

and that these are dependent on the sequence of the nine C-terminal amino acids of the bombesin molecule.

References

BERTACCINI, G., IMPICCIATORE, M., MOLINA, M. *ET AL.* (1973). Action of some natural and synthetic peptides on the motility of human gastrointestinal tract *in vitro*. *Rendic. Gastroenterol.*, 5, 136.

CORAZZIARI, E., DELLE FAVE, G.F., MELCHIORRI, P. *ET AL.* (1973). Effects of a new polypeptide, Bombesin, on gallbladder and duodeno-jejunal mechanical activity in man. *Rendic. Gastroenterol.*, 5, 140.

ERSPAMER, V., FALCONIERI, ERSPAMER, G., INSELVINI, M. *ET AL.* (1972). Occurrence of Bombesin and Alytesin in extracts of the skin of three European discoglossid frogs and pharmacological action of Beombesin on extravascular smooth muscle. *Br. J. Pharm.*, 45, 333-348.

Supersensitivity to the inhibitory effect of catecholamines on intestinal peristaltic reflex after sympathetic denervation

G.M. FRIGO*, S. LECCHINI & M. TONINI

Institute of Medical Pharmacology, University of Padua, Italy

Morphological and functional evidence indicates that in the intestinal musculature postganglionic sympathetic fibres make contact with both the smooth muscle cells and the intrinsic cholinergic neurons (Beani, Bianchi & Crema, 1969; Silva, Ross & Osborne, 1971). Sympathetic adrenergic transmission seems to involve, at postsynaptic sites, both α - and β -receptors on smooth muscle cells and only α -receptors at the level of cholinergic structures (Lee, 1970; Kosterlitz & Lees, 1972). Physiological sympathetic modulation of peristaltic reflex seems more likely to be accomplished indirectly through an action on the nervous pathway subserving peristaltic reflex than through a direct inhibition on the effector cells (Crema, Frigo & Lecchini, 1970).

The ability of reserpine and uptake inhibitors to alter adrenoceptor sensitivity in longitudinal

muscle is controversial (Fleming & Schmidt, 1962; Govier, Sugrue & Shore, 1969) and no attempt has been made to study the potency changes of catecholamines in inhibiting intestinal intrinsic reflex after sympathetic denervation.

Adrenergic-induced inhibition of peristaltic reflex has been investigated in the guinea-pig isolated distal colon. Quantal dose-response curves were constructed for noradrenaline (NA), isoprenaline (IPNA) and methoxamine, the observed response being the prevention of propulsion elicited by localized intraluminal distention. Papaverine was employed as a non-specific inhibitor. The rank order of activity (Table 1) in preventing peristaltic reflex was: NA > methoxamine = IPNA > papaverine. However, when the inhibitory activity was assayed in circular muscle strips, against the carbachol-induced contraction, the rank order was: IPNA > NA > papaverine > methoxamine.

Sympathetic denervation was carried out surgically by freezing the periaarterial plexus of the inferior mesenteric artery and by removing the colon 10 days after. In denervated preparations the efficacy of the adrenergic agents in blocking peristalsis was significantly increased as compared with control preparations, while the activity of papaverine was not modified. The activity changes

Table 1 ED₅₀ (g/ml) against peristalsis (95% fiducial limits in brackets)

Drugs	Control	After denervation	Activity ratio (95% F.L. in brackets)
Noradrenaline	1.38 (1.74-1.11) $\times 10^{-7}$	6.22 (7.72-5.02) $\times 10^{-9}$	17.82 (25.21-12.72)
Isoprenaline	1.95 (2.64-1.43) $\times 10^{-6}$	2.09 (2.82-1.56) $\times 10^{-7}$	9.16 (13.58-6.09)
Methoxamine	1.56 (2.09-1.16) $\times 10^{-6}$	1.69 (2.16-1.33) $\times 10^{-7}$	9.26 (13.5-6.36)
Papaverine	3.70 (6.31-2.66) $\times 10^{-6}$	3.23 (4.47-2.22) $\times 10^{-6}$	1.02 (2.14-0.32)

P values for NA vs IPNA and for NA vs methoxamine < 0.05.

of NA in modulating intramural cholinergic nerves were investigated by measuring the inhibition of acetylcholine release. After denervation, NA was significantly more active in reducing Ach release both at rest and during transmural stimulation, the calculated activity ratios being both > 5 .

