

## HOMEOSTATIC PLASTICITY HYPOTHESIS AND MECHANISMS OF NEOCORTICAL EPILEPSIES

### Homeostatic Synaptic Plasticity Can Explain Posttraumatic Epileptogenesis in Chronically Isolated Neocortex

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Cereb Cortex 2004 [Epub ahead of print]

Permanently isolated neocortex develops chronic hyperexcitability and focal epileptogenesis in a period of days to weeks. The mechanisms operating in this model of posttraumatic epileptogenesis are not well understood. We hypothesized that the spontaneous burst discharges recorded in permanently isolated neocortex result from homeostatic plasticity (a mechanism generally assumed to stabilize neuronal activity) induced by low neuronal activity after deafferentation. To test this hypothesis, we constructed computer models of neocortex incorporating a biologically based homeostatic plasticity rule that operates to maintain firing rates. After deafferentation, home-

ostatic upregulation of excitatory synapses on pyramidal cells, either with or without concurrent downregulation of inhibitory synapses or upregulation of intrinsic excitability, initiated slowly repeating burst discharges that closely resembled the epileptiform burst discharges recorded in permanently isolated neocortex. These burst discharges lasted a few hundred milliseconds, propagated at 1 to 3 cm/s and consisted of large (10–15 mV) intracellular depolarizations topped by a small number of action potentials. Our results support a role for homeostatic synaptic plasticity as a novel mechanism of posttraumatic epileptogenesis.

### Excitatory and Inhibitory Postsynaptic Currents in a Rat Model of Epileptogenic Microgyria

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J Neurophysiol 2005;93:687–696

Developmental cortical malformations are common in patients with intractable epilepsy; however, mechanisms contributing to this epileptogenesis are currently poorly understood. We previously characterized hyperexcitability in a rat model that mimics the histopathology of human four-layered microgyria. Here we examined inhibitory and excitatory postsynaptic currents in this model to identify functional alterations that might contribute to epileptogenesis associated with microgyria. We recorded isolated whole-cell excitatory postsynaptic currents and GABA<sub>A</sub> receptor-mediated inhibitory currents from layer V pyramidal neurons in the region previously shown to be epileptogenic (paramicrogyral area) and in homotopic control cortex. Epileptiform-like activity could be evoked in 60% of paramicrogyral (PMG) cells by local stimulation. The peak conductance of both spontaneous and evoked inhibitory postsynaptic currents was significantly larger in all PMG cells compared with controls. This difference in

amplitude was not present after blockade of ionotropic glutamatergic currents or for miniature (m) inhibitory postsynaptic currents, suggesting that it was due to the excitatory afferent activity driving inhibitory neurons. This conclusion was supported by the finding that glutamate-receptor antagonist application resulted in a significantly greater reduction in spontaneous inhibitory postsynaptic current frequency in one PMG cell group (PMG<sub>E</sub>) compared with control cells. The frequency of both spontaneous and miniature excitatory postsynaptic currents was significantly greater in all PMG cells, suggesting that pyramidal neurons adjacent to a microgyrus receive more excitatory input than do those in control cortex. These findings suggest that there is an increase in numbers of functional excitatory synapses on both interneurons and pyramidal cells in the PMG cortex, perhaps due to hyperinnervation by cortical afferents originally destined for the microgyrus proper.

## COMMENTARY

The mechanisms of mesial temporal lobe epilepsy have been intensively investigated in animal models as well as in human surgical and postmortem specimens. In contrast, the mechanisms underlying neocortical epilepsies remain uncertain. Neocortical epilepsies are common in childhood and are correlated to developmental abnormalities, but they also can arise in adulthood from head injury, stroke, or tumors. Many neocortical epilepsies are refractory to medical treatment. A better understanding of the neurobiologic mechanisms underlying neocortical epilepsies could potentially improve treatment strategies.

In the normal brain, the process of homeostatic plasticity (HSP) is thought to balance excitation and inhibition by maintaining neuronal firing at a relatively constant rate, thereby preventing unrestrained increases or decreases in activity. This process also is of particular importance during development, when the general environment of the cortex favors excitatory transmission, and pruning of the normal overly abundant axon collaterals occurs. When homeostatic processes become perturbed, the brain may no longer be capable of controlling or adjusting to changes in synaptic strength, and thus, the balance between excitation and inhibition may become unstable, leading to a hyperexcitable brain. Interfering with dysregulated HSP processes during aberrant cortical development or directly after a traumatic event may, therefore, reduce the risk of developing epilepsy. Similarly, investigating the mechanisms of HSP may reveal therapeutic candidates for epilepsy.

