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

Bruce Graham *Department of Computing Science and Mathematics, University of Stirling, U.K*
Adrian Wong, Brian Billups & Ian Forsythe *Cell Physiology & Pharmacology, University of Leicester, U.K.*

Contact: b.graham@cs.stir.ac.uk

Summary

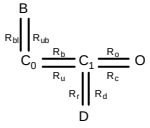
Short-term depression of EPSC amplitude during trains of stimuli occurs at many synapses, including the calyx of Held in the mammalian auditory system. Such depression may be mediated by presynaptic mechanisms, such as the depletion of releasable vesicles or postsynaptic factors such as receptor desensitization. Distinguishing between these mechanisms is difficult, since desensitization is a common outcome of receptor activation. Using kinetic models of AMPA receptor-mediated EPSCs that include 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 desensitization.

Methods

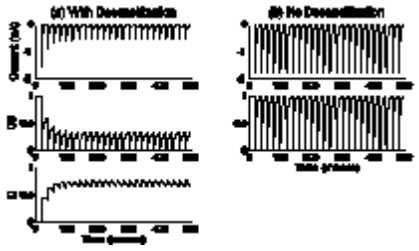
1. Numerical simulation of trains of glutamate pulses to 4-gate and 7-gate kinetic AMPA receptor pool models, with and without receptors entering blocked states due to the presence of an AMPA antagonist
2. Effect of antagonist in a model of the calyx of Held, which includes multiple active zones and presynaptic vesicle recycling and release.

4-Gate Kinetic AMPA Model

- Closed unbound (C0), bound (C1), open (O) and desensitized (D) states
- Presence of AMPA antagonist causes a fraction of the closed, unbound receptors to enter a blocked state, B
- Driven by trains of 1msec pulses of 1mM glutamate at 50Hz
- EPSCs depress by 67% due to desensitization when no antagonist.

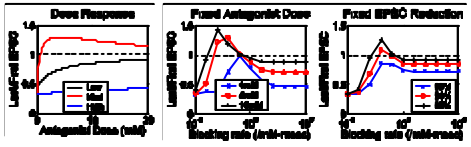


R_b=13/mM-msec
R_u=6/msec
R_o=60/msec
R_c=3/msec
R_d=4/msec
R_r=0.0002/msec



Dose Response of Antagonists

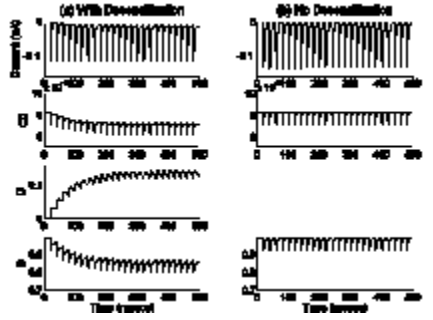
- Rapid blocking (low affinity) antagonists reduce level of depression due to desensitization in a dose dependent manner
- Medium affinity antagonists lead to facilitation at high doses
- High affinity antagonists have no effect on depression.



See example 50Hz responses in centre boxes

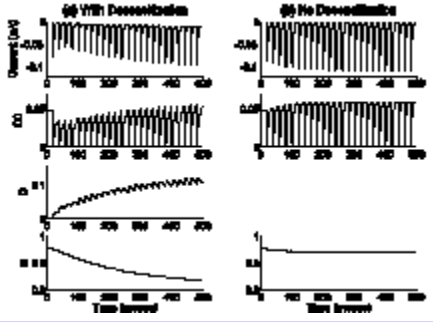
4-Gate AMPA, Low Affinity Antagonist

R_{bl}=10/mM-msec, R_{ub}=1/msec, dose 12mM



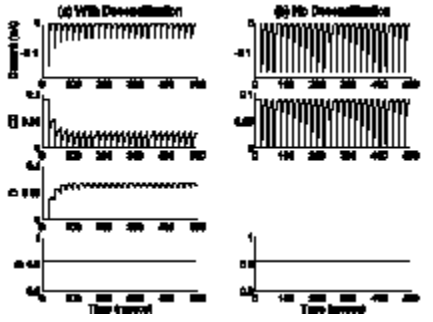
Medium Affinity Antagonist

R_{bl}=0.01/mM-msec, R_{ub}=0.001/msec, dose 2mM



High Affinity Antagonist

R_{bl}=10^{-5}/mM-msec, R_{ub}=10^{-6}/msec, dose 1mM



7-Gate Kinetic AMPA Model

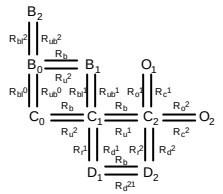
- Kinetics to match EPSCs from calyx of Held
- Multiple closed, open and desensitized states
- 3-state antagonist (blocking) model

AMPA Kinetics

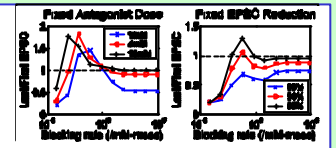
R_b=13/mM-ms
R_u^1=6/ms
R_o^1=60/ms
R_c^2=3/ms
R_d^1=6/ms
R_d^{21}=6/ms
R_u^2=12/ms
R_c^1=3/ms
R_c^2=0.35/ms
R_r^1=0.02/ms
R_r^2=0.02/ms

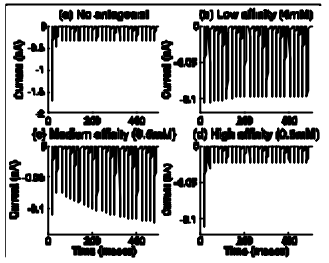
Low Affinity Antagonist

R_{bl}^0=70/mM-ms
R_{bl}^1=35/mM-ms
R_{bl}^{01}=13/mM-ms
R_{bl}^2=35/mM-ms
R_{ub}^0=6/ms
R_{ub}^1=6/ms
R_{ub}^{10}=6/ms
R_{ub}^2=12/ms



Medium Affinity: Low rates * 10^{-3}
High Affinity: Low rates * 10^{-6}





- **Qualitatively similar results to simple 4-gate model**

The Calyx of Held

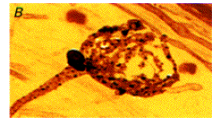
The calyx of Held is a giant excitatory synapse in the mammalian auditory system. It consists of hundreds of active zones operating in parallel.

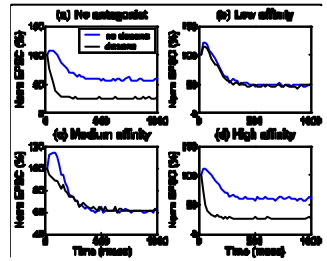
Model with 500 active zones [1]:

- Presynaptic vesicle replenishment and release
- 7-gate AMPA receptor model at active zones
- Short-term facilitation of release
- Depression due to vesicle depletion and AMPA receptor desensitization.

Results of 50Hz stimulation

- Average EPSCs from 10 runs at 50Hz for 1sec
- Time course and magnitude of depression with no desensitization is matched only with the presence of a low affinity antagonist.





[1] A. Wong, B. Graham, B. Billups and I. Forsythe, Distinguishing between presynaptic and postsynaptic mechanisms of short term depression during action potential trains, *J. Neuroscience*, 23:4868-4877, 2003.

Conclusions

- Given a *rapidly-dissociating (low affinity) antagonist* the magnitude of depression due to receptor desensitization 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 nondesensitized receptors to mediate the next EPSC.
- With a *high affinity antagonist* 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.
- *Medium affinity antagonists* 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.
- **Only low affinity antagonists are useful in robustly reducing the effects of desensitization.**

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