The role of the agonist binding site in Ca2+ inhibition of the recombinant 5-HT3A receptor

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The mechanism and site of action of Ca2+ at the recombinant murine 5-hydroxytryptamine (5-HT)3A receptor were investigated using whole-cell voltage clamp, radioligand binding and single-cell Ca2+ imaging. Inhibition of the 5-HT (3 ?M)-induced response by 10 mM Ca2+ reached a plateau at 68.5% inhibition, with half-maximal effect at 2.6 mM. This was due to an increase in EC50 from 2.35 to 3.87 ?M and a 30% reduction in Imax. Ca2+ also resulted in the inhibition of binding of both 5-HT3 receptor agonist [3H]m-chlorophenylbiguanide and antagonist [3H]granisetron due to an increase in Kd, with no change in Bmax. An increase in EC50 from 2.6 (1 mM Ca2+) to 4.7 ?M (10 mM Ca2+), with no change in maximal [Ca2+]i, was observed from Ca2+ imaging studies. Largely similar effects were observed with Mg2+. The combined data suggest that Ca2+ acting at a site that directly or indirectly influences the agonist binding site plays a significant role in its inhibitory effect at the 5-HT3 receptor. © 2001