in a high-potassium solution (126 mmol/l), even when atropine was present to remove any effects of acetylcholine which might be released by depolarizing intrinsic nerves.

These anticholinesterases not only prevent breakdown of acetylcholine; they also non-specifically enhance contraction and may promote the release of acetylcholine from nerve terminals.

Table 1 Effect of neostigmine (10^{-8} mol/l) on contractures caused by drugs and high-potassium (126 mmol/l) solution. Values are means ± s.e. mean; n = number of observations. EC_{50}: concentration producing half-maximal response

	Before Neostigmine		*After Neostigmine*	
	Max. tension (mN)	*EC_{50} (mol/l)*	*Max. tension*	*EC_{50}*
Acetylcholine (n = 14)	77 ± 18	1.1 ± 0.27 ($\times 10^{-6}$)	113 ± 17*	5 ± 0.08 ($\times 10^{-7}$)**
Histamine (n = 7)	137 ± 34	1.1 ± 0.37 ($\times 10^{-5}$)	119 ± 10	5 ± 1 ($\times 10^{-6}$)*
Carbachol (n = 8)	204 ± 25	5.7 ± 0.6 ($\times 10^{-8}$)	222 ± 29	4.7 ± 0.8 ($\times 10^{-8}$)
High-Potassium (n = 10)	59 ± 9	—	76 ± 9***	

* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

Evidence for histamine H_2 receptor mediated relaxation of rabbit trachea

J.P. JAMISON & R.K. McKINLEY
(introduced by I.C. RODDIE)
Department of Physiology, The Queen's University of Belfast

Fleisch & Calkins (1976) and Chand & Eyre (1977) reported a variable relaxation of rabbit trachea to histamine, which they were unable to antagonise. The present study was designed to confirm the relaxation to histamine and to investigate the effect of the selective H_1- and H_2-antagonists, mepyramine and cimetidine.

Isometric tension was recorded in transverse tracheal strips, mounted in 3 ml organ baths. Carbachol was perfused throughout in a steady dose (10^{-7} to 3×10^{-7} M) which increased tone by 1 ± 0.5 g. Histamine was perfused for 4 min periods in doses of 5×10^{-6} M and 10^{-5} M, with and without antagonist. The doses were added in random order, with 15 min washout between doses. In one strip, histamine responses without cimetidine were obtained first, and were repeated 30 min after commencing cimetidine. In another strip from the same trachea, responses during cimetidine were obtained first, and were repeated 30 min after recovery from cimetidine. In two further strips from the same trachea, mepyramine was used as the antagonist. Responses were measured as the difference between the mean tension during the 3 min immediately preceding histamine and the mean tension from the 2nd to 4th min during histamine. Analysis of variance was used to determine the probability level.

In the absence of antagonist, histamine produced a relaxation in 10 out of 11 trachea. Mean tensions showed a significantly dose-dependent relaxation to histamine ($P < 0.01$, $n = 11$). During cimetidine (10^{-5} M), there was either a reduced relaxation or a slight contraction to histamine. The means showed no significant effect. This was significantly different from the relaxation to histamine in the absence of cimetidine ($P < 0.01$, $n = 11$). Mepyramine (10^{-7} M) had no significant effect on the histamine relaxations ($P > 0.5$, $n = 10$) (Table 1).

Table 1 Mean histamine responses (± s.e. mean) in carbachol-contracted tracheal strips, relaxations negative (mg)

	Histamine	
	5×10^{-6} M	*10^{-5} M*
No antagonist	−131 ± 36	−359 ± 57
Cimetidine (10^{-5} M)	−3 ± 37	+24 ± 25
Mepyramine (10^{-7} M)	−184 ± 30	−393 ± 82

These results are consistent with an H_2 receptor mediated relaxation of the rabbit trachea to histamine.

R.K. McK. is an M.R.C. student.

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The effects of catecholamines on the rat isolated uterus

K.G. DIGGES & F.C. BOYLE

Department of Pharmacology, University of Glasgow, Glasgow G12 8QQ

Mammalian uteri contain both α and β adrenoceptors, the α-receptors being excitatory and the β-receptors inhibitory. The relative dominance of the two receptors appears to be under hormonal control, since in some species, the response of the uterus to exogenous catecholamines differs in pregnant and non-pregnant animals (Marshall, 1970). The aim of this study was to determine whether or not variations in responses to catecholamines occurred during the natural oestrous cycle of the rat. The stages of the oestrous cycle were identified from vaginal smears and the effects of noradrenaline (NA), adrenaline (Adr) and isoprenaline (Iso) were studied in each stage.

Uterine horns (2–3 cm) taken from adult virgin rats were mounted in paired 10 ml organ baths, containing Tyrode's solution, aerated with 95% O_2: 5% CO_2 and maintained at 37°C. The inhibitory effects of the catecholamines were measured as a percentage decrease in the response to concentration of acetylcholine which gave 70–80% of the maximum response.

Adr, NA and Iso were inhibitory in all 4 stages of the cycle; motor responses were never seen. The potency of the catecholamines varied with the stage of the cycle. Iso (10^{-10}–3×10^{-7} M) produced inhibition of 80% throughout the cycle. Adr (3×10^{-10}–3×10^{-7} M) and NA (10^{-7}–3×10^{-5} M) produced 80% inhibition in oestrus, but only 50% inhibition in proestrus, metoestrus and dioestrus. This difference was significant statistically at the 0.02 probability level.

Two possible explanations were, firstly, that stimulation of α-excitatory receptors, present during the non-oestrus stages of the cycle, might have reduced the inhibitory effects, and secondly, that tissue uptake of some catecholamines reduced their effectiveness, and this uptake varied with the cycle stage. The first possibility was excluded since azapetine 10^{-7} M, an α-antagonist, did not increase the maximum inhibitory effect of Adr and NA, and produced only a slight and variable leftwards shift in their dose-response curves. The second possibility was investigated by examining the effects of desmethylimipramine (10^{-6} M) to block neuronal uptake and normetanephrine (10^{-6} M) to block extra-neuronal uptake. In the presence of these blockers, the inhibitory effects of Adr and NA were increased to become equal to that of Iso in all stages, suggesting that uptake of Adr and NA was responsible for the diminished sensitivity during the non-oestrus stages of the cycle. Further confirmation was obtained in experiments estimating the uptake of [^{3}H]NA. This was significantly lower in oestrus than in the other three stages of the cycle ($P < 0.001$).

In conclusion, the response to catecholamines is qualitatively the same throughout the cycle, i.e. inhibitory, but the degree of inhibition varies, being greatest in oestrus. The variation may be attributed to uptake of some catecholamines into the uterus, which can be affected by oestrogen levels.

K.G.D. is an MRC student.

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