

Brief Report

IMPAIRED COUNTERREGULATION OF GLUCOSE IN A PATIENT WITH HYPOTHALAMIC SARCOIDOSIS

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HYPOGLYCEMIA stimulates rapid increases in the secretion of several hormones, including catecholamines, glucagon, cortisol, and growth hormone, that act in concert to increase the plasma glucose concentration. The chief role of the central nervous system in triggering the release of such counterregulatory hormones during hypoglycemia is well recognized. The specific region of the hypothalamus responsible for this process is probably the ventromedial region, because bilateral lesions or perfusion of D-glucose into this region reduces the increases in plasma glucagon and catecholamines in response to hypoglycemia in rats.^{1,2} We describe a patient with a hypothalamic sarcoid infiltrate who had complete loss of the counterregulatory response to hypoglycemia.

CASE REPORT

A 31-year-old woman in whom sarcoidosis had been diagnosed at the age of 27 years had an 18-month history of secondary amenorrhea, a 12-month history of weight gain of about 20 kg, and polydipsia and polyuria. Apart from the presence of obesity (weight, 86 kg; height, 171 cm) and a tendency toward hypothermia, the results of the physical examination were normal. A water-deprivation test confirmed the diagnosis of central diabetes insipidus. Measurements of plasma and urinary hormones disclosed partial pituitary insufficiency, with low plasma concentrations of free thyroxine and cortisol and hyperprolactinemia. Plasma luteinizing hormone and follicle-stimulating hormone concentrations were normal, but the responses to gonadotropin-releasing hormone were supranormal. Magnetic resonance imaging revealed a normal pituitary gland but multiple infiltrates in the brain, including one in the hypothalamic region. The diagnosis of sarcoidosis was confirmed by the findings of a high plasma angiotensin-converting enzyme concentration, bilateral hilar lymphadenopathy with reticular interstitial infiltrates on computed tomography of the chest, and typical findings on transbronchial biopsy. Treatment was initiated with 32 mg of methylprednisolone per day, 100 μ g of levothyroxine per day, 30 μ g of desmopressin acetate per day, and a combination of 30 μ g of ethinyl es-

tradiol and 75 μ g of gestodene given on days 1 to 21 of the menstrual cycle. After one month of methylprednisolone therapy, pituitary magnetic resonance imaging showed complete resolution of all the infiltrates except the one in the hypothalamus, and it remained unchanged thereafter.

During the next two years, the dose of methylprednisolone was gradually reduced to 6 mg per day and then replaced by cortisone acetate (37.5 mg per day). Shortly thereafter, the patient began to report episodes of faintness that lasted one to two hours and occurred about once a week. These episodes were unrelated to eating or activity and were not accompanied by other symptoms. The patient's only other symptoms were frequent episodes of hypernatremia resulting from impaired thirst perception, the development of cushingoid features, and progressive weight loss of 18 kg. She was hospitalized for assessment of faintness. On admission, her blood pressure and heart rate were normal but she still had hypothermia. Laboratory tests were normal except for a plasma glucose concentration (measured while she was fasting) of 55 mg per deciliter (3.1 mmol per liter), which prompted further evaluation of several aspects of glucose homeostasis. During the evaluation the patient continued to receive her usual treatment for hypopituitarism, except that her morning dose of 25 mg of cortisone acetate was delayed until the end of testing on each study day.

METHODS

The studies were approved by the ethics committee of the Faculty of Medicine of the University of Brussels, and the patient gave oral informed consent.

Plasma glucose was measured by a glucose oxidase method (Boehringer Mannheim, Mannheim, Germany), and glycosylated hemoglobin was measured by affinity high-pressure liquid chromatography (Bio-Rad Laboratories, Hercules, Calif.); the normal range is 4.0 to 6.5 percent. Plasma insulin, growth hormone, cortisol, glucagon, and pancreatic polypeptide were measured by radioimmunoassay.³⁻⁵ Plasma and urinary catecholamines were measured by high-pressure liquid chromatography with electrochemical detection.⁶

RESULTS

Base-Line Hormonal Status

Plasma growth hormone concentrations were undetectable, and plasma cortisol concentrations, measured approximately 14 hours after the evening dose of 12.5 mg of cortisone acetate, averaged 1.5 μ g per deciliter (41 nmol per liter), whereas plasma glucagon and catecholamine concentrations and urinary catecholamine excretion were within the normal range.

