Both cytoplasmic and extracellular dequalinium block olfactory CNGA2 channels

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Dequalinium has recently been reported to block CNGA1 and CNGA2 channels expressed in *Xenopus laevis*[1,2]. We have recently shown that dequalinium also blocks currents through the rat olfactory CNGA2 channel expressed in HEK293 cells. Cytoplasmic dequalinium interacts with a binding site that is about 1/3 to 1/2 of the way across the membrane electric field (from the intracellular end of the channel), with an IC_{50} of approximately 1.3 μM at a V_m of +60 mV[3]. Neutralization of the negatively-charged pore-lining glutamate acid (E342Q) led to a profound decrease in the voltage-dependence of block by cytoplasmic dequalinium[3]. Dequalinium remained an effective channel blocker of the mutant channel with an IC_{50} of approximately 1.9 μM at a V_m of +60 mV[3]. Our additional experiments suggest that block is more effective when saturating cAMP, rather than saturating cGMP, is used as the activating ligand. As the channel spends about 300-fold more time in the closed state in the presence of saturating cAMP compared to that in the presence of saturating cGMP[4], this suggests that dequalinium reduces currents by interacting predominantly with the closed channel. We now also report that extracellular dequalinium seemed to more effectively block the wild-type CNGA2 channel than did cytoplasmic application. The E342Q mutation significantly increased the IC_{50} of external dequalinium by about 10-fold, from 350 nM for wild-type to about 3 μM for mutant at a V_m of –60 mV. These results indicate that E342 contributes to the inhibition caused by this presumed pore-blocker for cytoplasmic application and possibly also forms a binding site for extracellular application.

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3. Qu et al. 2004. Proc. Aus. Soc. Biophys. (in press).
4. Gordon et al. 1995. Neuron, 14:857-864.