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ARE THE CONTRACTIONS OF RABBIT PERIPHERAL LUNG, GUINEA-PIG GALLBLADDER AND GUINEA-PIG UTERUS MEDIATED BY IDENTICAL RECEPTOR SUBTYPE ?

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Ghelardini et al. *(Life Sci. 52(5/6): 569, 1993)* reported that R-(+)-hyoscyamine is the first selective antagonist for the muscarinic receptors mediating immature guinea-pig uterus (IGPU) contractions, characterized by Dorje et al. *(Naunyn-Schmiedeberg's Arch. Pharmacol. 342:284, 1990)* as M_4-putative receptors. Lazareno et al. *(Mol. Pharmacol. 38:805, 1990)* described the predominance of M_4 receptors in rabbit peripheral lung and Kurtel et al. *(Arch. Int. Pharmacodyn. 308:39, 1990)* suggested the presence of the same subtype in guinea-pig gallbladder. Our aim was to verify, using R-(+)-hyoscyamine, whether postjunctional muscarinic receptors which mediate the contractile responses in rabbit peripheral lung strips (RPLS) and in guinea-pig gallbladder strips (GPGS), belong to M_4-putative subtype. Functional experiments were performed according to: Dörje et al. *(Naunyn-Schmiedeberg's Arch. Pharmacol. 342:284, 1990)* for IGPU, Vockert et al. *(Life Sci. 52(5/6): 551, 1993.)* for RPLS and Kurtel. et al. *(Arch. Int. Pharmacodyn. 308:39, 1990)* for GPGS. Cumulative concentration-response curves were constructed for carbachol (RPLS, IGPU) and acetylcholine (GPGS) in absence and in presence of increasing concentrations of antagonists. The pA_2 values of pirenzepine (reference drug) and R-(+)-hyoscyamine obtained constraining the slope of Schild plot linear regressions to the unity are listed below:

Antagonists	IGPU	RPLS	GPGS
Pirenzepine	6.95 ± 0.03	6.46 ± 0.21*	6.84 ± 0.04
R-(+) hyoscyamine	9.56 ± 0.01	7.15 ± 0.02	7.69 ± 0.05

pA_2 values are the mean ± SEM of 12-16 preparations. *pK_B value (10 μM).

The above results indicate that R-(+)-hyoscyamine has a 100-fold lower affinity for muscarinic receptors in RPLS and in GPGS than for those in guinea-pig uterus. In conclusion the differences in affinity values showed by R-(+)-hyoscyamine suggest that the postjunctional receptors mediating contractions in RPLS and in GPGS cannot be identified with the receptors present in IGPU.

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CHARACTERIZATION OF A NOVEL MUSCARINE RECEPTOR IN AVIAN SMOOTH MUSCLE

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The muscarine receptor in chick ileum responsible for contraction was investigated using various agonists and antagonists. This receptor has previously been reported not to be the mammalian M_3 receptor subtype (Choo et al., 1988). Ileum from 7-18 day old chicks was placed in an organ bath in physiological solution at 37°C. Cumulative dose response (D-R) curves to the agonists were obtained. In comparison to carbachol (-log EC_{50} 5.58 ± 0.09; n=8), both McN-A-343 and pilocarpine acted as partial agonists in the contractile response of this tissue. A range of antagonists (pirenzepine, benzhexol, himbacine, AF-DX 384, AF-DX 116, hexahydrodifenidol and parafluoro-hexahydrosiladifenidol) produced parallel shifts of the D-R curves to carbachol. Comparisons of pA_2 values were made to reported affinities obtained in binding and functional studies on other tissues. The values suggested that muscarine M_1, M_2, M_3 and M_4 receptors were not involved in the contractile response. Comparisons of the values obtained in the chick ileum with affinities reported in studies on the cloned m5 receptor (Dörje et al, 1991) reveal close similarities in the affinity profiles.

Choo et al, (1988) J Autonom Pharmacol, 8, 259-266.
Dörje et al, (1991) J Pharmacol Exp Ther, 256, 727-733.