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EFFECTS OF KRP-197, MUSCARINIC RECEPTOR ANTAGONIST ON CONTRACTION AND RELEASE OF [^{3}H]-ACETYLCHOLINE IN THE URINARY BLADDER.

Aims of Study. We previously reported the structure-activity relationships of imidazole butanamide derivatives concerning the affinity and selectivity for M3 muscarinic acetylcholine receptor subtype(The 116th Annual Meeting of The Pharmaceutical Society of Japan, Knazawa, March 1996) and the muscarinic receptor profile of KRP-197(4-(2-methylimidazolyl)-2,2-diphenylbutyramide) *in vitro* and *in vivo* which is a potent M1&M3 receptor subtype selective antagonist(27th Annual Meeting of JCS, Yokohama, September 1997)

In the present study we examined the effects of muscarinic receptor antagonist KRP-197 on acetylcholine(ACh) release and contractile response induced by electrical field stimulation(EFS) in the bladder smooth muscle

Methods: Bladder smooth muscle strips obtained from male guinea-pig were mounted in the thermostatically controlled organ bath for isometric tension recorded. [^{3}H]-ACh outflow evoked by EFS in strips of the rat bladder preloaded with [^{3}H]-choline was measured.

Electrical stimulation consisted of 200 shocks applied at a frequency of 20 Hz using monophasic rectangular waves 40 V, 1msec

The effects of KRP-197 and the muscarinic receptor antagonists on the contractile response and ACh release induced by EFS were evaluated

Results EFS-evoked contractile responses were dose-dependently inhibited by the treatment with KRP-197, muscarinic receptor subtype selective antagonists(pirezepine, methoctramine and 4-DAMP) and non-selective antagonist(atropine).The inhibitory concentration (IC_{50})of cholinergically-evoked smooth muscle contraction was well correlated with the affinity for M1 and M3 subtype receptors

KRP-197 blocked in the dose-dependent manner [^{3}H]-ACh outflow evoked by EFS in physostigmine-treated muscle strips Concentration range applied in this test ($3x10^{-10}$-$3x10^{-8}$M)was similar to those in contractile response test(10^{-10}-10^{-8}M)

Conclusions: These data suggest that uroselectivity of KRP-197(above mentioned ref) may be resulted from both postsynaptic M3 receptor antagonistic action and the inhibition of prejunctional M1-related facilitatory mechanism(s), in part.