The Effects of Pentagastrin on the Motility of the Ruminant Stomach

Pentagastrin, a synthetic pentapeptide which possesses many of the properties of the hormone gastrin, stimulates the motility of parts of the stomach in dogs and man[1], especially of the lesser curvature[2], as well as stimulating gastric secretion. The effects of this drug on the ruminant's stomach are especially interesting, since the stomach is divided into functionally and anatomically distinct compartments. It has been shown to increase activity of the pyloric antrum in sheep[3], but what are its effects on the forestomach, whose movements are so vigorous and complex?

The first chamber, the ruminoreticulum, forms a large vessel in which the food is fermented. Strong contractions of reflex origin pass over this organ about once a minute and are associated with marked electrical activity in the smooth muscle of its wall; more frequent rhythmic electrical activity can also be detected which is similar to the basic electrical rhythm of gut muscle in other species[4]. Food passes next through the omasum, a compact organ containing numerous leaves of epithelium which originate from its greater curvature. The contractions of the reticulo-omasal orifice have a rhythm associated with the rumino-reticular cycle, but those of the main body of the omasum follow a slower and less regular rhythm. The musculature of the wall also shows a rhythmic electrical discharge, greatly augmented during contractions[4]. The last compartment is the glandular abomasum, analogous in function to the stomach of monogastric species. Its fundus makes only weak movements but the pyloric antrum contracts strongly, its cycle of contraction distinct from those of the forestomach, and all parts show rhythmic electrical activity.

The effects of i.v. injection of pentagastrin (ICI, 50 123; Peptavlon) on the forestomach have been examined in a young bull, a cow and a sheep. The cattle had large rumen fistulas which allowed recording instruments to be introduced into the stomach by hand. Water-filled balloons connected to pressure transducers were placed in the rumino-reticulum and omasum, and electrodes were applied to the epithelium of the rumen by means of a suction cup.

Figure 1 shows the effects of an injection of pentagastrin, 1 µg/kg body weight, in the bull. After about 20 sec the contractions of the rumino-reticulum and the electrical activity of the dorsal sac of the rumen ceased altogether; the electrical activity reappeared after about 10 min and the contractions after 20 min. In contrast, the omasum contracted vigorously 20 sec after the injection: the pressure gradually declined to reach the baseline after 7 min and then the organ resumed its irregular activity. Respiration and heart rate were unaffected. Doses of 0.5 or 2.0 µg/kg gave similar responses, differing only in duration. Very similar responses were obtained in the cow.

The possibility that the increased pressure in the omasum was merely a passive reflection of unrecorded movements within the abdomen was examined in the sheep. This animal had stainless steel electrodes chronically implanted in the reticulum, omasum and abomasum. Some of the omasal electrodes were attached to the leaves, about 3 cm from their origin on the wall, others were attached to the greater curvature of the wall. Figure 2 shows that the leaves showed a rhythmic electrical discharge, the wall a less regular and independant activity. After injecting pentagastrin, 1 µg/kg, electrical activity in the reticulum and abomasum ceases altogether, while

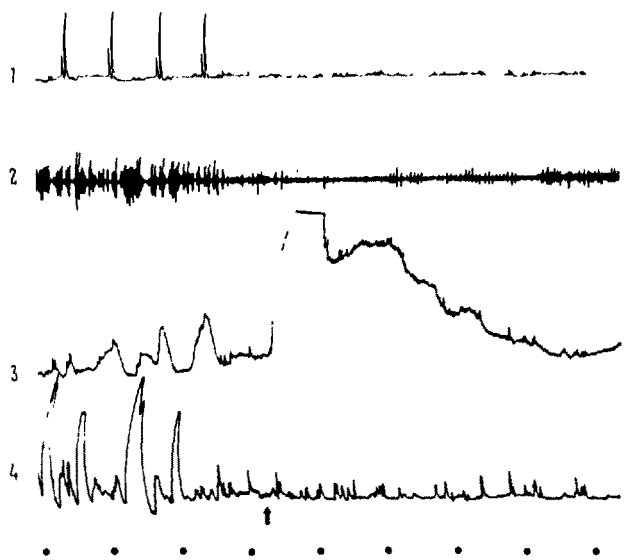

Fig. 1. Bull. Pentagastrin, 1 µg/kg, was given by rapid i.v. injection at the arrow. The record shows: 1, pressure in the reticulum; 2, electrical activity in the dorsal sac of the rumen; 3, pressure in the body of the omasum; and 4, pressure in the posterior dorsal sac of the rumen. Time scale: 1 min intervals.

