Neural Control of Counter-Regulatory Events during Glucopenia in Man

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ABSTRACT The effect of autonomic denervation on the metabolic and hormonal responses during intracellular glucopenia in man was investigated. 2-Deoxy-D-glucose (2 DG), a competitive inhibitor of glucose metabolism, was administered intravenously to nine normal volunteers and to five patients, three with complete cervical cord transection (C-6) and two with idiopathic orthostatic hypotension. Before, during, and after a 20 min infusion of 2 DG (50 mg/kg) plasma concentrations of glucose, lactate, FFA, total catecholamines, immunoreactive insulin (IRI), human growth hormone (HGH), and cortisol were determined for periods up to 150 min. In control subjects, the initial elevation of FFA, glucose, HGH, and cortisol corresponded with the rise in total catecholamines, with maximal levels attained at 60 min, lactate rose at a slower rate, reaching peak levels at 150 min; although no change in IRI was noted. In contrast, 2 DG-induced glucopenic stress in the autonomic denervated subjects was characterized by no detectable catecholamine release or significant rise in glucose, FFA, lactate, or IRI. However, HGH and cortisol responses in four of the five patients were of a similar or greater magnitude than controls.

These studies demonstrate that the integrity of the sympathoadrenomedullary axis is essential for the counter-regulatory response to intracellular glucopenia in man. Cortisol and HGH have no apparent role in these events.

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INTRODUCTION

It has long been recognized that the sympathetic nervous system plays an integral role in the regulation of carbohydrate and lipid metabolism. Considerable experimental evidence has accumulated indicating that the integrity of the sympathoadrenal axis is necessary for the hyperglycemic response to acute glucopenia (1–3). However, the relative importance of adrenal medullary catecholamines in the counter-regulatory events during hypoglycemia in man has yet to be defined (4). Since spinal cord transection or adrenergic blockade in animals prevented hypoglycemia, fatty acid mobilization, and the catecholamine secretory response to glucopenia (5, 6), it seemed appropriate to examine, in man, the effect of spinal cord transection and adrenergic insufficiency on the counter-regulatory response to acute glucose deprivation.

METHODS

Nine healthy volunteers, three female and six male, ages 19–25 yr served as control subjects. None had carbohydrate intolerance or a family history of diabetes mellitus and all were within 10% of their ideal weight (7).

Five patients, four men and one woman, with partial or complete autonomic dysfunction of various etiologies were studied. Three quadriplegic patients, S. G., R. D., and M. C., had segmental motor or sensory findings at the sixth spinal cord segment and bilateral long-tract signs. Two patients, L. I. and S. C. had autonomic dysfunction as evidenced by anhidrosis and severe orthostatic hypotension unaccompanied by reflex tachycardia. All patients maintained body weight for at least 6 mo before the study, were within 10% of their ideal weight (7), and were otherwise healthy. None had a family history of diabetes mellitus; however, one patient, L. I., had chemical diabetes mellitus. All subjects were studied in the postabsorptive state. After an initial control period, 2-deoxy-D-glucose (2 DG) 1

1 Abbreviations used in this paper: 2 DG, 2-deoxy-D-glucose; HGH, human growth hormone; IRI, immunoreactive insulin.
level of 90 mg/100 ml to a peak of 193 mg/100 ml at 120 min after the onset of 2 DG administration. Plasma lactate concentrations increased markedly (132% of control). Elevated levels of both glucose and lactate were sustained throughout the experimental period. There was a twofold rise in plasma FFA at 30 min and maximal levels of 1,613 μeq/liter were attained at 60 min. In contrast with glucose and lactate levels, FFA gradually fell toward control values during the final 90 min of the study. Plasma catecholamines rose significantly by 30 min, reaching a peak concentration of 1.7 μg/liter at 60 min, and remained elevated for the duration of the experiment.

A significant rise in plasma HGH and cortisol concentrations occurred between 30 and 60 min. Maximal levels of HGH (10.5±2.5 ng/ml) and cortisol (15±1.2 μg/100 ml) were observed at 60 and 90 min, respectively (mean ±SEM). The cortisol response was sustained for periods up to 150 min; HGH tended to fall toward baseline, but did not return to control levels.

Basal insulin levels ranged from 2.5 to 10.8 μU/ml with a mean of 10.4 μU/ml. Although a slight increase in mean IRI was noted at the end of the experiment, this change was not statistically significant from control values.

The individual curves of plasma glucose, lactate, FFA, catecholamines, HGH, cortisol, and IRI concentrations in patients with autonomic dysfunction are shown graphically in Fig. 1 and compared with the responses (mean ±SEM) of control subjects.

In marked contrast to the response seen in normal subjects, all patients studied exhibited a striking lack of plasma glucose, lactate, FFA, and catecholamine response to 2 DG infusion; insulin concentrations remained unchanged, as was seen in the control subjects. One quadriplegic patient, R. D., had unexplained elevated basal plasma lactate concentrations that progressively fell in the face of 2 DG stimulation.

Four of the five patients had a similar or greater HGH response when compared with controls. Three of these patients (S. C., S. G., and R. D.) had distinctly greater peak HGH levels than any single normal subject. The elderly female patient, L. I. with idiopathic orthostatic hypotension, exhibited no HGH rise. For all patients, the plasma cortisol response was comparable with that seen in the control subjects.

