Effect of glucocorticoids on gastrin secretion in man

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SUMMARY In order to investigate the effect of glucocorticoids on gastrin secretion, plasma gastrin levels were measured by radioimmunoassay in patients with Cushing's syndrome and those treated with glucocorticoids. Fasting plasma gastrin levels were significantly higher in these patients than in normal subjects, with exaggerated response to food. Conversely, short-term treatment or intravenous infusion of glucocorticoids had no significant influence on gastrin secretion in normal subjects. The possible mechanism by which glucocorticoids cause hypergastrinaemia are discussed.

It is well-known that 'steroid ulcer' is a frequent complication of treatment with glucocorticoids (Bollet *et al.*, 1955; Meltzer *et al.*, 1958), although the pathogenesis of this untoward complication still remains obscure. Accumulating evidence in recent years has suggested that gastrin is an important ulcerogenic factor among gastrointestinal hormones (Trudeau *et al.*, 1970; Gedde-Dahl, 1974; Walsh *et al.*, 1975). To our knowledge, however, very few studies have been reported on the effect of glucocorticoids on gastrin secretion (Watson *et al.*, 1973; Giordano and Marugo, 1974; Raptis *et al.*, 1976).

The present study was designed to investigate the acute and chronic effect of glucocorticoids on plasma gastrin levels in man.

Methods

FASTING GASTRIN LEVELS

Normal subjects

Forty-five normal subjects, 25 men and 20 women, aged 18 to 52 years, were used as controls. Their endocrine and gastrointestinal functions were apparently normal.

Subjects on short-term treatment with glucocorticoids

Eleven normal subjects, six men and five women,

aged 25 to 50 years, were studied after three days of oral prednisolone administration (30 mg/day).

Subjects on long-term treatment with glucocorticoids

A group of 10 patients was studied, which comprised five with bronchial asthma, two with collagen disease, two with idiopathic thrombocytopenic purpura, and one with polyneuropathy. These patients, five men and five women, aged 23 to 58 years, were thought to have no gastrointestinal disorders or abnormalities in renal function. They had received more than 500 mg (prednisolone equivalent) glucocorticoids altogether and for longer than three weeks. Anticholinergic drugs were withheld for at least five days before the experiment.

Cushing's syndrome

Six patients (two men and four women, aged 17 to 52 years), had Cushing's syndrome, surgically proven to be caused by bilateral adrenal hyperplasia. In two of these patients, fasting plasma gastrin levels were retested after their clinical symptoms had disappeared and their laboratory data had become normal by treatment.

EFFECT OF FOOD

In order to study the response of plasma gastrin to food, test meals were given to six untreated normal subjects, six subjects on short-term treatment with glucocorticoids, and six patients on long-term treatment with glucocorticoids. The meal consisted of 80 g carbohydrate, 15 g protein, and 10 g fat. The blood samples were obtained before and again 30 and 60 minutes after the meal.

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Fig. 1 Fasting plasma gastrin levels in untreated normal subjects, in subjects on short-term glucocorticoid treatment, and in patients on long-term glucocorticoid treatment and Cushing's syndrome.

INTRAVENOUS INFUSION OF GLUCOCORTICOIDS

To study the acute effect of glucocorticoids on gastrin secretion, five normal male volunteers, aged 21 to 38 years, were subjected to the following two experiments with an interval of at least one week between two tests. Either 250 mg or 500 mg hydrocortisone dissolved in 250 ml saline were administered to them intravenously over a period of 60 minutes. Blood was withdrawn immediately before and at intervals of 15 minutes after the start of the infusion as indicated in Fig. 3. All volunteers were informed of the nature, purpose, and potential risks of the procedure.

All experiments mentioned above were conducted in the early morning after an overnight fast and absolute bed rest for at least 30 minutes.

Blood was withdrawn into a heparinised disposable plastic syringe from the antecubital vein. An aliquot of the blood was used for determining blood glucose, using the Technicon AutoAnalyzer (Hoffman, 1937). The remaining portion was centrifuged and plasma was separated, frozen, and stored at -20°C until assayed. Plasma gastrin was measured by dextran-coated charcoal radioimmunoassay as previously described (Seino *et al.*, 1976).

Statistical analysis was performed using either Student's *t* test or the paired *t* test.

Results

FASTING GASTRIN LEVELS (Fig. 1)

The mean ($\pm$ SE) fasting plasma gastrin levels in

Fig. 2 Plasma gastrin response to food in normal subjects, in subjects on short-term glucocorticoid treatment, and in patients on long-term glucocorticoid treatment. Means $\pm$ SE are shown.

