EFFECT OF GLUCAGON ON GASTRIC SECRETION IN MAN

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Glucagon suppresses gastric acid secretion in normal subjects and in ulcer patients. It has no inhibitory effect while the stomach is under maximal histamine stimulation. The mechanism of action is discussed, and experiments are described which indicate that glucagon is unlikely to be of value in the treatment of peptic ulcer.

Glucagon, the hyperglycaemic-glycogenolytic factor of the pancreas, was discovered and named in 1923, but only recently, following its preparation in pure crystalline form (Staub, Sinn, and Bēhrens, 1953), has it been possible to accord to glucagon the status of a true hormone. A complete structure analysis of the glucagon molecule has been achieved (Bromer, Sinn, Staub, and Bēhrens, 1956), and is quite different from that of insulin. With the alpha cells of the islets of Langerhans as its source (Korp and Lecompte, 1955; Bencosme and Frei, 1956), glucagon raises the blood sugar by promoting glycogenolysis in the liver, and this in turn is due to activation of liver phosphorylase: there is no effect on muscle glycogen (Sutherland and Cori, 1948). The physiological role of glucagon, and recent developments in glucagon research, have been reviewed by Elrick, Staub, and Maske (1957), by Bēhrens and Bromer (1958), and by Lukens (1959).

When pure glucagon became available in small quantities for experimental purposes it was observed that the hormone produced metabolic and clinical effects unrelated to the action on hepatic glycogen. The renal excretion of electrolytes is enhanced (Staub, Springs, Stoll, and Elrick, 1957) and large doses have a protein catabolic effect (Ezrin, Salter, Ogryzlo, and Best, 1957). A suggestion (Summerskill, 1959) that glucagon might be the ulcerogenic factor in the syndrome described by Zollinger and Ellis (1955) has not been confirmed. In this syndrome, which is characterized by recurrent intractable multiple peptic ulceration, marked gastric hypersecretion, and the presence in most cases of alpha cell pancreatic tumours, the aetiology is still unknown: the observation by Fisher and Flandreau (1957) that, in a patient dying of this syndrome, a hyperglycaemic substance with some similarity to glucagon could be isolated from one of the alpha cell tumours had also stimulated interest in the possible effect of glucagon on the stomach. It has been reported (e.g., Elrick et al., 1957) that glucagon has an inhibitory effect on gastric secretion; in this communication experiments are described which confirm these reports and were undertaken to aid in the elucidation of the mode of action of the hormone on the stomach. The striking and consistent inhibitory effect of glucagon on spontaneous gastric secretion has suggested the possibility that it will prove useful in the treatment of peptic ulcer, and the potential value of the hormone in the management of this disease has also been investigated.

METHODS

In seven fasting patients, who had no alimentary symptoms and were free from any disease known to affect gastric secretion, a small-bore stomach tube was passed and the resting juice removed. With continuous gastric suction and the patient positioned on the left side gastric juice was collected for one hour. Glucagon, 0.01 mg. per kg., was injected intravenously and the collection proceeded for a second one-hour period. The samples were measured and titrated for free acidity. In all the following investigations patients with radiologically proven chronic duodenal ulcer were used. The investigations described above were repeated in five ulcer subjects. The augmented histamine test meal (Kay, 1953) was carried out in seven patients, and the maximum histamine response (M.H.R.) determined. Several days later the test was repeated, injecting glucagon, 0.02 mg. per kg. intravenously, at the beginning of the half-hour collection period. This investigation was repeated using another group of ulcer patients and doses of glucagon four times as great, i.e., 0.08 mg. per kg. intravenously. Using doses of 0.01-0.02 mg. per kg., moderate hyperglycaemic responses of about 30 mg. % of glucose were
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obtained, indicating a definite response to the hormone. There were no side-effects and glycosuria was not observed in any test.

In 10 ulcer patients a Ryle’s tube was passed nasally into the stomach and retained in position for 24 hours. Ordinary ward diet was allowed, the patients were permitted to move about the ward at will, and no drug treatment was given. Specimens of gastric juice were aspirated hourly for testing pH, positioning the patient as required to facilitate removal. During the 24-hour period glucagon, 1 mg. intramuscularly, was given at intervals of eight hours.

RESULTS

Glucagon had an inhibitory effect on the spontaneous gastric secretion of hydrochloric acid both in non-ulcer and in ulcer patients (Figs. 1 and 2). In Figs. 3 and 4 it is seen that the maximum histamine response of acid output is unaltered by glucagon in dosage of either 0.02 or 0.08 mg. per kg. (t<1 in each case). Of the 24-hour test meal specimens, those collected immediately before and one hour after glucagon injection may have been expected to reveal any changes in pH attributable to the hormone, and 27 paired results were available for statistical analysis (Table I), which fails to reveal any significant difference (t<1). In eight tests there was no change in pH, in 12 a fall occurred, and in only seven did the pH rise. The results in a typical case are shown in Fig. 5.
marked inhibitory effect on resting gastric secretion, and preliminary but confirmatory investigations were reported by Dall and Melrose (1959). Twenty-four patients were studied by Drelling and Janowitz (1959), who noted that glucagon caused depression of the rate of volume flow, acid formation, and pepsin secretion in gastric juice. Free acid secretion was completely inhibited in non-ulcer patients, but acid was not completely suppressed in ulcer subjects. The inhibitory effect was observed to last for up to five hours, and its existence in relation to spontaneous gastric secretion is now well established.

It is unlikely that the hyperglycaemia induced by glucagon takes part in the mechanism by which acid gastric secretion is inhibited. The hyperglycaemic period is brief, lasting 60 to 75 minutes, in contrast to the prolonged duration of acid suppression. Solomon and Spiro (1960) compared the acid inhibitory effects of intravenous infusions of glucose and of glucagon, and noted that glucose-induced acid suppression was very slight in degree while that of glucagon was marked. It has not been possible to demonstrate a local inhibitory effect of glucagon within the gastric mucosa. Irrigation of the stomach with glucagon solutions has no effect on gastric secretion, nor would any be expected, since glucagon is destroyed by the peptic activity of gastric juice. A local suppressive action of glucagon on the parietal cell population may be assumed if the hormone can be shown to inhibit the acid response to histamine, and the investigations of Cohen, Mazure, Drelling, and Janowitz (1959) are of interest. Using varying doses of glucagon and histamine given together, they reported that some inhibition of acid output could be achieved when the dose of histamine was small: larger doses of histamine were associated with smaller degrees of inhibition, which was markedly less in the second 20 minutes than in the first 20 minutes after injection of glucagon with prior histamine stimulation. Scrutiny of their data suggests that glucagon can produce a degree of inhibition during submaximal histamine stimulation; during the period of maximal histamine response, as defined by Kay (1953), and as studied in the present communication, glucagon fails to suppress acid gastric secretion. It is concluded that glucagon does not have a direct action on gastric mucosa, and the hormone may interfere with the regulatory mechanism for gastric secretion.

The suppressive effect of glucagon on gastric secretion has led Solomon and Spiro (1960) to speculate on its potential application in the treatment of peptic ulcer. Long-term administration would be required, and the possibility that chronic glucagon administration could induce a permanent diabetic state in man has not yet been completely excluded.
Large doses of glucagon have a catabolic effect, and the need for frequent injections would be a disadvantage. Eight-hourly injections of glucagon given while simulating normal activities and normal diet in 10 patients (subject to experimental conditions) have failed to produce significant elevation of the pH of gastric juice, and the results compare unfavourably with conventional methods of treatment. The provisional findings are not encouraging and it seems unlikely that glucagon will be found of value in the management of peptic ulcer.

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REFERENCES