MACINTOSH, F. C. & PERRY, W. L. M. (1950). *Methods in Medical Research*, **3**, 78. Chicago: The Year Book Publishers, Inc.

RADMANOVIĆ, B. & RAKIĆ, M. (1965). *IV kongres Jugoslavenskog društva za fiziologiju*, Ljubljana.

STERN, P., MILENKOVIĆ, M. & CETINIĆ, F. (1970). *Folia Medica Facultatis Medicinae Universitatis Saraeviensis*, **5**, 53–58.

STERN, P. & HADZOVIĆ, J. (1973). *Archs int. Pharmacodyn. Thér.*, in the press.

TREGEAR, G., NIALL, H. & POTTS, J. (1971). *Nature*, **232**, 87–89.

ZETLER, G. (1956). *Arch. exp. Path. Pharmak.*, **228**, 513–538.

Modification by caerulein of action potential activity in circular smooth muscle of isolated small intestine

Caerulein appears to be one of the more active gall-bladder contracting agents known at present and exhibits a potent stimulant action on the musculature of the gut (Erspamer, 1970, 1971). Moreover cholecystokinin-pancreozymin (CCK) whose C-terminal octapeptide shows a close resemblance to caerulein, affects intestinal motility in a way very similar to that of caerulein (Hedner, 1970). In the isolated intestine the efficiency of the peristaltic reflex is increased by caerulein (Frigo, Torsoli & others 1972) and propulsion of the intraluminal content is favoured at concentrations of caerulein much lower than those necessary to elicit contraction of the longitudinal muscle (Frigo, Lecchini & others, 1971). However no investigation has been made on the effect of caerulein on the electrical activity of the isolated small intestine.

The electrical activity of the small intestine as recorded with extracellular electrodes consists of rhythmic fluctuations of resting membrane (slow waves) and of rapid action potentials (spikes) which appear during slow wave depolarization (Baker, 1969; Bortoff, 1972). Spikes are accompanied by contraction of muscular layers and it has been found that the spikes synchronous with the contraction of circular fibres always occur after spike activity of the longitudinal fibres (Gonella, 1971). We now describe some experiments on the action of caerulein on the electrical activity made with a view to elucidating the mechanism by which caerulein improves propulsive activity.

Rabbits of either sex, 900–1200 g, were used. A piece of ileum, 5–6 cm length, was mounted in a horizontal bath containing Tyrode solution aerated with 5% carbon dioxide in oxygen, at 36°. Longitudinal contractions, intraluminal pressure and extracellular electrical activity were recorded as described by Gonella (1971). The frequency of the slow waves was 8–16 min^{-1} and the amplitude ranged from 2 to 4 mV. Each slow wave shows a burst of spikes of 4–6 mV associated with longitudinal contractions (Fig. 1). similar to those obtained from isolated longitudinal muscle by Gonella, (1970) and by Small & Weston (1971). Faster action potentials of 6–10 mV occurred occasionally after that of longitudinal muscle and were associated with localized contraction of circular muscle. As shown in Fig. 1, caerulein added to the bath at a final concentration of 0·2 ng ml^{-1} affected neither the frequency and the amplitude of slow waves nor the size of the spikes associated with longitudinal contractions. On the contrary in all preparations (30 expts) using concentrations of caerulein from (0·1–0·5 ng ml^{-1}) the frequency and the amplitude of action potentials associated with circular contractions were increased. The addition of caerulein to the bath caused the appearance of trains of spikes after a latency of 15–30 s and the action disappeared after 5–10 min. Development of tachyphylaxis could not be observed in any of the preparations. CCK added to the bath at final concentrations ranging between

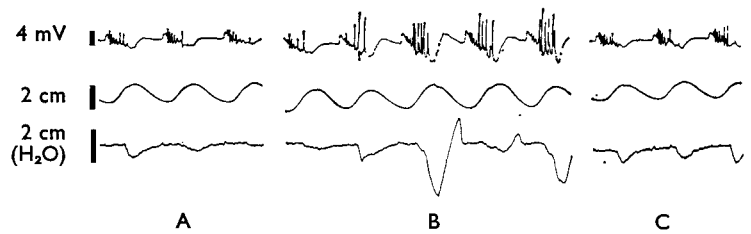

FIG. 1. Effect of caerulein on the electrical and mechanical activity of the isolated rabbit small intestine. From top to bottom records of extracellular electrical activity, longitudinal movements, and intraluminal pressure. A: control; B: in the presence of caerulein 0·2 ng ml^{-1}; C: after washing out caerulein. Time bar, 4s.

0·001 and 0·05 Ivy units ml^{-1} exhibited the same kind of response. In 12 out of 15 preparations tetrodotoxin (0·5–1 μg ml^{-1}) completely abolished the effect of caerulein.

Our results in the rabbit indicate that caerulein possesses a similar stimulant action on intestinal musculature to the natural hormone cholecystokinin. In the small intestine the action of caerulein seems to be mediated through nervous pathways inasmuch as tetrodotoxin is effective in preventing its response.

The relation between the behaviour of two muscular coats and their relevance to peristalsis has been questioned (Kosterlitz & Lees, 1964; Kottegoda, 1969). From our results it appears that two muscular coats can react independently. In fact caerulein at some concentrations is able to activate the circular muscle without interference with the longitudinal coat. This evidence obtained with electrophysiological methods supports that of Crema, Frigo & Lecchini (1970) in the colon and Gonella & Lecchini (1971) in the small intestine.

This work was supported in part by grants of C.N.R. (Rome). We wish to thank Farmitalia S.p.a. Laboratories for generous supplies of caerulein.

Department of Pharmacology S. LECCHINI
University of Pavia,
11 Piazza Botta, Pavia, Italy.

Department of Physiology J. GONELLA
CNRS, INP 1
13 Marseille 9, France.

October 25, 1972

REFERENCES

BAKER, R. D. (1969). *Amer. J. Surg.*, **117**, 781–797.
BORTOFF, A. (1972). *Ann. Rev. Physiol.*, **34**, 261–290.
CREMA, A., FRIGO, G. M. & LECCHINI, S. (1970). *Br. J. Pharmac.*, **39**, 234–345.
ERSPAMER, V. (1970). *Gut*, **11**, 79–87.
ERSPAMER, V. (1971). *Ann. Rev. Pharmac.*, **11**, 327–350.
FRIGO, G. M., LECCHINI, S., FALASCHI, C. DEL TACCA, M. & CREMA, A. (1971). *Naunyn-Schmiedebergs Arch. exp. Path. Pharmak.*, **268**, 44–58.
FRIGO, G. M., TORSOLI, A., LECCHINI, S., FALASCHI, C. & CREMA, A. (1972). *Archs int. Pharmacodyn. Thér.*, **196** (Suppl.), 9–24.
GONELLA, J. (1970). *J. Physiol. Paris*, **62**, 447–476.
GONELLA, J. (1971). *Pflügers Arch.*, **322**, 217–234.
GONELLA, J. & LECCHINI, S. (1971). *C. R. Acad. Sci. Paris*, **273**, 214–217.
HEDNER, P. (1970). *Acta physiol. scand.*, **78**, 232–235.
KOSTERLITZ, H. W. & LEES, G. M. (1964). *Pharmac. Rev.*, **16**, 301–339.
KOTTEGODA, S. R. (1969). *J. Physiol. Lond.*, **200**, 687–712.
SMALL, R. C. & WESTON, A. H. (1971). *J. Pharm. Pharmac.*, **23**, 280–290.