The GABA Response Enigma, Katherine L. Perkins, Department of Physiology and Pharmacology, SUNY Downstate Health Sciences University

GABA is the predominant inhibitory neurotransmitter in the brain, but under some conditions, even in adult animals, GABA can have an excitatory effect on the postsynaptic cell, even triggering epileptiform activity. We have been using electrophysiology to study the synaptic GABA response in brain slices from mature rodents in the convulsant 4-aminopyridine (4-AP). Under this condition, giant GABA-mediated postsynaptic potentials (GPSPs), resulting from synchronous interneuron activity, can be recorded from pyramidal cells and interneurons. In CA3 pyramidal cells, the GPSPs are composed of an early, hyperpolarizing component, and two later components, a depolarizing component and a hyperpolarizing $GABA_B$-mediated component. In the presence of intact glutamatergic transmission, the depolarizing component of some GPSPs triggers epileptiform discharges in CA3 pyramidal cells, particularly when a $GABA_B$ antagonist is applied. It has long been known that the $GABA_A$ receptor channel is permeable to chloride and bicarbonate ions. Manipulation of intracellular chloride and bicarbonate concentrations reveals that the late depolarizing GABA response has enhanced bicarbonate permeability compared to the early hyperpolarizing GABA response; in fact, the polarity of the biphasic response can be reversed with manipulation of intracellular anions. Subsets of interneurons experience monophasic depolarizing GABA, monophasic hyperpolarizing GABA, or biphasic GABA synaptic responses in 4-AP. We hypothesize that there exists a subunit configuration of the $GABA_A$ receptor channel that has enhanced permeability to bicarbonate and is responsible for the depolarizing GABA response. The depolarizing GABA response may offer a new target for pharmacological intervention for epilepsy patients who do not respond to available anticonvulsants.