G protein activation kinetics and spillover of \( \gamma \)-aminobutyric acid may account for differences between inhibitory responses in the hippocampus and thalamus

(synaptic transmission/neuromodulation/epilepsy)

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Communicated by Stephen Heinemann, The Salk Institute for Biological Studies, La Jolla, CA, June 14, 1995

ABSTRACT We have developed a model of \( \gamma \)-aminobutyric acid (GABA)ergic synaptic transmission mediated by GABA\(_A\) and GABA\(_B\) receptors, including cooperativity in the guanine nucleotide binding protein (G protein) cascade mediating the activation of K\(^+\) channels by GABA\(_B\) receptors. If the binding of several G proteins is needed to activate the K\(^+\) channels, then only a prolonged activation of GABA\(_B\) receptors evoked detectable currents. This could occur if strong

In this paper, we focus on the activation kinetics of GABA\(_B\) responses, in which K\(^+\) channels are activated through a guanine nucleotide binding protein (G protein) cascade (14, 15). We assume that this activation shows some "cooperativity," in the sense that independent binding of several G-protein subunits is needed to open the K\(^+\) channels.

METHODS
A  Postsynaptic membrane

B  1 μm

C  0.5 mM

D  1 μm

\[ \text{Time course of GABAergic synaptic currents under different conditions.} \]
Estimation of Parameters. All simulations were run using NEURON (28). The values of parameters were obtained by fitting the entire model, including release, uptake, diffusion, and receptor kinetics, directly to experimental recordings with a simplex algorithm (22). At each iteration of the simplex algorithm, the model was run and the least-squares error was response could be revealed for a relatively narrow range of densities of releasing terminals. Finally, for high densities of simultaneously releasing sites, both GABA_A and GABA_B IPSCs occurred and their time courses were prolonged in the absence of uptake ("Dense" in Fig. 2).

Because of receptor saturation, GABA_A-mediated currents
cooperativity ($n = 1$) was optimized identically as described above. In this case, GABA$_B$ responses were proportional to the stimulus (compare solid and open circles in Fig. 3 Bottom).

We simulated the properties of GABAergic responses in

**Time Course of GABA.** Our model of the release of GABA included spillover from adjacent terminals and uptake in a two-dimensional extracellular space. Diffusion dominated the initial time course of transmitter decay, and uptake strongly