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m2 Muscarinic Receptors Stimulate Neuronal Nitric Oxide Synthase

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In this work we investigated coupling of the m2 and m4 subtypes of muscarinic acetylcholine receptors expressed in chinese hamster ovary (CHO) cells to activation of neuronal nitric oxide synthase (nNOS). Stimulation of guanylate cyclase activity in detector neuroblastoma cells was used as an index of generation of nitric oxide (NO) in CHO cells. The agonist carbachol induced marked time and concentration-dependent enhancement of the activity of nNOS at m2 receptors. In sharp contrast, the response in CHO cells transfected with the m4 receptor gene was similar in magnitude to that observed in non-transfected cells, suggesting lack of significant coupling of m4 muscarinic receptors to NO signaling. This novel observation of functional divergence of the two muscarinic receptor subtypes at the level of activation of nNOS is quite intriguing, in light of the currently accepted dogma that they belong to the same functional class. This functional selectivity was not due to differential effects on intracellular Ca^{2+} concentration, since activation of both subtypes of muscarinic receptors produced a comparable, albeit quite small, Ca^{2+} signal. Taken together, our present data strongly suggest that the generally assumed functional equivalence of m2 and m4 muscarinic receptors should be carefully reexamined. These data also suggest the presence of alternate mechanisms of activation of nNOS, which might be operative in the absence of large changes in the concentration of cellular Ca^{2+}. The latter mechanisms are expected to be activated by m2, but not m4 muscarinic receptors. Both sets of findings are quits important in regards to refining the functional classification of muscarinic receptor subtypes and the cellular mechanisms of activation of NOS.