Glucose Homeostasis

Blood glucose was measured at least eight times per day throughout the 33-day hospitalization, and no hypoglycemia was detected. The lowest values occurred on waking; the mean (\pm SD) of these values was 58 ± 8 mg per deciliter (3.2 ± 0.5 mmol per liter). The mean blood glucose concentrations two hours and four hours after a meal were 110 ± 45 and 90 ± 35 mg per deciliter (6.1 ± 2.5 and 5.0 ± 1.9 mmol per liter), respectively. The mean value at 3 a.m. was 85 ± 28 mg per deciliter (4.7 ± 1.6 mmol per liter). The glycosylated hemoglobin value was 5.3 percent.

During a three-day fast, the patient's plasma glucose concentration fell from 66 mg per deciliter (3.7 mmol per liter) to 50 mg per deciliter (2.8 mmol per liter), and the plasma insulin concentration fell from

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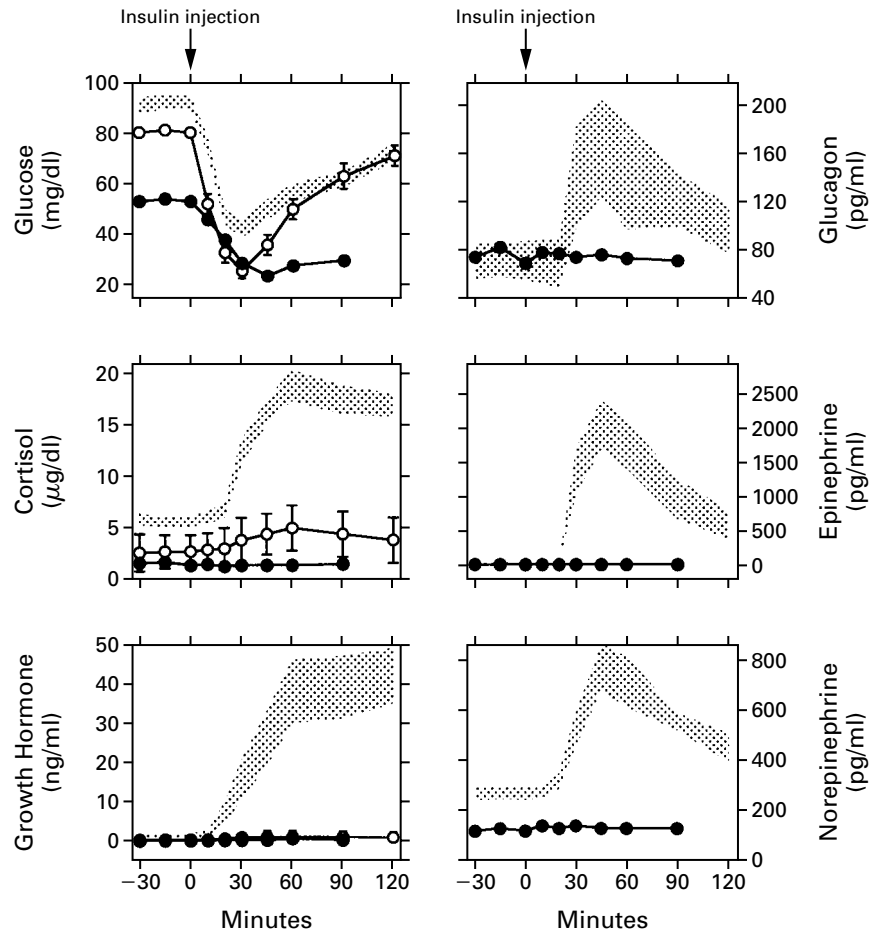


Figure 1. Changes in Plasma Glucose and Counterregulatory Hormone Concentrations Induced by the Intravenous Administration of Insulin in the Patient (Solid Circles) and in 16 Patients with Panhypopituitarism (Open Circles).