Fig. 3 Effect of hydrocortisone infusion on plasma gastrin and blood glucose levels in normal subjects. Means $\pm$ SE are shown.

untreated normal subjects and those on short-term glucocorticoid treatment were 43 ± 2 pmol/l and 43 ± 3 pmol/l, which were not significantly different from each other. In contrast, patients receiving long-term glucocorticoid treatment and those with Cushing's syndrome had plasma gastrin levels of 73 ± 10 pmol/l and 105 ± 20 pmol/l, both of which were significantly higher than that in normal subjects ($P < 0.01$).

When plasma gastrin levels were retested after treatment in two patients with Cushing's syndrome, they had dropped towards the normal range.

PLASMA GASTRIN RESPONSE TO FOOD (Fig. 2)

In normal subjects, the ingestion of the test meal caused a significant increase in plasma gastrin from the basal levels of 40 ± 5 pmol/l to the levels of 131 ± 11 pmol/l and 127 ± 24 pmol/l at 30 and 60 minutes, respectively. A similar response of plasma gastrin to food was observed in normal subjects treated with glucocorticoids for three days, showing the mean basal and postprandial (30 and 60 minutes) levels of 47 ± 5 pmol/l, 144 ± 23 pmol/l, and 124 ± 21 pmol/l, respectively. These values were not significantly different from those in untreated normal subjects.

On the other hand, food caused an exaggerated response of plasma gastrin in patients treated with glucocorticoid for more than three months. The mean basal and 30 minute postprandial plasma gastrin levels, 74 ± 10 pmol/l and 231 ± 41 pmol/l, respectively, were significantly higher than

the corresponding values in untreated normal subjects ($P < 0.05$).

PLASMA GASTRIN RESPONSE TO INTRAVENOUS INFUSION OF HYDROCORTISONE (Fig. 3)

Intravenous infusion of 250 mg hydrocortisone caused a slight but insignificant increase of plasma gastrin, with the highest value of 43 ± 3 pmol/l occurring at 30 minutes ($P > 0.05$ vs preinfusion level). A larger dose of hydrocortisone (500 mg) also caused a slight increase in plasma gastrin, with the highest value of 45 ± 8 pmol/l at 15 minutes, which was not significantly different from the basal level ($P > 0.05$). Blood glucose tended to rise, though not significantly, during the infusion of hydrocortisone.

Discussion

The present experiments demonstrate that basal plasma gastrin levels were raised, with an exaggerated response to food in patients on long-term treatment with glucocorticoids or with Cushing's syndrome. However, short-term treatment with glucocorticoids or acute infusion of hydrocortisone, even at a dose of 500 mg, had no significant effect. These results suggest that chronic exogenous or endogenous excess of glucocorticoids leads to hypergastrinaemia, whereas an acute excess has no significant influence on gastrin secretion.

Watson *et al.* (1973) and Raptis *et al.* (1976) reported that a bolus injection of glucocorticoids did not increase plasma gastrin, although four to five

days' treatment significantly enhanced both basal and stimulated gastrin secretion. These results partly disagree with our observation, that three days' treatment with glucocorticoids failed to influence either basal or stimulated gastrin secretion. The reason for this discrepancy may be explained by the difference in the total dose and duration of glucocorticoid treatment between experiments. The mechanism responsible for hypergastrinaemia induced by chronic excess of glucocorticoid, though not clear at present, deserves consideration. There seem to be several possible explanations for this phenomenon. First, glucocorticoids may act directly on gastrin secretion cell (G-cell), resulting in G-cell hyperplasia and hyperfunction. However, there has been no report on the histology of G-cells in glucocorticoid-treated animals or man.

Second, it is possible that glucocorticoids cause inhibition of gastric acid secretion, which, in turn, stimulates gastrin secretion through a negative feedback mechanism. Controversial results have been reported on the influence of glucocorticoids on gastric acid secretion. Some investigators reported increased gastric acidity (Villarreal *et al.*, 1955; Cooke and Grossman, 1966), while others observed no significant change or rather a decrease in gastric acidity in patients on treatment with glucocorticoids (Hirschowitz *et al.*, 1955; Dragstedt *et al.*, 1956). Although gastric acidity was not measured in the present experiment, inconsistent results in the previous experiments seem to militate against the second possibility.

The third and most likely explanation is that metabolic changes—for example, an increase of plasma amino acids—induced by glucocorticoids are responsible for enhanced gastrin secretion. In fact, protein catabolic effect of glucocorticoids has been well documented (Long *et al.*, 1940; Smith *et al.*, 1967) and an increase of plasma amino acids has been reported in patients with Cushing's syndrome or those treated with glucocorticoids (Wise *et al.*, 1973). As some amino acids are reported to be potent secretagogues of gastrin (Kalk *et al.*, 1973; Debas *et al.*, 1974), the increased plasma levels of amino acids induced by glucocorticoids may enhance gastrin secretion. The fact that chronic excess of glucocorticoids is a prerequisite for hypergastrinaemia may also favour the metabolism hypothesis. Further investigations should clarify the exact mechanism responsible for glucocorticoid-induced gastrin secretion.

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