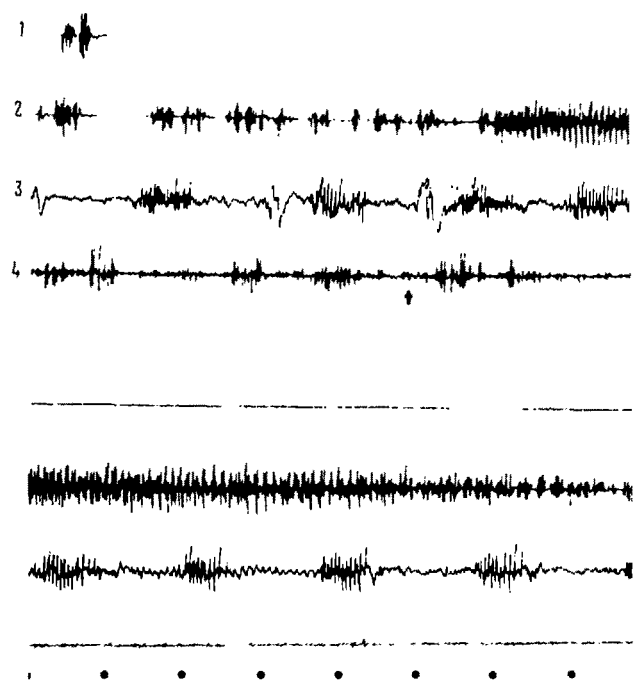

Fig. 2. Sheep. Pentagastrin, 1 µg/kg, was given by rapid i.v. injection at the arrow. The record shows the electrical activity of: 1, reticulum; 2, greater curvature of the omasum; 3, primary leaf of the omasum; and 4, medial side of abomasal fundus. The upper and lower parts of the record run continuously. Time scale: 10 sec intervals.

[1] A. Bennett, Jl R. Coll. Physicians, Lond. *2*, 269 (1968).
[2] K. R. Kelly, Am. J. dig. Dis. *15*, 399 (1970).
[3] Y. Ruckebusch, J. Fargeas and L. Bueno, Rech. Vétér. *3*, 131 (1969).
[4] Y. Ruckebusch, J. Physiol., Lond. *210*, 857 (1970).

the activity of the omasal wall was greatly augmented and became continuous. The rhythmic activity of the omasal leaves was slightly altered, the discharge becoming a little (about 20%) more frequent. The possible contribution of a response to abomasal acid secretion was eliminated by showing that injection of 50 ml of 0.1 *N* HCl into the omasal canal caused only a slight and passing electrical response.

The electrical activity of the omasum was related to pressure changes in the cattle. In the bull, electrical activity of the greater curvature of the omasal wall was recorded by means of chronically implanted electrodes; and in the cow the activity of the leaves was detected by use of a balloon bearing several silver electrodes which was inflated within the omasum. These records showed that pentagastrin greatly increased the activity of the wall but only slightly affected the leaves, as with the sheep, and that the increased electrical activity paralleled the increase in omasal pressure.

This pattern of effects, inhibition of rumino-reticulum and stimulation of the omasum, was not shown by other smooth muscle stimulants. Rapid i.v. injection of hypertensin 2 µg/kg, or serotonin, 20 µg/kg, stimulated the electrical activity of the musculature of all compartments of the stomach, as did pilocarpine, 100 µg/kg, and carbachol, 4 µg/kg. Adrenaline, 2 µg/kg, after a brief stimulating effect, inhibited all compartments. Secretin, 1 IU/kg, and pancreozymin, 2 IU/kg, had no effect. The injection of atropine, 200 µg/kg, arrested all pressure changes and electrical activity; injection of pentagastrin, 2 µg/kg, about 6 min later, always produced an omasal response that was not much less than normal.

