FOOD-DEPENDENT CUSHING'S SYNDROME MEDIATED BY ABERRANT ADRENAL SENSITIVITY TO GASTRIC INHIBITORY POLYPEPTIDE

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Abstract  Background. Some patients with Cushing’s syndrome have nodular adrenal hyperplasia. In most the disease is corticotropin-dependent, but in others it is corticotropin-independent. The cause of the adrenal hyperplasia in the latter patients is not known.

Methods. We studied a 49-year-old woman with Cushing’s syndrome and nodular adrenal hyperplasia in whom food stimulated cortisol secretion. Plasma cortisol concentrations were measured in response to the ingestion of mixed meals, glucose, protein, and fat and after the administration of various gastrointestinal and other types of hormones. We also studied the ability of the long-acting somatostatin analogue octreotide to prevent the food-induced increase in plasma cortisol concentrations and to ameliorate the clinical manifestations of Cushing’s syndrome in this patient.

Results. The patient’s fasting plasma cortisol concentrations were subnormal, ranging from 3.0 to 7.5 µg per deciliter (83 to 207 nmol per liter), and they increased to as high as 16.5 µg per deciliter (455 nmol per liter) after a mixed meal. Her urinary cortisol excretion ranged from 164 to 250 µg per day (453 to 690 nmol per day) and could not be suppressed by a large dose of dexamethasone. Plasma corticotropin concentrations were virtually undetectable at all times. The ingestion of glucose, protein, and fat increased plasma cortisol concentrations to 3.6, 2.2, and 4 times the base-line value, respectively; the meal-induced and glucose-induced increases were inhibited by octreotide. The infusion of gastric inhibitory polypeptide (GIP) increased the patient’s plasma cortisol concentration to 3.7 times the base-line value, but had no effect in normal subjects. The patient’s fasting plasma GIP concentrations were normal both before and after a meal, and there was a close correlation between her plasma cortisol and GIP concentrations. Treatment with octreotide decreased urinary cortisol excretion and ameliorated the clinical manifestations of Cushing’s syndrome.

Conclusions. The development of aberrant adrenal sensitivity to GIP can result in food-dependent adrenal hyperplasia and therefore in Cushing’s syndrome. (N Engl J Med 1992;327:981-6.)

The most common causes of spontaneous Cushing’s syndrome are hypersecretion of corticotropin, from either a pituitary adenoma or a non-endocrine tumor, and unilateral adrenal tumors. Although they are generally considered autonomous, adenal tumors that are responsive to various stimuli, including food, corticotropin, and vasopressin, have been reported. Corticotropin-independent Cushing’s syndrome due to nodular hyperplasia is rare, and its cause is poorly understood, although adrenal stimulation by antibodies has been demonstrated in some cases.

We describe a patient with corticotropin-independent Cushing’s syndrome, who had low plasma cortisol concentrations during periods of fasting and whose concentrations increased after the ingestion of glucose, fat, or proteins and the intravenous infusion of gastric inhibitory polypeptide (GIP). As exemplified by this patient and the patient described by Lacroix et al. in an abstract and in more detail in the preceding article, Cushing’s syndrome can be food-dependent.

Case Report

A 49-year-old woman had a five-year history of fatigue, muscular weakness, and weight gain (total, 8 kg); these symptoms developed during the year after a hysterectomy with oophorectomy. Physical examination revealed that the patient had a round face, interdigital mycosis, proximal myopathy, hypertension (blood pressure, 180/90 mm Hg), and mild depression. She had no striae, hirsutism, clitoromegaly, or osteoporosis. Her mean daily food intake was estimated to be 1895 kcal, with 16 percent of the calories coming from protein, 42 percent from fat, and 42 percent from carbohydrate. The fasting and post–glucose loading plasma glucose concentrations were normal, as were the results of other routine biochemical tests.

