Commentary

Does impaired inhibition cause epilepsy? Does epilepsy alter inhibitory circuits? These longstanding questions have few clear answers. A recent study by Jin et al. provides a fascinating view of the inputs and outputs of an inhibitory circuit in chronically epileptic neocortex and highlights the complexity of circuit reorganization following injury.

The choice of experimental model is an important strength of this investigation. Brain trauma is a common cause of human epilepsy, and the cellular mechanisms linking injury and seizures are obscure. For nearly 2 decades, Prince and his colleagues have skillfully and doggedly investigated a rodent model of chronic injury—the undercut neocortex—using physiological, anatomical, and molecular techniques (1). Partial surgical isolation of a cortical region leads, after a delay of about 10 days, to ongoing epileptiform activity. Paroxysms are accompanied by a wide variety of changes in structure and function. The cortex thins. Pyramidal cells decrease in number and size, but the remaining cells increase their intrinsic excitability. Axons of pyramidal cells sprout, and electrophysiology suggests that this increases their excitatory synaptic connections.

Hyperconnected, hyperexcitable pyramidal cells sound like a recipe for seizure activity, but inhibitory systems of neurons are also altered by chronic injury (2). The notion that dysfunctional synaptic inhibition is involved in human seizure disorders is at least as old as the identity of inhibitory neurotransmitters themselves (3). The inhibition hypothesis has much to recommend it. Normal activity in the cerebral cortex reflects a constantly shifting balance of synaptic excitation and inhibition (4). Reducing inhibition, even modestly, is one of the simplest ways to induce seizures (5). Increasing inhibition, for example by transplanting inhibitory interneurons, can ameliorate seizures (6), and a wide variety of genetic mutations that impair inhibition have seizures as a phenotype (7).

Indeed, earlier studies from the Prince group suggested that pyramidal neurons in the undercut cortex receive lower rates of spontaneous inhibitory inputs compared with uninjured neurons (8). Other measures of inhibition showed mixed effects after chronic injury, however; numbers of inhibitory interneurons and synapses were stable, but their dendrites and axons were thinner and shorter, and their synapses were smaller (9).

This set the stage for the experiments of Jin et al. They knew that injured pyramidal cells in layer 5 sprout new axons in response to injury; but would that lead to increased excitation of pyramidal cells and inhibitory interneurons? If so, would the additional excitation of the two cell types be balanced? What about the influence of reorganized interneuron axons? Jin et al. used an elegant method—laser scanning photostimulation of caged glutamate—to map the spatial patterns and strengths of excitatory and inhibitory synaptic inputs onto layer 5 pyramidal cells and onto a specific subset of fast-spiking (FS), parvalbumin-expressing inhibitory interneurons identified by their expression of green fluorescent protein.
The results were surprising. Consistent with earlier work from the Prince laboratory, Jin et al. found that inhibitory inputs to pyramidal cells were modestly reduced in injured neurons. This finding fits with a simple “reduced inhibition” hypothesis of epilepsy. Responses from inhibitory interneurons of undercut cortex complicated the situation, however. Excitatory synaptic inputs to injured FS interneurons were actually enhanced. Just as important, injured FS interneurons received lower than normal amounts of synaptic inhibition; interneurons normally inhibit interneurons, and this is one factor that regulates overall network excitability. The general picture that emerges is, in one sense, neatly consistent: injury affects synaptic drive to pyramidal cells and FS interneurons similarly, increasing their excitatory inputs and decreasing their inhibitory inputs. But, if the net input to FS interneurons is so much stronger, why is the inhibitory input to pyramidal cells and FS interneurons weaker?

The answer may lie somewhere along the output axons and synapses of the interneurons. Structural studies of FS interneuron axon terminals suggested they are generally smaller in undercut cortex (9). Small synapses tend to be weaker than large synapses, so the enhanced inputs to FS cells noted by Jin et al. may be negated by the feeble output synapses of FS cells onto pyramidal cells. Interpretation of the data is complicated because the functional status of other types of interneurons known to contribute inhibitory inputs to pyramidal cells has not yet been assessed. The glutamate-uncaging technique does not discriminate among the presynaptic interneuron subtypes it activates, so lower net inhibition could be a consequence of dysfunctional non-FS interneurons. The uncaging method also did not test possible changes in synapse dynamics. Inhibitory synapses from some cells, such as those of somatostatin-expressing interneurons, are weak and unreliable when activated at low frequencies but become much stronger as they facilitate at higher, seizure-like frequencies; synapses from FS interneurons have opposite dynamics, starting strong and depressing with continued use (10). It will be interesting to test the efficacy of inhibition with realistic temporal patterns of activation.

The important observations of Jin et al., together with the Prince group’s previous studies of undercut cortex, underscore just how pervasive and complex are the effects of chronic injury on neural circuits. Nearly every feature of the pyramidal cell-FS interneuron axis is altered after trauma. It seems likely that some of these changes are relevant to epileptogenesis, but which of them are a direct consequence of injury, which are secondary to seizure activity, and which are unrelated is not clear. Another technique for controlling neurons with light, optogenetics, allows selective control of neuron subtypes. Applying these tools to models of chronically injured cortex may further illuminate the causes of post-traumatic human epilepsy.

by Barry W. Connors, PhD

References
Instructions
The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

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