Concluding, both α - and β -receptors are involved in direct circular muscle relaxation and in the inhibition of peristaltic reflex. However, the different order of activity against peristalsis and carbachol-induced contractions indicated that α -receptors, not located in smooth muscle, are involved in peristaltic inhibition. The pattern of hypersensitivity observed in our preparations does not completely fit to any of the types of hypersensitivity described in other smooth muscle preparations supplied by an adrenergic motor innervation. In our preparations hypersensitivity is specific for adrenergic receptor stimulating agents and a mechanism involving contractile machinery outside the receptors can be excluded. Both muscular and nerve-mediated effects undergo sensitivity changes. Since IPNA and methoxamine are not taken up by adrenergic terminals, a postsynaptic mechanism seems to operate. However, the higher hypersensitivity to NA indicates that probably a presynaptic mechanism is also involved. Inasmuch as NA uptake is not highly effective at the intestinal neuroeffector junction (Bowman & Hall, 1970), the higher hypersensitivity to NA could be explained by the effectiveness of a presynaptic mechanism at the

level of adrenergic nerve endings impinging on the intramural nervous structures.

References

- BEANI, L., BIANCHI, C. & CREMA, A. (1969). The effect of catecholamines and sympathetic stimulation on the release of acetylcholine from the guinea-pig colon. *Br. J. Pharmac.*, **36**, 1-17.
- BOWMAN, W.C. & HALL, M.T. (1970). Inhibition of rabbit intestine mediated by α - and β -adrenoceptors. *Br. J. Pharmac.*, **38**, 399-415.
- CREMA, A., FRIGO, G.M. & LECCHINI, S. (1970). A pharmacological analysis of the peristaltic reflex in the isolated colon of the guinea-pig or cat. *Br. J. Pharmac.*, **39**, 334-345.
- FLEMING, W.W. & SCHMIDT, J.L. (1962). The sensitivity of the isolated rabbit ileum to sympathomimetic amines following reserpine pretreatment. *J. Pharmac. exp. Ther.*, **135**, 34-38.
- GOVIER, W.C., SUGRUE, M.F. & SHORE, P.A. (1969). On the inability to produce supersensitivity to catecholamines in intestinal smooth muscle. *J. Pharmac. exp. Ther.*, **165**, 71-77.
- KOSTERLITZ, H.W. & LEES, G.M. (1972). Interrelationships between adrenergic and cholinergic mechanisms. In: *Catecholamines*, Handb. exp. Pharmac. N.S. Vol. 33, ed. Blaschko, H. & Muscholl, E., pp. 764-812.
- LEE, C.Y. (1970). Adrenergic receptors in the intestine. In: *Smooth Muscle*, ed. E. Bülbring, pp. 549-557. London: E. Arnold.
- SILVA, D.G., ROSS, G. & OSBORNE, L.W. (1971). Adrenergic innervation of the ileum of the cat. *Am. J. Physiol.*, **220**, 347-352.

Evidence that substances capable of increasing the duodenal content exert a spasmogenic effect on the pylorus

MARIANNINA IMPICCIATORE

Department of Pharmacology, University of Parma, 43100 Parma, Italy

A series of natural and synthetic compounds were studied on the anaesthetized rat for their contracting activity on the gastroduodenal junction, by means of a technique described in a previous paper (Bertaccini, Impicciatore & De Caro, 1973). It was found that many substances (in particular two natural peptides, caerulein and bombesin) were endowed with a striking stimulant action on the pyloric sphincter. This activity, however, seemed to be unrelated to unspecific spasmogenic effects since many true spasmogenic (like bradykinin, physalaemin, histamine, etc.) and spasmolytic (like sodium nitrate, papaverine, atropine, etc.) compounds, failed to affect

significantly the tone of the pyloric sphincter. Conversely substances endowed with stimulant activity on biliary or pancreatic secretion (like caerulein, some choleretic drugs, secretin, etc.) constantly exerted a strong contracting activity. It is therefore suggested that the contraction of the pylorus is a constant feature of substances capable of increasing the duodenal content and this might have a 'physiological' protective action towards the possible regurgitation into the stomach of alkaline duodenal juice. The spasmogenic activity was found to be direct on the smooth muscle and independent from the autonomic nervous system. In very preliminary experiments, performed in human volunteers we found that some of the most effective compounds behaved in man exactly as in the rat.

Reference

- BERTACCINI, G., MARIANNINA IMPICCIATORE & DE CARO, G. (1973). Action of caerulein and related substances on the pyloric sphincter of the anaesthetized rat. *Eur. Jour. Pharmacol.*, **22**, 320-324.