These effects of pentagastrin on the smooth muscle of the forestomach appear specific and quite unusual, for 1. unlike other smooth muscle excitants or cholinomimetic drugs with a nicotinic action, excitation of the omasum was accompanied by cessation of rumino-reticular activity, and 2. unlike parasympathomimetic effects, the contraction of the omasum could be produced after atropinization of the organ. The specific excitation of the omasum accords well with its origin from the central part of the lesser curvature of the embryonic gastric spindle[5], since this is the region which is most responsive to pentagastrin in monogastric species[2].

Résumé. L'injection i.v. de 6 µg/kg de gastrine synthétique (ICI 50123) est suivie, chez les herbivores ruminants, malgré une inhibition prolongée de la motricité rumino-réticulaire, d'une importante contraction de l'omasum (feuillet). La réponse excito-motrice persiste après atropine et semble spécifique du feuillet qui équivaut, sur le plan embryologique, à la partie moyenne de la petite courbure de l'estomac.

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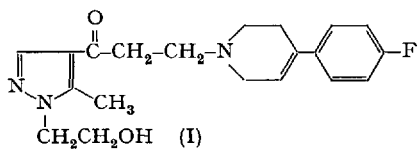
[5] R. S. COMLINE, I. A. SILVER and D. H. STEVEN, *Handbook of Physiology*, Section 6: Alimentary Canal (American Physiological Society, Washington 1968), chapter 125.

Antihypertensive Agents III. Synthesis and Antihypertensive Activity of 3-[4-(*p*-Fluoro-phenyl)-1,2,3,6-tetrahydro-1-pyridyl]-1-[1-(2-hydroxyethyl)-5-methyl-4-pyrazolyl]-1-propanone[1-3]

CIBA 4416/B-Go, which is 3-[4-(*p*-fluorophenyl)-1, 2, 3, 6-tetrahydro-1-pyridyl]-1-[1-(2-hydroxyethyl)-5-methyl-4-pyrazolyl]-1-propanone citrate (I), has been studied to ascertain its antihypertensive properties in experimental animals.



(I)

Go 4416 is a potent hypotensive agent in experimental animals. It produces a prolonged fall of blood pressure of 40–50 mm Hg lasting for about 2 h at a dose of 0.25 mg/kg, when given i.v. or intra-intestinally in pentobarbitone-anaesthetized dogs and cats. At this dose the adrenaline effect is either reversed or blocked. The noradrenaline effect is slightly reduced. The substance inhibits the carotoid occlusion pressor response and antagonizes the pressor response elicited by tyramine and amphetamine.

This compound affects central vasomotor regulating mechanisms as evidenced by the production of prolonged fall of blood pressure after intra-arterial injection into vertebral artery of anaesthetized cats (10–20 µg/kg).

Go 4416 lowers significantly the blood pressure of renal hypertensive rats (−21 to −82) at a dose of 5–30 mg/kg p.o. when given daily for 10 days. The compound has no ganglion-blocking activity, as evidenced by similar diminution of contraction of the nictitating membrane of the cat following pre- and post-ganglionic cervical sympathetic stimulation. The diminished contraction of the nictitating membrane (43% at 1 mg/kg i.v.) following Go 4416 could be attributed to α-adrenoreceptor block. This compound does not block transmission in the adrenergic neurons, as demonstrated in the Finkelman preparation.

Go 4416 produces a significant depletion of heart (39%) and brain (55%) noradrenaline at 10 and 30 mg/kg respectively. Brain dopamine and 5-hydroxy-tryptamine are also significantly lowered (about 50%) with the higher dose.

The compound produces marked peripheral vasodilation. This has been shown on the isolated perfused hind limb of a cat and on femoral blood flow in the anaesthetized dog. The blood flow is increased by 64 and 120% with 50 and 100 µg/kg i.v. respectively, as measured by an electromagnetic flow meter.

A convenient method of preparation of Go 4416B is as follows: Ethoxymethylene acetylacetone is reacted

[1] Citrate = CIBA 4416/B-Go.

[2] Previous paper: V. P. ARYA, R. S. GREWAL, C. L. KAUL, S. P. GHATE, D. V. MEHTA and T. GEORGE, J. Pharm. Sci. *58*, 432 (1969).

[3] Contribution No. 243 from CIBA Research Centre.