

O2G-3-1 Opposite inotropic action induced by activation of M2 and M3 muscarinic receptors in mouse atrium

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The expression and functional role of muscarinic receptors (MR) in the mouse atrium were examined by pharmacological and molecular biological studies using MR knockout mice (M2KO, M3KO and M2/M3-double KO) and wild-type (WT) mice. M2R was a dominant subtype in the mouse atrium, but M1, M3, M4 and m5 were also expressed as minor subtypes. Carbachol (CCh) induced a negative inotropic action in the isolated atrium of the WT mouse. However, the inhibition of electrical stimulation-induced contraction by CCh was transient and the contraction increased depending on incubation time. CCh produced only a positive inotropic action in the atria of pertussis toxin-treated mice, which was antagonized by 4-DAMP. The transient inhibition by CCh was changed to a sustained inhibition in the atria of M3KO mice, but CCh caused a positive inotropic action in the M2KO mice. Neither a negative nor positive inotropic action was produced by CCh in the atria of M2/M3-double KO mice. In conclusion, in the mouse atrium the dominant M2R subtype is involved in the negative inotropic action by MR agonists whereas the M3R subtype causes positive inotropic actions. The present mechanism probably prevents excessive depression of heart functions by the vagus nerve.