The Role of the Kidney in Gastrin Metabolism in the Rat

Since EDKINS[1] discovered gastrin in 1905, much work has been done on it by many workers, but there are some aspects that are not yet clear. The natural form or forms in which gastrins exist in the pyloric mucosa and in circulation are not well known, and little is known about the fate of gastrin in the body. The influence of starvation on gastrin storage in the pyloric antral mucosa had recently been shown by OLOWO-OKORUN[2]. The blood concentration of a drug or hormone depends on both the rate at which it enters the circulation and the rate of its removal from circulation. In cases in which the mechanism or mechanisms for removing the hormone gastrin from the blood become impaired, it may be possible to have hypergastrinaemia even though the antrum is secreting normal amounts of gastrin. The biological activity of synthetic human gastrin I (SHGI) has been found unaffected by transit through the liver (GILLESPIE and GROSSMAN[3], CLARKE, HALL, DEVOR and RIZER[4], LICK, WELSCH, HART, BRUCKNER, BALSER and GURTNER[5], MCGUIGAN, JAFFE, and NEWTON[6], and TEMPERLEY, STAGG and WYLLIE[7]). In dogs and rats, the small bowel has been found to be an important site of gastrin inactivation (TEMPERLEY et al.[7]).

The present work was done to demonstrate the role that the kidney of rats play in the metabolism of i.v. injected synthetic human gastrin I (SHGI), cow pyloric extract (crude cow gastrin) and histamine dihydrochloride.

Methods. Cow pyloric extract was extracted from fresh smooth mucosa of the abomasum of cow (the part analogous to pyloric antrum in man) by using a modified extraction method of BLAIR, HARPER, LAKE, REED and SCRATCHERD[8]. The dried extract was weighed and the weight per g wet weight of the mucosa was determined. Solution of a known weight of the crude extract was prepared using 0.9% NaCl as solvent, with the insoluble precipitate removed after centrifuging for 10 min at 2,500 rpm.

The continuous stomach perfusion technique described by GHOSH and SCHILD[9] was modified for the assay. Adult male Wistar Strain rats weighing between 180–210 g were used. The animals were anaesthetised with urethane 25% w/v solution given i.p. at 0.6 ml/100 g body wt. The operative procedures on the control rats were similar to those described by GHOSH and SCHILD[9] but the femoral vein was cannulated for injecting the stimulants. Also in some rats, called the test rats, the renal blood vessels to both kidneys were ligated and cut.

The stomachs of the rats were perfused with 0.15 *M* normal saline warmed to the rat's body temperature, and the flow rate of the perfusate into the stomach was adjusted to give an effluent volume of 1 ± 0.1 ml/min.

Basal gastric acid secretion rates determined for 450 min in both the control and test rats by collecting the effluents at 10 min intervals and titrating to pH 8.8 with 0.01 *N* sodium hydroxide using the Automatic Titrator (Radiometer Copenhagen).

The following graded doses of the saline solution of the cow pyloric extract (250, 500, 1000 and 2000 µg) and of synthetic human gastrin I (15.75, 31.5, 63.0 and 126.0 ng) and of histamine dihydrochloride (62.5, 125, 250 and 500 µg) were injected i.v. through the femoral vein into the anaesthetized male rats. The pH 8.8 was chosen so as to determine the total titratable acid in the collected effluents. The mean rates of acid secretion in µEq/10 min to the different doses of the 3 stimulants were determined according to the method of LAI[10]. The log dose-response data showed parallel straight lines for the 500 and 1000 µg of the saline solution of the cow pyloric extract 31.5 and 63.0 ng of the synthetic human gastrin I and also 250 and 500 µg of histamine dihydrochloride. These doses were then used for the 2 + 2 (4-point) assay procedure. The low and high doses of the stimulants were injected in a 4-point assay fashion into both the control and test rats, and the effluents were collected at 10 min intervals for 450 min. In each rat used, the response to the first injected dose of the stimulant was rejected.

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Gastric acid secretion in rats receiving i.v. injections of synthetic human gastrin I, histamine dihydrochloride and saline solution of the cow pyloric extract.

Type of secretagogue	Dose	Mean rate of acid secretion (µEq/10 min ± S.D.)		
		Control rats	Test rats	*P*
Synthetic human gastrin I	31.5 ng	1.55 ± 0.23	2.15 ± 0.27	< 0.001
	63.0 ng	2.86 ± 0.38	4.01 ± 0.28	< 0.001
		(7)	(7)	
Cow pyloric extract	500 µg	1.37 ± 0.20	1.95 ± 0.28	< 0.001
	1000 µg	2.47 ± 0.42	3.36 ± 0.32	< 0.001
		(7)	(7)	
Histamine dihydrochloride	250 µg	2.50 ± 0.45	2.76 ± 0.52	> 0.10
	500 µg	3.15 ± 0.41	3.46 ± 0.38	> 0.10
		(7)	(7)	

Numbers in parenthesis indicate number of rats used.

