Modelling the effects of competitive glutamate antagonists on AMPA receptor desensitisation and EPSC amplitude

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Bruce P. Graham, Adrian Y.C. Wong, Brian Billups and Ian D. Forsythe

Short-term depression of EPSC amplitude during trains of stimuli occurs at many synapses, including the calyx of Held in the mammalian auditory system. Such depression may be mediated by presynaptic mechanisms, such as the depletion of releasable vesicles or postsynaptic factors such as receptor desensitisation. Distinguishing between these mechanisms is difficult, since desensitisation is a common outcome of receptor activation. Using a kinetic model of AMPA receptor-mediated EPSCs that includes blocked receptor states to mimic the effects of bath application of competitive glutamate antagonists, we demonstrate that low affinity antagonists, such as gamma-D-Glutamylglycine or kynurenate, significantly reduce the effects of desensitisation. In computer simulations, the receptor pool was stimulated by 1msec pulses of 1mM glutamate at 50Hz for 2secs. With no antagonist present the EPSCs depressed by 80%. In the presence of a rapidly-dissociating antagonist the magnitude of depression is reduced in an antagonist dose-dependent manner until it is eliminated. Rapid equilibration of the unblocked receptors with the much larger pool of blocked receptors between stimuli releases a new pool of nondesensitised receptors to mediate the next EPSC. Antagonists with slower kinetics produce different effects. At very slow blocking rates virtually no receptors are exchanged between blocked and glutamate-bound states, thus only the small pool of unblocked receptors contributes to the EPSCs and depression is not reduced. At faster, but intermediate rates, the antagonist can actually cause a facilitation of the response. Equilibration of the blocked and unblocked receptors is not completed between glutamate pulses, resulting in a gradual increase in the pool of unblocked receptors and a consequent increase in EPSC amplitude. Thus only low affinity antagonists are useful in robustly reducing the effects of desensitisation.