The values in the patients with hypopituitarism are means (\pm SE), and the stippled areas are the mean (\pm SE) values in normal subjects.⁷ The patient received 10 g of glucose intravenously at minute 30. To convert values for glucose to millimoles per liter, multiply by 0.0556; to convert values for cortisol to nanomoles per liter, multiply by 27.59; to convert values for epinephrine to picomoles per liter, multiply by 5.458; and to convert values for norepinephrine to nanomoles per liter, multiply by 0.0059.

12 μ U per milliliter (72 pmol per liter) to 5 μ U per milliliter (30 pmol per liter). No ketones were detected in urine during the fast.

The response to the ingestion of 100 g of glucose was abnormal and delayed, with peak plasma glucose and insulin concentrations of 181 mg per deciliter (10.1 mmol per liter) and 120 μ U per milliliter (720 pmol per liter), respectively, at 120 minutes. The plasma glucose concentration was 42 mg per deciliter (2.3 mmol per liter) at 240 minutes and 38 mg per deciliter (2.1 mmol per liter) at 300 minutes; the corresponding plasma insulin concentrations were 16 and 11 μ U per milliliter (96 and 66 pmol per liter). The patient had no sympathoadrenal symptoms during the hypoglycemia.

Effect of Acute Hypoglycemia on the Release of Counterregulatory Hormones

After the intravenous injection of 0.15 U of human insulin per kilogram of body weight, the plasma glucose concentration decreased from 54 mg per deciliter (3.0 mmol per liter) to 29 mg per deciliter (1.6 mmol per liter) in a 30-minute period. The patient was then given 10 g of glucose intravenously. Despite this injection, the plasma glucose concentration remained low for the next 60 minutes, when she received another 10-g injection of glucose and drank a cola. This experimentally induced hypoglycemia did not activate any hormonal counterregulatory response.

To be able to distinguish between deficiencies of growth hormone and cortisol and a deficiency of oth-

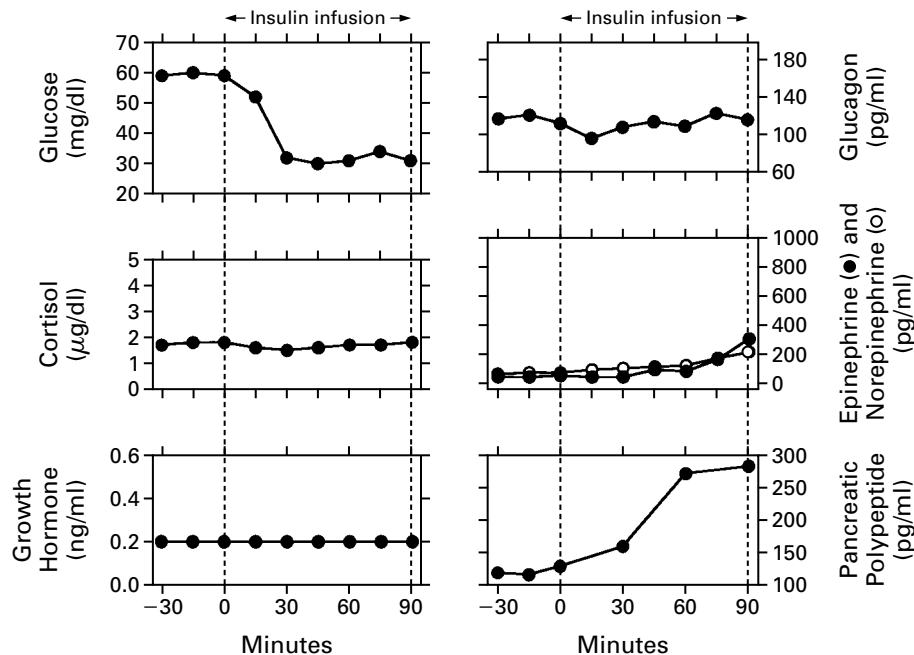


Figure 2. Plasma Glucose, Counterregulatory Hormone, and Pancreatic Polypeptide Concentrations during a Hypoglycemic-Clamp Study in the Patient.

