

## THE EPILEPTIC GABA<sub>A</sub> RECEPTOR: A TARGET FOR EPILEPTOGENESIS AND FOR NEW AEDS?

### Pharmacological Plasticity of GABA<sub>A</sub> Receptors at Dentate Gyrus Synapses in a Rat Model of Temporal Lobe Epilepsy

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In the lithium-pilocarpine model (li-pilocarpine) of temporal lobe epilepsy,  $\gamma$ -aminobutyric acid (GABA)<sub>A</sub> receptor-mediated inhibitory postsynaptic currents (GABA<sub>A</sub> IPSCs) were recorded in dentate gyrus granule cells (GCs) from adult rat hippocampal slices. The properties of GABA<sub>A</sub> IPSCs were compared before and after superfusion of modulators in control conditions (li-saline rats) and in li-pilocarpine rats 24 to 48 hours and 3 to 5 months (epileptic rats) after status epilepticus (SE). The mean peak amplitude of GABA<sub>A</sub> IPSCs increased by about 40% over li-saline values in GCs 24 to 48 hours after SE and remained higher in epileptic rats. In li-pilocarpine rats, studied at 24 to 48 hours after SE, diazepam (1  $\mu$ M) lost 65% of its effectiveness at increasing the half-decay time ( $T_{50\%}$ ) of GABA<sub>A</sub> miniature IPSCs (mIPSCs). Diazepam had no effects on mIPSC  $T_{50\%}$  in epileptic rats. The benzodiazepine ligand, flumazenil (1  $\mu$ M), acting as an antagonist in li-saline rats, exhibited a potent inverse agonistic effect on GABA<sub>A</sub> mIPSCs of GCs from li-pilocarpine rats 24 to 48 hours and 3 to 5 months after SE. The neurosteroid, allopregnanolone (100 nM), which considerably prolonged GABA<sub>A</sub> mIPSCs in li-saline rats, totally lost its effect in rats studied 24 to 48 hours after SE. However, this decrease in effectiveness was transient and totally restored in epileptic rats. In addition to the upregulation in the number of receptors at individual GC synapses, we propose that these “epileptic” GABA<sub>A</sub> receptors possess benzodiazepine binding sites with altered allosteric properties. The failure of benzodiazepine and neurosteroid to potentiate inhibition early after SE may be a critical factor in the development of epileptogenesis and occurrence of seizures.

### COMMENTARY

This article provides a pharmacologic analysis of spontaneous and miniature inhibitory postsynaptic currents after epileptogenesis and offers insights into how new antiepileptic drugs (AEDs) could be developed. The study corroborates and extends earlier work indicating that epileptogenesis is associated with changes in  $\gamma$ -aminobutyric acid (GABA)-mediated inhibition, involving both pre- and postsynaptic mechanisms. The tendency in the field has been to consider GABAergic signaling as increased or decreased but recent research indicates the need for exploration of complex changes in GABA systems at the molecular, cellular, and circuit levels.

A host of prior studies using molecular biologic and electrophysiologic techniques have argued that GABA<sub>A</sub>-receptor subunits are altered after status epilepticus and that at least some of these alterations persist into the chronic epileptic state. The changes in GABA<sub>A</sub>-receptor subunits are associated with modified receptor function, particularly manifest as altered effects of intrinsic and extrinsic neuromodulators, such as zinc, neurosteroids, and benzodiazepines (BZDs). Do these modified GABA<sub>A</sub> receptors directly contribute to epilepsy, and if so, how would this work? This study is consistent with several previous articles supporting the hypothesis that GABA<sub>A</sub>-receptor function is *augmented* (at least as evidenced by increased mean amplitude of GABA<sub>A</sub> receptor-mediated synaptic currents), which would seem to argue against a direct role in epileptogenesis. Implied is the concept that GABA<sub>A</sub> receptors have undergone compensatory changes in response to epileptogenic mechanisms that are activated during and after status epilepticus. One alteration of the GABAergic system that occurs immediately after status epilepticus is a loss of specific populations of GABAergic interneurons. The increased responsiveness of the GABA<sub>A</sub> receptors of pilocarpine-treated rats could compensate for this interneuronal loss.

These studies also suggest that the effects of extrinsic and intrinsic modulators are altered after status epilepticus, which leads to the hypothesis that chronic epileptogenesis might alter how modulators regulate GABAergic transmission, thus resulting in a propensity for epileptic seizures. Further research will be needed to determine whether this is one of many changes after status epilepticus that have comparatively small effects on

epileptic susceptibility or whether this is actually a direct cause of epilepsy.

This research contributes to the growing body of data suggesting the existence of epileptic ion channels and that one of these channels is the GABA<sub>A</sub>-receptor complex. The concept that ion channels may be altered in the epileptic state suggests that new AED development should include animal models of chronic epilepsy, because the unique epileptic receptor channels, with altered subunits and sensitivities to exogenous and endogenous molecules, might respond differently from those in nonepileptic animals. The principle would be to develop

new pharmacologic therapies that specifically target the transformed epileptic receptor channels in a manner that would be protective against seizures but would have no effect on normal receptors and channels. Although the epilepsy research community has yet to implement this approach, future research focusing on GABA<sub>A</sub> receptors and, potentially, other epileptic receptors and channels could yield new AEDs with greatly enhanced specificity for blocking seizures with few or no effects on normal brain function.

*by F. Edward Dudek, Ph.D.*