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.

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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