In two normal subjects, a comparison was made of the metabolic and hormonal responses to 2 DG with and without former administration of nicotinic acid, a specific inhibitor of catecholamine-induced lipolysis. Nicotinic acid effectively inhibited the FFA response to 2 DG, however, glucose, lactate, HGH, insulin, and cortisol as well as catecholamine responses were not affected.

RESULTS

The patterns of metabolic and hormonal responses to 2 DG infusion in nine healthy volunteers are indicated in Fig. 1. Plasma glucose rose progressively from a basal

![Figure 1 Patterns of metabolic and hormonal responses to 2 DG infusion (50 mg/kg for 20 min) in nine healthy volunteers, three quadriplegic patients (□, R.D.; ○, S. G.; ▲, M. C.), and two patients with idiopathic orthostatic hypotension (△, S. C.; О, L. I.). Zero time values represent the mean plasma concentrations of samples obtained at −15 and 0 min. Shaded areas indicate the mean ±SEM for the healthy volunteers.](image-url)
DISCUSSION

Much of our knowledge concerning the role of the autonomic nervous system in regulating carbohydrate and lipid metabolism in man has been derived from observations of the effects of various ganglionic, and adrenergic-blocking agents during glucopenic stress. However, the results of such studies are difficult to interpret since the degree of pharmacologic blockade cannot be quantitated precisely. Moreover, certain ganglionic and adrenergic-blocking agents actually induce depolarization or catecholamine release (15), and local alterations in blood flow could theoretically influence various metabolic events. To avoid the difficulties inherent in the use of pharmacological blockade, patients with either anatomical disruption of the sympathetic outflow tract or with severe adrenergic dysfunction were studied during intracellular glucopenia induced by 2 DG administration. Previous studies have shown that administration of this glucose analogue is associated with fatty acid mobilization, hyperglycemia, enhanced catecholamine excretion, and growth hormone release (16). In addition, 2 DG is an effective inhibitor of insulin release (17), and therefore, allows assessment of several metabolic parameters without the influence of concomitant changes in insulin secretion.

The degree of hyperglycemia seen in normal subjects after 2 DG infusion was similar to that observed by others (16). In contrast, blood glucose remained unchanged in all five patients with adrenergic insufficiency. The maintenance of normal glucose homeostasis in these patients suggests incomplete inhibition of glucose utilization; thus it is likely that the hyperglycemia seen in the normal subject is more directly related to the glycogenolytic effects of epinephrine rather than the direct result of 2 DG-induced inhibition of intracellular glucose metabolism.

Glucagon is also a potent stimulator of hepatic glycogenolysis (18) and 2 DG-induced glucopenia could result in enhanced glucagon secretion since insulin-induced hypoglycemia has been shown to enhance glucagon release (19). However, blood glucose remained unchanged for periods up to 150 min in all the patients studied. It is possible that the lack of catecholamine response may directly effect the ability to secrete glucagon (20). Alternatively, if glucagon was secreted in these patients, it did not play an important role in the acute counter-regulatory response to glucopenic stress. Finally, there is evidence that glucagon secretion is, in part, under neural control (21, 22) and thus disruption of neural pathways could result in inhibition of glucagon release.

Evidence exists that epinephrine, but not norepinephrine, is associated with significant increases in lactate production that is blunted after ganglionic blockade (23). In the absence of a detectable catecholamine response in the patients, there was no lactate rise, strongly implicating epinephrine as the primary stimulus for lactate mobilization.

The prompt rise in FFA, with concomitant elevations in plasma catecholamines observed in the normal subjects after 2 DG administration suggests that the enhanced lipolysis was causally related to sympathoadrenal stimulation. The effective blockade of lipolysis during glucopenia by nicotinic acid, a known inhibitor of catecholamine-induced lipolysis, in the face of elevated catecholamines, supports this concept. The lack of plasma FFA response seen in all the denervated patients indicates that neural-adrenal pathways must be intact if catecholamine-induced fatty acid mobilization is to occur during periods of acute glucose deprivation. A peripheral resistance to epinephrine in these patients is unlikely in that one patient had a normal FFA and glucose response to exogenously administered epinephrine.

The present study confirms the previously observed stimulatory effect of 2 DG administration on HGH secretion (16) and demonstrates 2 DG-induced glucopenia results in a significant and sustained cortisol secretory response. In spite of significant HGH and cortisol responses during glucopenia, no discernible changes in glucose or FFA were observed in the denervated patients indicating that these hormones play an insignificant role in the acute counter-regulatory response to glucopenic stress.

The study of the response to acute glucopenia in patients with various forms of sympathetic denervation has clearly demonstrated the importance of the autonomic nervous system in initiating the metabolic responses to hypoglycemia. In several animal studies, direct hypothalamic stimulation is associated with hyperglycemia (24), increased epinephrine (25), and glucagon (21) secretion. These observations suggest that stimulation of glucoreceptors in the hypothalamus leads to activation of neural pathways, which travel via sympathetic fibers, resulting in activation of hepatic glycogenolytic enzymes (26) as well as stimulation of epinephrine and glucagon secretion. The present experiments are in agreement with this hypothesis. The striking similarity in metabolic responses to 2 DG-induced glucopenia in the denervated subjects in this study and that previously observed in adrenalectomized subjects (2, 16), strongly implicates epinephrine as the primary hormone necessary for the glycogenolytic and lipolytic responses seen after acute hypoglycemia. The precise counter-regulatory role of glucagon and direct neural stimulation of hepatic glycogenolysis deserves further consideration.
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