The patient’s plasma cortisol concentrations were 4.5 µg per deciliter (124 nmol per liter) at 8 a.m. and 12.0 µg per deciliter (331 nmol per liter) at 8 p.m., and urinary cortisol excretion ranged from 164 to 250 µg (453 to 690 nmol) per day (Table 1). Plasma corticotropin was undetectable before and after the administration of lysine vasopressin and metyrapone. Plasma and urinary cortisol values did not change in response to either a small or a large dose of dexamethasone. The results of hourly measurements of plasma cortisol for two days revealed prominent meal-related peaks (Fig. 1), and plasma corticotropin concentrations were virtually undetectable at all times. The patient’s plasma aldosterone concentration was normal (and was not stimulated by glucose ingestion). Abdominal computed tomography revealed enlarged adrenal glands (right, 4.5 cm long and 1.5 cm wide; left, 3.5 cm and 1.5 cm), and the left adrenal gland appeared nodular. There was bilateral uptake of [131I]iodocholesterol by the adrenal glands. Computed tomography of the pituitary gland showed no abnormalities.

There was no evidence of familial Cushing’s syndrome, and the patient’s brother and her three daughters had normal fasting (measured at 8 a.m.) and postprandial (measured at 8 p.m.) plasma cortisol concentrations.

Studies were undertaken to determine the responsiveness of the patient’s adrenal glands to corticotropin, GIP, mixed meals, carbohydrate, fat, and protein after a fast lasting overnight or longer. The interval between studies was at least one week. During this period, the patient continued the cyclic transdermal estradiol and oral progesterone therapy that had been initiated when she had a hysterectomy, but she received no other medications. On the morning of each test, she remained supine and had an indwelling catheter placed in a forearm vein to allow repeated blood sampling. The patient subsequently declined to undergo bilateral adrenalectomy.

and therefore was treated with octreotide, a somatostatin analogue, on the basis of its ability to inhibit glucose-induced cortisol secretion in an earlier study. She was treated for 2 weeks with 0.05 mg of octreotide subcutaneously before lunch each day, then for 12 weeks with a dose of 0.05 mg daily before her afternoon snack, and finally with a dose of 0.1 mg three times daily. She was advised to eat normally during treatment.

Human GIP (Bachem, Bubendorf, Switzerland) was dissolved in saline with 1 percent albumin, sterilized by membrane filtration, and stored at -20°C until it was used.

**METHODS**

**Normal Subjects**

Four normal men ranging in age from 25 to 52 years were studied as described below while being given dexamethasone to suppress corticotropin-dependent cortisol secretion (1 mg orally at 4 p.m. and 11 p.m. the day before the test and at 7 a.m. on the morning of the test). Three normal men ranging in age from 27 to 52 years were studied during a 24-hour fast and then after eating a 1130-kcal meal containing 82 g of carbohydrate, 40 g of protein, and 53 g of fat at 8 p.m.

All the studies were approved by the local ethics committee, and the patient and all the normal subjects gave informed consent.

**Hormone Assays**

Plasma cortisol, corticotropin, aldosterone, and insulin concentrations were measured by commercial radioimmunoassay kits purchased from Incstar (Stillwater, Minn.), the Nichols Institute (San Juan Capistrano, Calif.), Behring-Calbiochem (San Diego, Calif.), and Pharmacia (Uppsala, Sweden), respectively. Plasma GIP was measured by radioimmunoassay as described previously. The sensitivity of the corticotropin and GIP assays was 1 pg and 20 pg, respectively. All plasma samples from each study were measured in duplicate in the same assay. Urinary cortisol excretion was measured by radioimmunoassay, and urinary 17-hydroxycorticosteroid and 17-ketosteroid excretion was measured by standard colorimetric methods.

**In Vitro Studies**

The potential steroidogenic effect of the patient’s serum was tested by incubation of serum in vitro with adrenal cells from a normal adult. The cells were cultured in 1 ml of a 1:1 solution of Ham’s F12 medium and Dulbecco’s modified Eagle’s medium. On the second day of culture, the medium was removed and replaced by fresh medium that contained corticotropin, serum, or IgG fractions of serum obtained from the patient or a normal subject during periods of fasting. The mixtures were then incubated at 37°C for 24 hours, after which the cortisol concentrations in the medium were measured in quadruplicate by radioimmunoassay.

**RESULTS**

**In Vivo Adrenal Responsiveness to Various Stimuli**

The patient’s plasma cortisol concentrations increased from 3.7 to 26.0 µg per deciliter (102 to 718 nmol per liter) 60 minutes after the intravenous administration of 0.25 mg of corticotropin at 8 a.m. and from 13.0 to 33.0 µg per deciliter (359 to 911 nmol per liter) when the corticotropin was given at 8 p.m.

