

XANOMELINE BINDING TO AND ACTIVATION OF MUSCARINIC RECEPTORSJ. Jakubik¹, E. Machova¹, E.E. El-Fakahany², V. Dolezal¹¹*Institute of Physiology CAS, v.v.i., Prague, Czech Republic,* ²*University of Minnesota Medical School, Minneapolis, United States*

Despite its recognized M₁/M₄ muscarinic receptor selectivity, xanomeline is an agonist that reversibly binds to the orthosteric site of all five subtypes of muscarinic receptor with similar high affinity. Xanomeline also binds in an unusual wash-resistant manner to an allosteric site on all subtypes. This site has similar lower affinity, develops more slowly, its formation is not sensitive to orthosteric antagonist, and depends on the length of O-alkyl side chain that apparently anchors the ligand to receptor. Xanomeline activates M₁ receptor-induced GTP-γS binding but had no effect at M₂ receptor. However, it reduces the potency of orthosteric agonist carbachol at both subtypes indicating competitive action of free xanomeline. In contrast, wash-resistently bound xanomeline (in the absence of free xanomeline) activates both subtypes with lower potency and exhibits mixed competitive and non-competitive mode of action. In concert, xanomeline addition does not alter M₂ receptor-mediated inhibitory effect on evoked acetylcholine release from rat cortical slices while wash-resistently bound xanomeline induces mixed competitive and non-competitive inhibition. These results evidence agonistic effects of wash-resistently bound xanomeline that make this drug an interesting template for designing muscarinic agonists with prolonged action.

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