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The Effects of Increased Spontaneous Activity on Potentiation of the $GABA_A$ Receptor by Allosteric Modulators

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The γ-aminobutyric acid Type A ($GABA_A$) receptor is the major inhibitory ion channel in the central nervous system. Its activation leads to cellular inhibition or dampening of the effects of excitatory ion channels. Many anesthetics drugs, such as the intravenous anesthetic propofol, directly activate or potentiate the response of the $GABA_A$ receptor to its endogenous ligand GABA. Previous studies have identified amino acid residues whose substitutions have divergent effects on direct activation and potentiation by propofol. For example, the gain-of-function α_1(L263S) mutation enhances receptor activation by propofol but reduces its ability to potentiate GABA-elicited currents. These observations have sometimes been interpreted as different structural elements underlying direct activation and potentiation. In this study, I tested the hypothesis that changes in receptor spontaneous activity affect observed potentiation. We employed the concerted transition model, a simple four-parameter function introduced by Monod, Wyman, and Changeux, that allows us to analyze and predict the behavior of the $GABA_A$ receptor in the presence of one or more activators. The model predicts increased direct activation and reduced apparent potentiation as the level of spontaneous activity increases. The predictions were confirmed by two-electrode voltage clamp electrophysiology experiments on α1β3 and concatemeric α1β2γ2L $GABA_A$ receptors.