After an overnight fast and while the patient continued fasting, her plasma cortisol concentrations, measured hourly, averaged 4.3 µg per deciliter (119 nmol per liter) between 8 a.m. and 8 p.m. Her plasma cortisol concentration increased to 16.5 µg per deciliter (455 nmol per liter) 60 minutes after she ate a 690-kcal mixed meal (116 g of carbohydrate, 27 g of protein, and 14 g of fat) at 8 p.m. (Fig. 2A); plasma GIP increased from 245 to 1060 ng per liter (49 to 212 pmol per liter). This evening postprandial increase in plasma cortisol did not occur in the three normal men, although their postprandial increase in plasma GIP was prolonged because of the higher fat content of the meal they received (Fig. 2B).

The administration of both oral (75 g) and intravenous (25 g) glucose increased the patient’s blood glucose and plasma insulin concentrations. By contrast, only the oral
administration of glucose was followed by a rise in both plasma cortisol, from 4.1 to 18.0 µg per deciliter (113 to 497 nmol per liter), and GIP, from 105 to 1100 ng per liter (21 to 220 pmol per liter) (Fig. 3A). The oral glucose–induced increase in plasma cortisol and GIP concentrations was inhibited when the patient was given 0.1 mg of octreotide subcutaneously one hour before the administration of oral glucose (Fig. 3B). The effects of a protein-based meal (490 kcal; 87 percent protein, 8 percent carbohydrate, 5 percent fat) and a fat-based meal (490 kcal; 82 percent fat, 16 percent carbohydrate, 2 percent protein), each eaten at 10 a.m., are shown in Figures 3C and 3D. Both meals were followed by increases in plasma cortisol and GIP concentrations. Plasma cortisol concentrations did not increase after the intravenous administration of 1 mg of glucagon, 0.1 unit of insulin (and glucose) per kilogram of body weight, or 0.5 µg of pentagastrin per kilogram (data not shown). The intravenous infusion of glucose for three hours with simultaneous infusion of 0.6 µg of GIP per kilogram for the last hour resulted in an increase in plasma cortisol concentrations from 4.0 to 14.8 µg per deciliter (110 to 408 nmol per liter) during the last hour (Fig. 4A). In contrast, the same infusions had no effect on plasma cortisol concentrations in four normal subjects who received dexamethasone (Fig. 4B). These subjects and the patient did have an increase in plasma cortisol in response to corticotropin given 90 minutes after the GIP and glucose infusion was stopped. In all subjects, plasma insulin concentrations increased during the infusion of GIP, resulting in transient hypoglycemia after both the glucose and GIP infusions were discontinued.

The plasma concentrations of GIP and cortisol were positively correlated (P<0.001) in the samples collected during the studies in which the patient received oral glucose, the protein-based meal, and the fat-based meal.

In Vitro Studies

The human adrenal cells cultured in vitro responded to corticotropin in a dose-dependent manner: the mean (±SD) cortisol content in basal medium after 24 hours of incubation was 4.8±0.2 µg per milligram of protein, and it was 9.2±0.2, 12.5±2.5, and 27.8±3.3 µg per milligram of protein after incubation with 10⁻¹², 10⁻¹¹, and 10⁻¹⁰ mol of corticotropin per liter, respectively. The patient’s serum stimulated cortisol production in these cells (8.5±1.5 and 13.7±2.1 µg per milligram of protein after the addition of 20 and 40 µl of serum, respectively), as did normal serum (7.2±1.1 and 11.9±1.0 µg of cortisol per milligram of protein). The IgG (200 µg and 400 µg) prepared from the patient’s serum and from normal serum had no steroidogenic effect. Therefore, this patient’s Cushing’s syndrome was not due to adrenal-stimulating immunoglobulins.

Therapeutic Effects of Octreotide

The food-induced increase in plasma cortisol in the patient was inhibited for six hours after a subcutaneous injection of 0.05 mg of octreotide (data not shown). The effectiveness of the subsequent treatment was initially monitored by measurements of urinary cortisol excretion in the evening (6 to 10 p.m.). Urinary cortisol excretion ranged from 240 to 440 µg (662 to 1214 nmol) per gram of creatinine before treatment (normal, 8 to 30 µg [22 to 83 nmol] per gram of creatinine), 36 to 310 µg (99 to 856 nmol) per gram of creatinine when octreotide was injected before lunch, and 72 to 153 µg (199 to 422 nmol) per gram of creatinine when octreotide was injected before the patient’s afternoon snack. After three months of treatment, her
Figure 3. Effects of Intravenous and Oral Glucose Administration (Panel A), Oral Glucose One Hour after the Injection of Octreotide (Panel B), a Protein-Based Meal (Panel C), and a Fat-Based Meal (Panel D) on Plasma Concentrations of Cortisol (○), Glucose (●) or Triglycerides (X), Insulin (△), and GIP (■) in a Patient with Food-Induced Cushing's Syndrome.