Proposed mechanisms of HSP may be broken down into two major categories: 1) altering intrinsic electrical properties of individual neurons, and 2) changing synaptic connections between neurons. Intrinsic properties are determined by the distribution of intrinsic ion channels, such as sodium, delayed-rectifier potassium, and calcium channels, to mention just a few. For a neuron to maintain an appropriate firing rate, it might selectively alter the surface expression of these ion channels. Other experiments have measured changes in synaptic strength through recording miniature excitatory postsynaptic currents, which arise postsynaptically from the random, spontaneous presynaptic release of single vesicles of neurotransmitter. Altering synaptic activity predictably changes the amplitude or frequency (or both) of miniature excitatory postsynaptic currents, such that reduced activity generates increased amplitude or frequency of miniature excitatory postsynaptic currents, and vice versa (1). Mechanisms for up- or downregulating synaptic transmission include altered synaptic receptor number, changes in the probability of presynaptic vesicular release, increased or decreased synaptic area, changes in the number of presynaptic inputs, and reduced or increased quantal size.

In the present article, Houweling et al. used computational models of neocortex to investigate mechanisms of HSP that might contribute to the hyperexcitability observed in vivo in permanently isolated neocortex of cats. Their computational model of acutely deafferented cortex displayed strongly reduced levels of activity that eventually led to slow oscillatory network activity, presumably as a result of the activation of homeostatic synaptic plasticity. Almost complete deafferentation was required to obtain periodic bursting. The burst discharges occurred spontaneously or could be evoked by activating excitatory  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid synapses onto neighboring pyramidal cells. A certain threshold amount of HSP was required to obtain bursts of spikes that propagated through the neural network. The threshold value was dependent on stimulus intensity—much like that observed in the evoked epileptiform events of permanently isolated live slices. By increasing the amount of HSP, the authors observed increased burst rate, number of spikes per burst, and velocity of burst propagation.

Houweling and colleagues analyzed mechanisms underlying burst generation and found that burst discharges could be increased by blocking calcium-activated potassium current, blocking short-term synaptic depression, or increasing *N*-methyl-D-aspartate receptor-mediated current. The frequency of the bursting depended not only on how much HSP was allotted, but also on the spontaneous firing rate of the virtual pyramidal cells. Homeostatic regulation of synaptic conductance could restore the firing rate of pyramidal neurons in partially deafferented cortices, either through upregulation of pyramidal–pyramidal synapses ( $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid  $\pm$  *N*-methyl-D-aspartate components) or downregulation of interneuron–pyramidal synapses. Intrinsic excitability was examined as another possible strategy of homeostatic regulation, modeled by an upregulation of fast and persistent sodium conductances and a downregulation of potassium conductances in pyramidal cells. It was observed that intrinsic excitability changes alone could restore a normal asynchronous state without burst generation, similar to that of intact cortex. Thus, homeostatic synaptic plasticity increased network excitability to restore normal firing rates, but on large increases in conductance of excitatory synapses, network bursting was elicited.

The developing brain is constantly changing in response to sensory stimulation, growth factors, changing synaptic strengths, arborization pruning, and various other factors. Additionally, a perinatal injury could alter HSP mechanisms such that an imbalance between excitatory and inhibitory transmission occurs within or around the injured area, predisposing the brain to hyperexcitability. The recent study by Jacobs and Prince used a rat model of focal, unilateral four-layered microgyria to explore mechanisms of hyperexcitability in a developmentally malformed brain. This model was created by freezing a small

area of the skull of newly born rats whose cortical development had not yet been completed. The deep layers of the cortex migrate first and are eliminated in the area of the traumatic lesion. Cells born later migrate through this area of damage to create the superficial cortical layers. These events result in a region of brain that lacks appropriate lamination (i.e., a microgyrus) surrounded by a normally layered cortical region (i.e., a paramicrogyral region) (2). After a 10- or 11-day latency, epileptiform activity could be evoked in slices of lesioned brain (3), and this activity was most readily elicited in the paramicrogyral zone that surrounds the microgyrus (4).

Jacobs and Prince concluded that because the injured region of brain was lacking in the deep cortical layers, the normal afferents making synaptic targets with those cells, instead, must have found comparable partners with the surviving neurons in the surrounding paramicrogyral region. This phenomenon resulted in increased excitatory inputs onto the pyramidal cells in the paramicrogyral zone, which led to hyperexcitability. A compensatory upregulation in inhibitory synapses or sprouting of inhibitory interneurons may have occurred, which is one of the mechanisms of HSP mentioned by Houweling et al. In addition to the compensatory increase in inhibition, the increased afferentation of the paramicrogyral zone may not have been restricted to pyramidal neurons; it also may have included an increased number of inputs onto inhibitory interneurons that synapse onto the pyramidal neurons, thereby increasing inhibition in a hyperexcitable environment.

Although progress has been made in understanding neocortical epilepsies, several questions still must be addressed, such as what are the cellular substrates responsible for the hyperexcitability associated with upregulation of excitatory synapses, downregulation of inhibitory synapses, and increases in intrinsic excitability? Does HSP function at the individual neuron level or over whole networks? Is the enhanced inhibition seen in freeze-lesion animals an actual compensatory process, or does this contribute to the spread of epileptogenic activity? Perhaps most important, is it possible to intervene in these homeostatic processes to prevent the development of synchronous burst discharges?

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