The Relation between Cholecystokinin and Substance P

Eric H. Hultman

Chemistry Department II, Karolinska
Institutet, Stockholm, Sweden

The fact that a hormonal mechanism is responsible for contraction and emptying of the gallbladder was first demonstrated by Ivy (1928)¹, who named the hormone cholecystokinin. The methods for biological determinations of the hormone have varied since then, from pressure measurements on anaesthetized animals to intestinal bath experiments on isolated gallbladder. In experiments on isolated organs, cholecystokinin preparations have proved to contract not only the gallbladder, but also the isolated intestine of the guinea-pig. As late as 1953 and 1954, Gershbein *et al.*^{2,3} stated that the guinea-pig intestine is as well suited as the gallbladder for a study of the cholecystokinin effect. The relation to substance P, studied by von Euler and Gaddum⁴ and by Pernow⁵, has been discussed, and the question whether these two substances are identical has been raised.

In experiments on the purification of cholecystokinin preparations, it was found that the intestinal effect could be entirely removed (Hultman 1955)⁶, and that the factor in the crude preparations which produced intestinal contractions *in vitro* is, in all probability, substance P. Purified cholecystokinin preparations proved to have an effect *in vitro* on the guinea-pig gallbladder but not on the intestine, whereas substance P preparations were active on the guinea-pig intestine but not on the gallbladder (Table 1).

Table 1. Intestinal bath experiment (10 ml. intestinal cuvettes, readings in mm on a scale).

		Intestine	Gallbladder
Substance P	3.3 units	10	0
H 289	0.05 mg	0	10
Substance P	3.3 units	9	0
H 289	0.05 mg	0	10
Substance P	6.6 units	10	0
H 282	0.07 mg	10	0
Substance P	1.2 units	2	0

Substance P obtained from Dr. Pernow. H. 282: a fraction obtained from the crude cholecystokinin. H 289: purified cholecystokinin (after removal of H 282).

The strongest preparations of cholecystokinin produced maximal contraction of the isolated guinea-pig gallbladder in doses of 1 µg/ml of fluid in the bath. On some sensitive gallbladders, a good effect was obtained with 0.5–0.1 µg/ml.

Table 2. Intestinal bath experiments as above (10 ml cuvettes).

		Gallbladder
P.S. 117	0.05 mg	10
H 271	0.005 mg	10
H 272	0.025 mg	12
Acetylcholine	0.001 mg	20

P.S. 117, H. 271, H 272: different purified cholecystokinin preparations.

Intravenous administration of the preparations produced a powerful secretion of bile in the anaesthetized cat.

In paper electrophoresis the purest substance showed an isoelectric area around pH 7. The preparations have, in addition, a strong effect on the secretion of pancreatic enzymes.

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On the Rate of Excretion of Bile Acids in the Rat

Sven Lindstedt and Arne Norman

Department of Physiological Chemistry,
University of Lund, Lund, Sweden

Rats were given [24-¹⁴C]-labelled bile acids intraperitoneally. The excretion of activity in the faeces was followed. Practically all of the isotope appeared in the faeces¹. From the rate of excretion the half life of a bile acid molecule was estimated to be 2–3 days.

A certain amount of bile acid is thus lost during each enterohepatic circulation. One of the factors influencing the magnitude of this loss might be the intestinal microorganisms.