Results. The basal gastric acid secretion rates in the control and test rats were 2.25 ± 0.23 and 2.27 ± 0.25 μEq/10 min respectively. The difference was not significant, $P > 0.10$.

From the Table, it can be seen that the mean rates of acid secretion were higher in the test rats than in the control rats. The differences were significant for the low and high doses of synthetic human gastrin I and cow pyloric extract, $P < 0.001$ respectively, while non-significant for the low and high doses of histamine dihydrochloride $P > 0.10$, using the Student's *t*-test. The percentage increase in the mean rates of acid secretory responses obtained in the test rats to both the low and high doses of synthetic human gastrin I were 38.7 and 40.1% respectively, while those for the saline solution of cow pyloric extract were 42.3 and 36.0% respectively and for histamine dihydrochloride were 10 and 9.8% respectively.

The period of response to the i.v. injections of both the low and high doses of the saline solution of the cow pyloric extract and the synthetic human gastrin I was between 30–40 min in the control rats and between 50–60 min in the test rats. The period of response to both the low and high doses of histamine dihydrochloride was between 40–50 min in both the control and test rats.

The histamine content of the cow pyloric extract was found to be 34.4 ± 2.5 ng/mg cow pyloric extract powder using the isolated guinea-pig terminal ileum by the method of superfusion[11]. The anaesthetized rats used required a minimum i.v. dose of 8 μg histamine dihydrochloride to produce the smallest noticeable increase in acid secretion. This showed that the histamine content of the cow pyloric extract was not responsible for the increased acid secretion obtained, but the gastrin contained in the extract, since the pattern of response was similar to that obtained for the synthetic human gastrin I.

Discussion. There was no significant difference observed in the basal rate of gastric acid secretion in both the control and test rats over the 450 min collection period, which showed that the metabolites which could have accumulated in the blood of the test rats did not significantly affect their gastric acid secretion pattern. It was also observed that the mean rates of acid secretion and the periods of responses to the i.v. injected synthetic human gastrin I and the saline solution of the cow pyloric extract were lower in the rats with intact renal blood vessels (control rats) than in rats with cut renal blood vessels (test rats) which indicated that the kidneys of the rat may be involved in the inactivation and/or removal of both the synthetic human gastrin I and the cow pyloric gastrin from circulation. There was no significant difference observed in either the mean rate of acid secretion or the period of response when doses of histamine dihydrochloride were i.v. injected into the control and test rats. This work identifies the kidneys of rats, like those of the dogs[12], as an important site for the uptake of gastrin from the circulation.

Résumé. Les taux moyens de sécrétion d'acide gastrique due à l'injection par voie i.v. du SHGI et de gastrine bovine brute ont été sensiblement plus élevées et les périodes de réaction plus longues chez les rats testés que chez les rats de contrôle. Aucune différences significative n'a été observée ni dans le taux moyen de sécrétion acide ni dans la période de réaction chez les deux types de rats, après injection d'histamine dihydrochloride.

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Appearance of Lamellar Structures in the Purkinje Cells of Rat Cerebellum after Administration of β-Aminopropionitrile

Lamellar structures were scarcely observed in the nerve cells under normal conditions[1], and their physiological significance remains unsettled. Recently, the authors have frequently found a kind of lamellar structures in the specimens of Purkinje cells of rat cerebellum after treatment with β-aminopropionitrile (BAPN). This chemical is known as one of the inducers of lathyrism[2].

Materials and methods. Adult rats were given 200 mg of BAPN-fumarate by vinyl tubes. BAPN was dissolved in 1 ml of physiological saline. On the 5th and 15th days after the ingestion, the cerebellum was fixed in 5% glutaraldehyde, and postfixed in 1% osmium tetroxide buffered with cacodylate-HCl, pH 7.4. The specimens were dehydrated in ethanol and embedded in Epon 812 as usual. Fixation in glutaraldehyde was performed by perfusion. After cutting with a Porter-Blum microtome, silver sections were stained with uranyl acetate and lead acetate[3], and examined with Hitachi HU-12A electron microscope.

Results and discussion. On the 5th day after treatment, the animals were seen to reduce their movements and to become hypersensitive to mechanical stimulation from outside.

Electronmicroscopic observations on cerebellum show that Purkinje cells are somewhat swollen and contain some neurotubules, a lot of ribosomes, and round or rod-shaped mitochondria with distinct cristae. Mitochondria do not bring about any changes in shape and in electron opacity. Flattened membranous structures, presumably ergastoplasm, in the cells elongate and take on irregular forms. Some parts of them are opposed closely to mitochondria. Sometimes, 2 or 3 of those membranous structures accumulate around mitochondria and are arranged in parallel. The Golgi apparatus seems to be active and rich in vesicles (Figure 1). On the

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