

Receptor Endocytosis in Treatment of Refractory Status Epilepticus

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Status epilepticus (SE) is a state of continuous seizures in a patient for more than 20 minutes. This condition of continuing seizures is a neurologic emergency since it can lead to serious neurologic sequelae or death. Intravenous administration of rapid-acting benzodiazepines (BZD) is usually successful in stopping SE. However, in a significant number of such patients seen in emergency rooms, these seizures become refractory to benzodiazepines. There are a number of reasons why status epilepticus may be refractory to pharmacologic treatment. One of the primary neurophysiologic mechanisms that, when functioning normally, limits seizures, consists of inhibitory neurotransmission due to GABA liganding to its postsynaptic receptors (GABA_AR) to produce inhibitory postsynaptic currents by opening Cl⁻ channels (see text). That is why a number of potent antiseizure medicines in use, benzodiazepines in particular, are those that potentiate GABAergic inhibitory transmission (see Ch. 40).

Experimental studies have demonstrated refractoriness to benzodiazepines at GABAergic synapses after 10–20 min of seizure activity and that seizures become self-sustaining even after blockade of the original stimulus. Glutamatergic excitatory synapses (see Ch. 17), in contrast, do not become refractory to blockade of NMDA receptors by ketamine or MK801 even after an hour of seizure activity (Mazarati et al., 2010).

Studies of mouse hippocampal slices *in vitro* have shown that prolonged stimulation of GABA receptors leads to a marked decrease in the miniature inhibitory postsynaptic currents (mIPSC) and an increase in mEPSC, thus implying decrease in functional GABA receptors and increase in functional glutamate receptors (Naylor, 2010). The majority of BZD-sensitive GABA receptors in brain are composed of $\alpha, \beta, \gamma 2$ subunits (see text). Synapses are particularly highly

enriched in γ 2 and these are responsible for phasic inhibition, the type that interrupts seizures. GABA receptors composed of α , β , and δ subunits are extrasynaptic and mediate tonic inhibition. These are insensitive to BZD. SE reduces selectively the proportion of GABA_A R with the α , β , γ 2 subunits that are expressed at the plasmalemma surface, but not the total in the cell. This implies that the trafficking of these particular GABA_A receptors to the plasmalemma is altered by the SE. The reduction is found accompanied by SE-dependent reduction in PKC-stimulated phosphorylation of the Ser408/9 residues in the β 3 subunit. This phosphorylation site lies within the AP2-binding motif, which binding is critical to clathrin-dependent endocytosis of the subunit (Goodkin et al., 2008; Terunuma et al., 2008). The mechanism by which SE leads to inhibition of GABA_AR phosphorylation may involve Ca^{2+} -calmodulin-dependent calcineurin phosphatase activity, which is increased by SE. The activation of the phosphatase by SE is accompanied by decreased phosphorylation of GABA_AR β 2/3 while FK506, a potent inhibitor of the phosphatase, suppresses the calcineurin activity and reverses the SE-induced dephosphorylation of GABA_AR β 2/3 (Wang et al., 2009). Of course, modifications of local Ca^{2+} concentrations either through release from ER or membrane channels may be involved in regulating the calcineurin activity.

From these investigations, it follows that discovery of means to pharmacologically control calcineurin phosphatase activity or AP2 binding/clathrin-induced endocytosis of GABA_AR may help in treating refractory epilepsy (see also Jadeep Kapur in Noebels et al., 2011).

References

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