Mechanisms of Postprandial Glucose Counterregulation in Man

PHYSIOLOGIC ROLES OF GLUCAGON AND EPINEPHRINE VIS-A-VIS INSULIN IN THE PREVENTION OF HYPOGLYCEMIA LATE AFTER GLUCOSE INGESTION

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ABSTRACT The transition from exogenous glucose delivery to endogenous glucose production late after glucose ingestion is not solely attributable to dissipation of insulin and, therefore, must also involve factors that actively raise the plasma glucose concentration—glucose counterregulatory factors. We have shown that the secretion of two of these, glucagon and epinephrine, is specific for glucose ingestion and temporally related to the glucose counterregulatory process. To determine the physiologic roles of glucagon and epinephrine in postprandial glucose counterregulation, we produced pharmacologic interventions that resulted in endogenous glucagon deficiency with and without exogenous glucagon replacement, adrenergic blockade, and adrenergic blockade coupled with glucagon deficiency starting 225 min after the ingestion of 75 g of glucose in normal subjects. Also, we assessed the effect of endogenous epinephrine deficiency alone and in combination with glucagon deficiency late after glucose ingestion in bilaterally adrenalectomized subjects. Glucagon deficiency resulted in nadir plasma glucose concentrations that were ~30% lower ($P < 0.01$) than control values, but did not cause hypoglycemia late after glucose ingestion. This effect was prevented by glucagon replacement. Neither adrenergic blockade nor epinephrine deficiency alone impaired the glucose counterregulatory process. However, combined glucagon and epinephrine deficiencies resulted in a progressive fall in mean plasma glucose to a hypoglycemic level late after glucose ingestion; the final glucose concentration was 40% lower ($P < 0.02$) than the control (epinephrine deficient) value in these patients, and was nearly 50% lower ($P < 0.001$) than the control value and ~30% lower ($P < 0.05$) than the glucagon-deficient value in normal subjects.

We conclude (*a*) the transition from exogenous glucose delivery to endogenous glucose production late after glucose ingestion is the result of the coordinated diminution of insulin secretion and the resumption of glucagon secretion. (*b*) Epinephrine does not normally play a critical role in this process, but enhanced epinephrine secretion compensates largely and prevents hypoglycemia when glucagon secretion is deficient.

INTRODUCTION

The physiologic factors that regulate the transition from exogenous glucose delivery to endogenous glucose production and thus prevent hypoglycemia late after glucose ingestion have not been fully defined. Our study of the specificity, temporal relationships, and quantitative aspects of the neuroendocrine responses to glucose ingestion (1) indicates that this transition is not solely the result of the dissipation of insulin and, therefore, must also involve a factor or factors that actively raise the plasma glucose concentration—glucose counterregulatory factors. Among the candidate counterregulatory factors, sympathetic neural norepinephrine release is not specific for glucose ingestion and does not occur in temporal relation to the counterregulatory process (1), growth hormone secre-

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tion is temporally related but of marginal specificity (1), and cortisol secretion is unaltered (1). Furthermore, the hyperglycemic actions of both growth hormone (2) and cortisol (3) are too slow. On the other hand, resumption of glucagon secretion (after initial suppression) and late epinephrine secretion are both specific for glucose ingestion and temporally related to the counterregulatory process (1). Also, glucagon and epinephrine are rapidly acting counterregulatory hormones (4, 5). Although the increments in plasma epinephrine late after glucose ingestion are substantial (1, 6), plasma epinephrine concentrations do not commonly achieve the threshold level required to affect basal glucose metabolism (7).

Given these findings, we hypothesized that the transition from exogenous glucose delivery to endogenous glucose production late after glucose ingestion is the result of coordinated diminution of insulin secretion and resumption of glucagon secretion, and that epinephrine does not normally play a critical role. Based upon the known physiology of hypoglycemic glucose counterregulation (8–10), however, we further hypothesized that epinephrine compensates largely for deficient glucagon secretion. To test these hypotheses, we produced pharmacologic interventions that resulted in endogenous glucagon deficiency with and without exogenous glucagon replacement, combined α- and β-adrenergic blockade, and adrenergic blockade coupled with glucagon deficiency late after glucose ingestion in normal human subjects. Also, we assessed the effect of endogenous epinephrine deficiency alone and combined with glucagon deficiency late after glucose ingestion in bilaterally adrenalectomized subjects.

METHODS

Subjects. Eight normal adults (seven males and one female), ages 23–28 yr, consented to participate in these studies. All were within 16% of ideal body weight (Metropolitan Life Insurance Co. tables). Five patients (two males, three females) who had previously undergone bilateral adrenalectomies for the treatment of Cushing's disease also participated. They ranged in age from 24 to 57 yr and in ideal body weight from 63 to 174%. Each was shown to have a markedly deficient plasma epinephrine response to insulin-induced hypoglycemia. Mineralocorticoid therapy with 9 α-fluorohydrocortisone (Florinef) was continued unchanged; glucocorticoid therapy was changed to dexamethasone (Decadron), 0.5 mg in the morning and 0.25 mg in the late afternoon, 3–4 d prior to study. This included a 0.5-mg dose of dexamethasone at 0530 h on the day of study. All subjects gave informed, written consent for these studies, which were approved by the Washington University Human Studies Committee.

Study protocol. Normal subjects were studied on five occasions, separated by at least 1 wk, as outpatients at the Washington University Clinical Research Center. Adrenalectomized patients were studied as inpatients at the Clinical Research Center, generally on two consecutive days. The sequence of the studies was varied.

