aspects of TLE pathophysiology remain elusive, and even the role of hippocampal sclerosis is unsettled.

Almost 13 years ago, Pierre Gloor expressed this mindful conviction in a letter addressed to Dan McIntyre, stating: "...even though we know that most temporal lobe seizures in humans originate from the mesial structures, we are far from understanding which structures are essential or play what role, which is or are the sites of seizure onset and which are the routes of propagation of the seizure discharge. There has been, in my opinion, a simplistic view that the hippocampus is possibly the sole center of action. Hippocampal sclerosis is certainly the most outstanding neuropathological finding in resected temporal lobes of temporal lobe epileptics. And since patients with proven hippocampal sclerosis do best after surgery, the conclusion was that is the sclerotic hippocampus that is the site of origin of the seizures. This may be so, but remains unproven

and there are difficulties with this explanation (2).” Then, he continued: “The experimental neurophysiologists who work on normal hippocampi consistently identify CA3 as the site of origin of discharge in a variety of models of experimental hippocampal epilepsy. . . . It is hard to see how in an abnormal, sclerotic hippocampus this could be the mechanism of seizure genesis and propagation with hardly any neurons left in either CA3 or CA1 (2).”

To date, investigations on the pathophysiology of TLE mainly have focused on the role of the dentate gyrus in gating the arrival of the epileptic discharge to the hippocampus. The dentate gyrus is the obligatory route by which impulses reach the hippocampus and are elaborated to regain access to the limbic cortices through the trisynaptic pathway (i.e., the loop composed of the entorhinal cortex→dentate gyrus→CA3→CA1-subiculum and back again to entorhinal cortex). Indeed, in the epileptic hippocampus, the dentate gyrus undergoes changes consisting of the loss of dentate hilus interneurons, appearance of newly formed ectopic granule cells, and sprouting of mossy fibers, thus, suggesting a high remodeling of dentate-hippocampal circuits in strict correlation to epileptogenesis (3). However, the recent paper published by Ang and colleagues appears to limit the role of the dentate gyrus in TLE, as it shows that this hippocampal structure has comparable responses in both epileptic and control rats.

These authors addressed the role of the dentate gyrus in epileptogenesis by comparing control and pilocarpine-treated epileptic rats; the latter present with electrographical and neuropathological abnormalities that are similar to those of TLE patients. The fact that activation of the dentate gyrus occurs in epileptic animals to a degree similar to what is seen in controls suggests that the gate-keeping function of dentate gyrus is maintained in epileptic rats. In addition, Ang et al. found low degrees of activation in the CA3 of both animal groups. Since the CA3 pyramidal layer is activated by stimulating the Schaffer collaterals antidromically, the authors proposed that lack of CA3 hyperactivity (at least in pilocarpine-treated epileptic rats) cannot be explained by CA3 damage. Interestingly, a similar finding recently was reported in the same TLE model by imaging the intrinsic optical signals evoked by direct CA3 activation (4).

According to Gloor’s comment (2), CA1 damage also could impair hippocampal output activity, because even when CA3 is intact, to be effective the epileptic discharge must be transmitted through CA1 to reach the other hippocampal regions. Far from being hypoactive, Ang and coworkers found a dramatic increase of the synaptic excitatory responses of CA1 networks. However, such a finding was unrelated to CA3 activity as it depended upon inputs arriving to CA1 from a network alternative to the classic trisynaptic pathway, that is, the temporoammonic pathway (5). This pathway originates in layer III of the

entorhinal cortex, which is known to initiate limbic seizures both in TLE patients (6) and in animal models of epileptiform synchronization (5). Moreover, as properly discussed by these investigators, since temporoammonic inputs travel directly to the CA1 area, the transformation of the responses of CA1 pyramids from predominantly inhibitory to powerfully excitatory can supplement an efficacious reverberating loop that is well suited for sustaining seizure activity.

Some findings reported in this paper, however, are not fully addressed by Ang and colleagues. The first relates to the reduction in downstream transmission from CA3 to CA1, tested here by activating the Schaffer’s collaterals. This evidence is in line with the finding of an impaired ability of CA3 and CA1 networks to generate pharmacologically induced interictal activity after status epilepticus (5) as well as with recent *in vitro* and *ex vivo* results indicating that the pilocarpine-treated CA3 area is less excitable than in controls (4). This characteristic may be relevant to TLE, as hypofunctional CA3/CA1 outputs may be unable to control entorhinal cortex excitability while contributing to the transformation of the responses of CA1 neurons to temporoammonic activation (5). Possible explanations for the finding include: (a) changes in the intrinsic properties of CA3 pyramidal neurons, and if true, then it would be important to know why such modifications are specific of this hippocampal area; and (b) the presence of an inhibitory tone contributed by dentate gyrus afferents, as suggested by experiments conducted in other animal models of TLE (7). These phenomena remain to be explored in the pilocarpine model.

The second finding by Ang and colleagues deserving discussion is that stimulation of the perforant pathway induces similar dentate excitatory responses in control and epileptic slices. The investigators concluded that the dentate area retains its gatekeeper role in this animal model of TLE; however, such a conclusion is unexpected because in both epileptic animals and humans, structural and functional changes occur in this area (8). Why these changes (i.e., sprouting in the inner molecular layer and interneuron loss in the hilus) are unable to alter the response to inputs arriving from the perforant path awaits an explanation. Alternatively, from these studies, it could be proposed that remodeling of dentate gyrus networks is oriented to the maintenance of the gate-keeping function.

As acknowledged by Ang and colleagues, their findings await verification in *in vivo* animal models of TLE. Nonetheless, they yield meaningful support to the hypothesis that changes in excitability restricted to defined areas of the limbic system and even to specific inputs contribute to epileptogenesis. Within this context, it is reasonable to anticipate that future studies on changes in excitability that characterize different epileptic limbic areas as well as the interactions among them can provide new

insight into therapeutic approaches that may be implemented in TLE.

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