To convert values for glucose to millimoles per liter, multiply by 0.0556; to convert values for cortisol to nanomoles per liter, multiply by 27.59; to convert values for epinephrine to picomoles per liter, multiply by 5.458; to convert values for norepinephrine to nanomoles per liter, multiply by 0.0059; and to convert values for pancreatic polypeptide to picomoles per liter, multiply by 0.239.

er counterregulatory hormones, we compared the patient's responses to hypoglycemia with those observed under similar experimental conditions in 16 patients with panhypopituitarism (mean age, 42 ± 10 years; body-mass index [the weight in kilograms divided by the square of the height in meters], 23.5 ± 2.7) (Fig. 1). In these patients the hypoglycemia was corrected as efficiently as in normal subjects, despite deficiencies of cortisol and growth hormone but presumably normal secretion of glucagon and catecholamines.⁸

Effect of a Hypoglycemic Clamp on the Release of Counterregulatory Hormones

We performed a hypoglycemic-clamp study in the patient to assess the response of counterregulatory hormones. During a primed constant intravenous infusion of insulin, administered at a rate of 4.5 mU per kilogram per minute for 90 minutes, the plasma glucose concentration decreased from 59 mg per deciliter (3.3 mmol per liter) to a mean of 31 ± 2 mg per deciliter (1.7 ± 0.1 mmol per liter) between minutes 30 and 90 (Fig. 2). There were no changes in plasma cortisol, growth hormone, or glucagon concentrations at any time. Plasma epinephrine and norepinephrine concentrations did not change during the first hour and then increased slightly, averaging 185 pg per milliliter (1009 pmol per liter) and 178 pg per mil-

liliter (1.05 nmol per liter), respectively, during the last 30 minutes of the clamp study. These values are 60 to 80 percent lower than those reported for normal subjects in whom hypoglycemia of a similar magnitude was induced.⁹⁻¹² The plasma pancreatic polypeptide concentration rose, reaching a maximal value of 281 pg per milliliter (67 pmol per liter) at 90 minutes. Throughout the test, the patient had moderate symptoms of neuroglycopenia (slow speech and drowsiness) but no sympathoadrenal symptoms.

Changes in Muscle Sympathetic-Nerve Activity in Response to Hypoglycemia, Chemoreceptor-Reflex Activation, and Baroreflex Deactivation

The patient's muscle sympathetic-nerve activity was recorded continuously from the peroneal nerve posterior to the fibular head with a nerve-traffic analyzer (Bioengineering Department, University of Iowa, Iowa City) during the hypoglycemic-clamp study and several other experimental conditions. Sympathetic bursts were identified by inspection of the neurogram.

The sympathetic-nerve activity and heart rate tended to decrease during hypoglycemia (from 42 bursts per minute to 30 bursts per minute and from 68 beats per minute to 63 beats per minute, respectively) (Fig. 3). In contrast, sympathetic-nerve activity increased (to 50 bursts per minute) during activation of the chemoreceptor reflex by maximal end-expiratory ap-

