

O3E1-2 Synergistic activation of receptor-operated cationic channels by M₂ and M₃ muscarinic receptors in mouse ileal smooth muscle cells.

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In visceral smooth muscles, muscarinic acetylcholine receptor activation opens cationic channels, resulting in excitation and contraction. To shed light on this signal pathway, we analyzed cationic channel activity in gut myocyte derived from M₂ or M₃ muscarinic receptor knockout (KO) mice. In voltage-clamped ileal smooth muscle cells from wild-type (WT) mice, carbachol (CCh; 100 μ M) activated a sustained cationic channel currents (I_{cat}). In contrast, the amplitudes of I_{cat} in cells from M₂-KO and M₃-KO mice were less than 11% of the amplitude of WT I_{cat}, indicating that WT I_{cat} is not a simple mixture of M₂ and M₃ receptor responses. Strikingly, no appreciable current was observed in cells from M₂/M₃-double KO mice. Single channel analysis revealed that CCh activated 68 pS and 124 pS cationic channels in WT cells, and that the 124 pS channel was opened via stimulation of only M₃ receptor, whereas the 68 pS channel via both M₂ and M₃ receptors in such a way that M₃ receptor permissively opens the channels, and M₂ receptor synergistically transmits the open state to a long-lasting mode. These results provide novel insights into the regulation of visceral smooth muscle cationic channel activity.