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Cohen I, Navarro V, Clemenceau S, Baulac M, Miles R: On the origin of interictal activity in human temporal lobe epilepsy in vitro. **Science** 298:1418–1421, 2002

Abstract:

The origin and mechanisms of human interictal epileptic discharges remain unclear. Here, we describe a spontaneous, rhythmic activity initiated in the subiculum of slices from patients with temporal lobe epilepsy. Synchronous events were similar to interictal discharges of patient electroencephalograms. They were suppressed by antagonists of either glutamatergic or gamma-aminobutyric acid (GABA)-ergic signaling. The network of neurons discharging during population events comprises both subicular interneurons and a subgroup of pyramidal cells. In these pyramidal cells, GABAergic synaptic events reversed at depolarized potentials. Depolarizing GABAergic responses in neurons downstream to the sclerotic CA1 region contribute to human interictal activity.

Comment:

Temporal lobe epilepsy (TLE) is the most frequent form of adult focal epilepsy and is commonly refractory to medical therapy. Cohen, et al.,¹ provided some important insight into the mechanisms of the development of epileptic seizures in their in vitro study of hippocampal tissue resected in patients with TLE. Traditionally, there have been several factors thought to contribute to the development of epileptic discharges: a population of excitatory neurons with the ability to develop intrinsic bursts; an increase in excitatory (glutamatergic) synaptic transmission, particularly via recurrent connections and a decrease in inhibitory (γ -aminobutyric acid [GABA]-mediated) connections.^{2,3} It has thus been proposed that an imbalance between excitatory and inhibitory synaptic activity that favors excitation will promote an epileptic discharge.

This “traditional imbalance” theory has been challenged by the observations that GABA may not always inhibit neuronal activity. In this study, Cohen, et al., have identified a group of excitatory pyramidal neurons that are depolarized by interneurons-released GABA (bringing the neuronal resting membrane potential closer to firing threshold) in the subicular zone of the isolated hippocampus. Electrode-based recordings from these subpopulations has shown synchronous activity that resembled the

discharges seen on the electroencephalographic studies obtained in patients in whom the specimens were derived.

The mechanism by which GABA produces depolarization in these subpopulations of pyramidal neurons is unknown. This observation, however, may have important clinical implications. It poses the possibility that if there were a specific GABA receptor on the aberrantly-responding pacemaker pyramidal neurons, specific pharmacological receptor blockade may be a feasible approach to treat seizures in these notoriously medically-refractory temporal lobe epilepsy patients. This would represent a more refined approach than most traditional pharmacotherapy, which nonspecifically reduces cellular excitability, and results in the undesirable side effects so commonly seen with the use of these agents.

References

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