

## **Models of GABA<sub>A</sub> Synapses Show a Reduction of Post-synaptic Receptor Number and Predict the Loss of Inhibitory Tone Seen During Status Epilepticus.**

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Many GABAergic agents lose effectiveness as status epilepticus (SE) proceeds, and brief convulsant stimuli result in a diminished inhibitory tone of hippocampal circuits (as indicated by loss of paired-pulse inhibition *in vivo*). To examine the effects on GABA<sub>A</sub> synapses, whole-cell patch-clamp recordings from dentate gyrus granule cells were performed with mathematical modeling of the results. SE was induced in 6-8 wk old rats by lithium (3 mEq/kg ip)-pilocarpine (40 mg/kg ip) and compared to controls. Miniature IPSCs (mIPSCs) recorded from granule cells in slices prepared 1 hr into SE show a decrease peak amplitude to 61.8±11.9% of controls (-31.5±6.1 pA for SE vs. -51.0±17.0 pA for controls;  $p < .001$ ) and an increase of decay time to 127.9±27.6% of controls (7.75±1.67 ms for SE vs. 6.06±1.17 ms for controls;  $p < .001$ ). Unlike mIPSCs, tonic currents increase amplitude to a mean of -130.0 (±73.6) pA in SE vs. -44.8 (±19.2) pA in controls ( $p < .05$ ), and the increase of baseline holding current standard deviation prior to application of the GABA<sub>A</sub> antagonist SR95531 is 11.05±2.31 pA for SE and 6.10±1.53 pA for controls ( $p < .001$ ). Possible explanations for the peak amplitude decrease of mIPSCs include GABA<sub>A</sub> receptor internalization, decreased binding/gating, and/or desensitization during SE. Mean-variance fluctuation analysis and 7-state GABA<sub>A</sub> receptor models suggest SE has a reduction in post-synaptic receptor number of 47% (from 34±7 [control] to 22±5 [SE] receptors per synapse;  $p < .001$ ). Explanations for larger tonic GABA<sub>A</sub> currents include higher GABA concentrations, effects on binding/gating, and/or increase in tonic receptor numbers. Our math models of tonic currents suggest that the increased tonic current can be explained by an increase in extracellular GABA concentration to 5-10 μM. When our synaptic model for mIPSCs was adapted to fit perforant path evoked IPSCs from granule cells, the loss of paired pulse inhibition was predicted after entering the parameters obtained for mIPSCs from SE animals. In conclusion, a decrease in synaptic GABA<sub>A</sub> currents and an increase in tonic currents are observed with SE. An increase in extracellular GABA during SE can explain the tonic current increase (extrasynaptic), while desensitization/internalization of post-synaptic GABA<sub>A</sub> receptors from increased GABA exposure can explain the decrease amplitude of synaptic mIPSCs. The reduced functional synaptic receptor numbers also may explain the diminished effect of GABAergic drugs as SE proceeds.