

IS MODULATION OF CORTICAL SYNAPSES AFTER BRAIN TRAUMA HOMEOSTATIC? OR, SINCE WHEN IS EPILEPSY NORMAL?

Synaptic Strength Modulation after Cortical Trauma: A Role in Epileptogenesis. Avramescu S, Timofeev I. *J Neurosci.* 2008;28(27):6760–6772. Traumatic brain injuries are often followed by abnormal hyperexcitability, leading to acute seizures and epilepsy. Previous studies documented the rewiring capacity of neocortical neurons in response to various cortical and subcortical lesions. However, little information is available on the functional consequences of these anatomical changes after cortical trauma and the adaptation of synaptic connectivity to a decreased input produced by chronic deafferentation. In this study, we recorded intracellular (IC) activities of cortical neurons simultaneously with extracellular (EC) unit activities and field potentials of neighboring cells in cat cortex, after a large transection of the white matter underneath the suprasylvian gyrus, in acute and chronic conditions (at 2, 4, and 6 weeks) in ketamine–xylazine-anesthetized cats. Using EC spikes to compute the spike-triggered averages of IC membrane potential, we found an increased connection probability and efficacy between cortical neurons weeks after cortical trauma. Inhibitory interactions showed no significant changes in the traumatized cortex compared with control. The increased synaptic efficacy was accompanied by enhanced input resistance and intrinsic excitability of cortical neurons, as well as by increased duration of silent network periods. Our electrophysiological data revealed functional consequences of previously reported anatomical changes in the injured cortex. We suggest that homeostatic synaptic plasticity compensating the decreased activity in the undercut cortex leads to an uncontrollable cortical hyperexcitability and seizure generation.

COMMENTARY

Although many changes are known to occur after brain insults that lead to acquired epilepsy, the degree to which these different potential mechanisms contribute directly to the development of chronic epilepsy (i.e., epileptogenesis) remains unclear. One mechanism that recently has been invoked to account for posttraumatic epilepsy is homeostatic plasticity (1), which is a hypothetical process whereby neurons increase their electrical activity when they have been subjected to conditions that decrease their activity (i.e., a compensatory return to normal). After brain trauma and loss of synaptic inputs to neurons near the injury, homeostatic plasticity would cause the synaptic input to return to its original level.

Another theoretical mechanism for acquired epilepsy, potentially related to homeostatic plasticity, is an increase in recurrent excitation after injury-induced loss of synaptic inputs to principal cells in cortical structures, ranging from the subfields of the hippocampus (2,3) to the neocortex. The observation of mossy fiber sprouting in the dentate gyrus, based initially on the use of the Timm stain in resected tissue from patients with intractable temporal lobe epilepsy, led to this general hypothesis (2,3). Previous electrophysiological experiments on neocortical

slices using the animal model of undercut cortex showed increases in the frequency of EPSCs (4). Subsequent work, using focal flash photolysis of caged glutamate to stimulate individual (or small populations of) neurons surrounding a recorded pyramidal cell, showed that local excitatory input was increased after injury (5).

The aim of the paper by Avramescu and Timofeev was to determine the altered local synaptic mechanisms responsible for posttraumatic epilepsy (e.g., recurrent excitation and inhibition). The experiments involved *in vivo* recordings from anesthetized cats that had undergone a knife cut of the white matter underneath the suprasylvian cortex. Extracellular recordings were used to identify presynaptic action potential activity near intracellularly recorded neurons; then, these presynaptic spikes were used as a trigger for averaging the subsequent changes in membrane potential (thus, “spike-triggered averaging”). The presence in the averaged traces of “spike-triggered” EPSPs and IPSPs allowed assessment of the strength and number of excitatory and inhibitory synaptic connections from the neuron generating the extracellularly recorded presynaptic spikes. This approach is more direct than previous *in vitro* studies, since the EPSPs and IPSPs are linked temporally to presynaptic action potentials (i.e., the EPSPs and IPSPs arose from action potentials generated by the nearby neuron). This and other methods are surrogates, however. Paired intracellular or whole-cell recordings, in which the presynaptic neuron can be stimulated

directly and the properties of the EPSPs and IPSPs can be measured quantitatively, are much more direct than other methods but also are considerably more difficult to perform, particularly in vivo.

A strength of this study is recording in an in vivo preparation. Intact animal preparations have the full complement of neural circuits (unlike brain slices), and recordings from awake animals are optimal, if not essential, for studies of spontaneous recurrent seizures. In spite of the difficult and elegant nature of this study, in vivo recordings do have some limitations. As the authors point out, the use of ketamine–xylazine anesthesia leads to oscillations and paroxysmal discharges. When combined with the high level of background synaptic activity, these events reduce the signal-to-noise ratio for the monosynaptic EPSPs and IPSPs, which was addressed at least in part with spike-triggered averaging.

The authors recorded from five different animal groups, including controls, those with acute injury, and three groups of experimental animals at 2, 4, and 6 weeks after the injury. The amplitude of the EPSPs was increased in the chronic phase at weeks 2 and 6 after the injury, but surprisingly, a decline was observed at 4 weeks. One would expect an increase in EPSP amplitude at 4 weeks as well, but the authors argue that, based on previous work, the decrease is expected (6). They suggest that homeostatic plasticity, a potential compensatory process, could account for the enhancement. Avramescu and Timofeev also describe a higher frequency of occurrence of EPSPs, which suggests an enhancement in the number of excitatory connections occurring during the chronic phase after the injury. The increase in excitatory connections was similar over the 2-, 4- and 6-week assessments, but increased recurrent excitation hypothetically depends on axonal growth and synaptogenesis, which develops progressively over weeks and months in animal models (7–9). Whether homeostatic plasticity mediates the increase in the amplitude and frequency of spike-triggered EPSPs deserves further study, however both of these changes would be expected to be epileptogenic.

The reported increases in the amplitude of the EPSPs have been interpreted by the authors to represent homeostatic plasticity; however, homeostasis involves the physiological concept of maintenance of a constant normal physiological state in spite of an external perturbation. The perturbation in these studies was a knife cut to the white matter and loss of synaptic input to the pyramidal cells. The observation that the cortical neurons

responded by forming new synapses could be interpreted to be homeostatic, since the neurons were hypothetically forming new synapses to compensate for the loss of synapses from the knife cut. However, the original concept of homeostatic plasticity was based on the observation that AMPA receptors were upregulated when the activity of presynaptic glutamatergic neurons was reduced. Here, the presynaptic inputs essentially were transected, and the “homeostatic” changes reportedly lead to an epileptic state. Therefore, the concept that the physiological mechanism of homeostasis (defined classically as a return to normalcy) leads to an epileptic state (defined as “abnormal”) is incongruous, unless one assumes that the physiological response to injury severely overshoots normalcy.

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