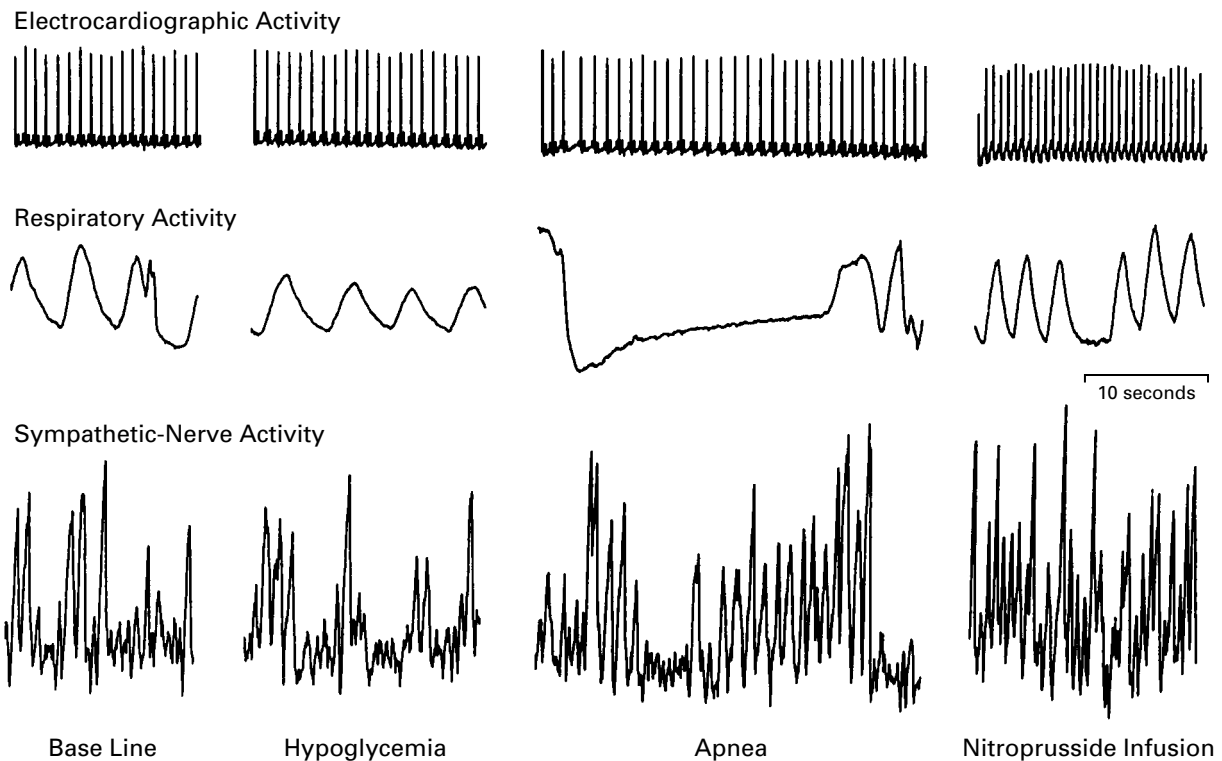


Figure 3. Electrocardiographic, Respiratory, and Muscle Sympathetic-Nerve Activity in the Patient at Base Line and during Hypoglycemia, Maximal End-Expiratory Apnea, and an Infusion of Sodium Nitroprusside.

The plasma glucose concentration was 30 mg per deciliter (1.7 mmol per liter) during hypoglycemia. Sodium nitroprusside ($0.4 \mu\text{g}$ per kilogram per minute) was infused intravenously for 10 minutes.

nea, especially at the end of the period of apnea, when stimulation of the chemoreceptor reflex is maximal. Baroreflex deactivation by an intravenous infusion of sodium nitroprusside ($0.4 \mu\text{g}$ per kilogram per minute) for 10 minutes also markedly increased the heart rate, to 94 beats per minute, and muscle sympathetic-nerve activity, to 84 bursts per minute.

Release of Counterregulatory Hormones in Response to Other Stimuli

To determine whether the defect in the release of counterregulatory hormone was specific for hypoglycemia, we evaluated the secretory capacity of the pancreatic alpha cells and the response of the autonomic nervous system to other stimuli. A 30-minute intravenous infusion of arginine induced a 7.5-fold rise in the plasma glucagon concentration and a 10-fold rise in the plasma insulin concentration. The plasma norepinephrine concentration increased sixfold, and the heart rate increased from 60 beats per minute to 92 beats per minute once the patient stood up after having been lying down for 10 minutes.