To convert values for glucose to millimoles per liter, multiply by 0.0556; to convert values for triglycerides to millimoles per liter, multiply by 1.14; to convert values for GIP to picomoles per liter, multiply by 0.2; to convert values for cortisol to nanomoles per liter, multiply by 27.6; and to convert values for insulin to picomoles per liter, multiply by 7.175.
Clinical condition improved: she had lost 5 kg, her well-being and strength improved, and her face became less round. However, her 24-hour urinary cortisol excretion remained elevated, ranging from 240 to 320 µg (662 to 883 nmol) per day. During the fourth month of therapy, clinical signs of Cushing’s syndrome recurred; increasing the dose of octreotide to 0.1 mg three times daily resulted in clinical improvement and the return of urinary cortisol excretion to normal levels (100 µg [276 nmol] per day).

**DISCUSSION**

In our patient, Cushing’s syndrome, which was manifested by both clinical symptoms and increased urinary cortisol excretion, was clearly due to food ingestion. Her plasma cortisol concentrations were subnormal when she fasted, and they increased after meals, whether she ate mixed meals or meals largely consisting of protein, fat, or carbohydrate. The increases in plasma cortisol concentrations were not mediated by corticotropin secretion, since plasma corticotropin concentrations were virtually undetectable at all times and dexamethasone did not suppress plasma cortisol concentrations or urinary cortisol excretion. Plasma cortisol concentrations increased in response to the administration of oral glucose, but not intravenous glucose, and this increase was suppressed by octreotide, a somatostatin analogue that is known to directly stimulate the adrenal glands by GIP due to aberrant sensitivity of the cortisol receptors capable of binding GIP as well as corticotropin. Whether or not other peptides can stimulate our patient’s adrenal glands is unknown. The failure of lysine vasopressin, glucagon, insulin, and pentagastrin to produce such an effect does not rule out the possibility that some other known or unknown peptides contribute to the patient’s adrenal hypersecretion.

Whatever the mechanism involved, it must differ from that which elicits the food-dependent increase in plasma cortisol concentrations that occurs in some normal subjects. Although some investigators have not found any effect of meals on cortisol secretion in normal subjects, others have found a lunch-related...
increase in plasma cortisol concentrations. This increase is due to the ingestion of proteins, mainly those containing tyrosine and tryptophan; fat and carbohydrate have no discernible effect. The sight and taste of food, without ingestion, do not evoke an increase in plasma cortisol. This after-lunch cortisol secretion in normal subjects is suppressed by dexamethasone and is therefore a corticotropin-dependent phenomenon. Gastrin-releasing peptide may participate in the corticotropin-dependent postprandial peak, since this peptide and its receptors are present in the hypothalamus, and the concentrations of both corticotropin and cortisol are increased, in a dose-dependent manner, by the infusion of this peptide. The increase in plasma cortisol concentrations induced by the intravenous infusion of vasoactive intestinal polypeptide in patients with Cushing's disease was also related to corticotropin secretion by the pituitary adenoma, and it disappeared after successful adrenalectomy.

The ability of octreotide to block the increase in plasma cortisol concentrations induced by oral glucose in our patient led us to use this drug as an alternative to bilateral adrenalectomy. We believed that this treatment was logical and permissible in our patient, at least for some time, since her Cushing's syndrome was mild and she declined to undergo adrenalectomy.

The initial treatment with a single injection before lunch or in the afternoon was designed to reproduce an almost normal diurnal cycle of cortisol secretion by maintaining the meal-stimulated morning peak and inhibiting any cortisol increase later in the day. However, as a result of insufficient cortisol suppression, we had to increase the dose to 0.1 mg three times daily. With this regimen, the patient's urinary cortisol excretion decreased to the upper limit of normal. Therefore, octreotide had an incomplete effect in this patient, and its use as a long-term treatment remains questionable.

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References