ATP acts as both a competitive antagonist and a positive allosteric modulator at recombinant NMDA receptors

A. Kloda[1], J.D. Clements[2], R. Lewis[1] and D.J. Adams[1], [1]School of Biomedical Sciences, University of Queensland, Brisbane, QLD 4072 and [2]Synaptic Dynamics Lab, John Curtin School of Medical Research, Australian National University, Canberra ACT 0200, Australia.

ATP and glutamate are excitatory neurotransmitters in the CNS, and both modulate synaptic plasticity and LTP in hippocampal neurons (Wieraszko and Ehrlich, 1994). NMDA receptors are primarily responsible for the modulatory actions of glutamate, but the mechanisms underlying ATP´s modulatory effects remain uncertain. In the present study, we investigated the effect of ATP on recombinant NR1a+2A and NR1a+2B NMDA receptors expressed in Xenopus oocytes. ATP inhibited currents evoked by low concentration of glutamate. ATP shifted the glutamate concentration-response curve to the right, suggesting a competitive interaction with the agonist binding site. It was a more potent inhibitor at NR1a+2A receptors than at NR1a+2B receptors. The inhibition was voltage-independent indicating that ATP acts outside the membrane electric field. Other nucleotides including ADP, GTP, CTP and UTP inhibited glutamate-evoked currents with different potencies indicating that the inhibition is dependent on the phosphate chain as well as the nucleotide ring structure. Surprisingly, ATP potentiated currents evoked by saturating concentrations of glutamate. At these concentrations, glutamate out-competes ATP at the agonist-binding site. Therefore the potentiation must be due to ATP binding at a separate site, where it acts as a positive allosteric modulator of channel gating. A simple model of the NMDA receptor was constructed, with ATP acting both as a competitive antagonist at the glutamate binding site and as a positive allosteric modulator at a distinct site. The model reproduced all of the main features of the data. Wieraszko, A and Ehrlich, Y.H. (1994)., J. Neurochem.63:1731-1738. This work was funded by ARC Postdoctoral Fellowship awarded to A.K. and ARC Large Grant (A00105778). J.D.C is funded by an ARC Senior Research Fellowship.