Does a prostaglandin modulate cholinergic transmission in the guinea-pig ileum?

YETUNDE O.O. SOKUNBI
(introduced by D.T. OKPAKO)

Department of Pharmacology & Therapeutics, University of Ibadan, Ibadan, Nigeria

Prostaglandins E_1 and E_2 inhibit noradrenaline release from sympathetic nerves (Von Euler & Hedqvist, 1969). In the parasympathetic nervous system, inhibitory (Hedqvist & Wennmalm, 1971) and facilitatory (Erheinpreis, Greenberg & Belman, 1973) roles have been attributed to PGE_1 and PGE_2.

In this communication, the effects of prostaglandin synthetase inhibitors (PSI) on contractions evoked by nicotine (0.5–8 μg/ml), acetylcholine (ACh), (0.5–8 ng/ml) and transmural stimulation (TMS) in isolated guinea-pig ileum were investigated.

Segments of ileum suspended in Tyrode solution (37°C) and gassed with air were stimulated transmurally with supramaximal voltage (40 V), 2 ms pulse width and 0.1 pulses/s. Contractions were recorded by force displacement transducers from a baseline tension of 1 g. Contractions to nicotine and TMS were abolished by tetrodotoxin (100 ng/ml) and atropine (100 ng/ml).

Indomethacin and ketoprofen (10 μg/ml each) and sodium meclofenamate (5 μg/ml) significantly ($P < 0.005$) reduced nicotine but not TMS or ACh induced contraction. The effects required a latent period of 30–45 min and were not reversed by washing out the inhibitor. The effects of PSI were completely reversed by PGE_2 (0.1–2.5 ng/ml). Hexamethonium (200 ng/ml) blocked nicotine contractions to the same extent but not ACh or TMS contractions. Hexamethonium block was not reversed by PGE_2. This and other characteristics of the hexamethonium block showed that PSI reduced nicotine contractions by a mechanism different from that of hexamethonium.

The results show that PSI block a prostaglandin sensitive step in ACh release mechanism. This step is more sensitive to block when ACh release is evoked by nicotine than when it is evoked by TMS of post ganglionic parasympathetic nerves.

References

EULER, V.S. VON & HEDQVIST, P. (1969). Inhibitory action of Prostaglandins E_1 and E_2 on the neuromuscular transmission in the guinea-pig vas deferens. *Acta physiol. scand.* **77**, 510–512.

ERHEINPREIS S., GREENBERG, J. & BELMAN, S. (1973). Prostaglandins reverse inhibition of electrically-induced contractions of guinea-pig ileum by morphine, indomethacin and acetyl-salicyclic acid. *Nature New Biol.* **245**, 280–282.

HEDQVIST, P. & WENNMALM, A. (1971). Comparison of the effects of Prostaglandins E_1, E_2 & F_2 on the sympathetically stimulated rabbit heart. *Acta physiol scand.* **82**, 156–162.

The contracture produced in tracheal smooth muscle by anticholinesterases

C.T. KIRKPATRICK & P.J. ROONEY
(introduced by C.N. SCHOLFIELD)

Physiology Department, The Queen's University of Belfast

During an attempt to collect and assay the acetylcholine released from bovine tracheal smooth muscle during stimulation of its intrinsic nerves, it was found that the anticholinesterase drugs applied to prevent breakdown of acetylcholine were causing marked spasm. Both eserine and neostigmine (10^{-7} to 10^{-4} mol/l) caused slowly-developing sustained contractures which were abolished by atropine (5×10^{-7} mol/l).

Such contractures might have been caused by (a) a direct effect of the drugs on the muscarinic receptor, (b) simple augmentation of the effect of spontaneously released acetylcholine by preventing its breakdown, (c) stimulation of extra release of transmitter by the drugs or (d) a non-specific effect on the muscle, enhancing drug-receptor interaction or excitation-contraction coupling.

The application of hemicholinium-3 (2.5×10^{-4} mol/l) for one hour abolished the contractile response to neostigmine; thus anticholinesterase was not directly stimulating the muscarinic receptor, as the contracture depends upon the release of acetylcholine from intrinsic nerves.

A non-specific effect of anticholinesterases in potentiating contractions was detected. Neostigmine at a concentration which does not itself cause spasm (10^{-8} mol/l) not only potentiated the action of acetylcholine as expected (Table 1); it also significantly potentiated histamine-induced contractions and slightly, though not significantly, augmented the responses to carbachol (Table 1). Neostigmine also markedly potentiated the contracture produced by soaking the tissue

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.