Other Tests

The rectal temperature, monitored continuously with a calibrated thermic probe, averaged $36.0 \pm 0.5^\circ\text{C}$.

Resting energy expenditure, determined by indirect calorimetry, was 65 percent of the predicted value adjusted for sex, age, and lean body mass.¹³

DISCUSSION

Sarcoid granulomas have a predilection for the hypothalamus, and patients with neurosarcoidosis frequently present with panhypopituitarism resulting from the loss of the ability of the hypothalamus to release certain hormones.¹⁴ These patients also commonly have central diabetes insipidus, impairment of thirst, and alterations in body temperature associated with a low metabolic rate.¹⁵ In addition to these symptoms, our patient had selective loss of the counterregulatory response to hypoglycemia.

The fact that our patient did not have hypoglycemia during a three-day fast is not surprising, because in normal subjects a selective, drug-induced deficiency of any counterregulatory hormone lowers plasma glucose concentrations after three days of fasting but does not cause hypoglycemia.¹⁶ On the other hand, the patient's late, persistent hypoglycemia after the ingestion of glucose is similar to that in patients with a combined deficiency of epinephrine and glucagon.¹⁷

Glucagon and epinephrine have a crucial role in

the recovery from insulin-induced hypoglycemia, whereas cortisol and growth hormone are of minor importance.^{7,18,19} The normal pattern of glucose recovery that we found in the patients with pituitary insufficiency but presumably normal responses of other counterregulatory hormones⁸ further illustrates this concept and points to defective catecholamine and glucagon responses as the factors responsible for the persistent hypoglycemia after intravenous injection of insulin in our patient.

Besides stimulating the release of pituitary hormones, the hypoglycemia-mediated activation of hypothalamic centers increases the activity of peripheral cholinergic and sympathetic neurons, which in normal subjects markedly increase the heart rate and muscle sympathetic-nerve activity.²⁰ In our patient, both the heart rate and sympathetic-nerve activity decreased during hypoglycemia, possibly as a consequence of unopposed parasympathetic activation. The fact that sympathetic reflexes involving brain-stem neurons (activation of the chemoreceptor reflex and deactivation of the baroreflex) were preserved suggests that the defective counterregulation was related to the hypothalamic lesion. The findings of normal increases in plasma norepinephrine and the heart rate during the postural test provide further evidence of the integrity of the sympathetic nervous system.

Although the role of the autonomic nervous system in mediating the secretion of glucagon during hypoglycemia in humans is controversial,^{21,22} the complete abrogation of glucagon release in our patient during hypoglycemia, together with the large increase induced by arginine, supports the concept that the autonomic nervous system has a major role in the alpha-cell response to hypoglycemia.

The glycemic threshold for the activation of counterregulation is about 65 mg per deciliter (3.6 mmol per liter) in normal subjects,⁹⁻¹² but it is lower in patients with intensively treated diabetes mellitus who have recurrent hypoglycemia,²³ in patients with insulinomas,¹⁰ and in normal subjects in whom hypoglycemia is induced 12 to 24 hours before testing.^{11,12} Therefore, the possibility that the low plasma glucose concentrations in our patient lowered the threshold for sympathoadrenal activation cannot be ruled out. However, this possibility is unlikely, because in normal subjects, after the plasma glucose concentration has been maintained at 52 mg per deciliter (2.9 mmol per liter) for 56 hours, stepwise lowering of the plasma glucose concentration to 45 mg per deciliter (2.5 mmol per liter) induces an increase in the secretion of catecholamines and glucagon.²⁴

A defect in the defense against hypoglycemia like that found in our patient may not be rare, but it is difficult to diagnose because of the absence of sympathoadrenal symptoms of hypoglycemia.

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