After an overnight fast, subjects remained supine through 1200 h. Intravenous catheters for blood sampling and drug infusions were inserted at 0530 h. Blood samples were drawn at 0600, 0615, 0630 and 0645 h, glucose ingestion (75 g) was begun at 0655 h, and blood samples were drawn every 10 min from 0700 through 1200 h. Heart rates and blood pressures were determined immediately after each blood sample.

Interventions, begun at 1040 h and continued through 1200 h (225 through 305 min after the start of glucose ingestion), included intravenous infusions of: (*a*) saline; (*b*) somatostatin (250 $\mu g \cdot hr^{-1}$) with insulin replacement (100 $\mu U \cdot kg^{-1} \cdot min^{-1}$); (*c*) somatostatin with insulin and glucagon replacement (1.0 $ng \cdot kg^{-1} \cdot min^{-1}$ in 6, 1.5 $ng \cdot kg^{-1} \cdot min^{-1}$ in 2); (*d*) phentolamine (0.5 $mg \cdot min^{-1}$ after injection of 5.0 mg over 3 min), an α-adrenergic antagonist, and propranolol (0.08 $mg \cdot min^{-1}$ after an injection of 5.0 mg over 3 min), a β-adrenergic antagonist; and (*e*) phentolamine-propranolol plus somatostatin (with insulin replacement) in normal subjects. In adrenalectomized subjects, interventions were limited to (*a*) saline and (*b*) somatostatin (with insulin replacement). Comparable volumes of all agents were infused with an infusion pump.

Somatostatin was purchased from Beckman Instruments, Bioproducts Division, Fullerton, CA; glucagon and regular insulin from Eli Lilly Co., Indianapolis, IN; phentolamine (Regitine) from Ciba-Geigy Corp., Pharmaceuticals Division, Summit, NJ; and propranolol (Inderal) from Ayerst Laboratories, New York, NY.

Analytical methods. As previously referenced (1), plasma insulin, glucagon, cortisol, and growth hormone were measured by radioimmunoassay; plasma epinephrine and norepinephrine by single isotope derivative assay; and plasma glucose by a glucose oxidase method. Antiserum 30K was used to measure glucagon. For purposes of this report, plasma epinephrine values below the analytical detection limit of 10 pg/ml were assigned that value for calculating the means.

Statistical methods. Mean values at comparable time points were compared with *t* tests for paired or unpaired data where appropriate. P values < 0.05 were considered to indicate significant differences. Data are expressed as the mean±SE in this manuscript.

RESULTS

Effects of glucagon deficiency and glucagon replacement. Somatostatin infusion (with insulin replacement) from 225 through 305 min after glucose ingestion resulted in decrements in plasma glucose to levels significantly below control (saline infusion) values from 255 through 305 min, the final sampling point (Fig. 1). Mean plasma glucose fell from a pre-intervention value of 89±5 mg/dl to a nadir of 62±3 mg/dl at 275 min, significantly ($P < 0.01$) lower than the corresponding control value of 85±6 mg/dl. From its nadir, plasma glucose rose slightly to 68±3 mg/dl at 305 min, still significantly ($P < 0.01$) lower than the control value of 88±4 mg/dl. This effect was prevented by glucagon replacement. Somatostatin infusion (with insulin replacement) plus glucagon infusion from 225 through 305 min after glucose ingestion resulted in

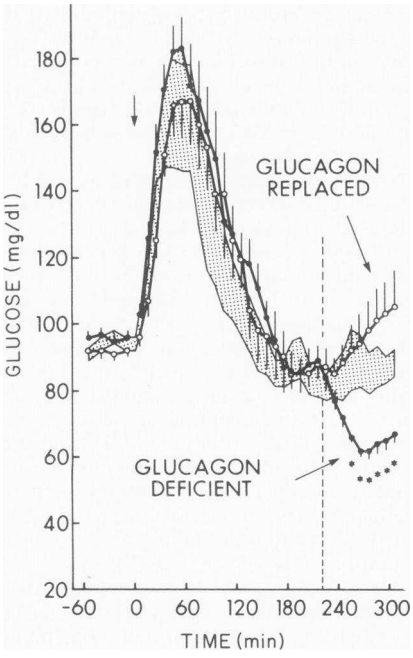

FIGURE 1 Plasma glucose concentrations before and after ingestion of 75 g of glucose (arrow) in eight normal human subjects. The stippled area is one SE around the mean when saline was infused from 225 through 305 min, the closed symbols mean (±SE) values when somatostatin (with insulin replacement) was infused from 225 through 305 min (glucagon deficient), and the open symbols mean (±SE) values when somatostatin (with insulin replacement) was infused and glucagon was replaced from 225 through 305 min (glucagon replaced). The asterisks denote data points significantly different from the corresponding points during saline infusion.

plasma glucose concentrations that were not significantly different from control values (Fig. 1), although they tended to exceed control values at the end of the study. This was true even when the data from the two subjects who received the larger dose of glucagon were excluded.

Somatostatin infusion caused a small decrease, averaging ~15%, whereas addition of glucagon caused a similarly small increase, averaging ~18%, in measured immunoreactive glucagon (Fig. 2). Plasma insulin concentrations were identical to control values (saline infusion) during infusion of somatostatin with insulin replacement with or without glucagon replacement (Fig. 2). During somatostatin infusion, the mean plasma epinephrine concentration rose to a peak of 265±62 pg/ml, significantly ($P < 0.02$) higher than the corresponding control value of 106±22 pg/ml, at 285 min after glucose ingestion (Fig. 2), likely a response to the decrement in plasma glucose (Fig. 1). Plasma epinephrine did not exceed control values during somatostatin with glucagon replacement (Fig. 2). Plasma norepinephrine was unaffected by somatostatin with or without glucagon replacement (Fig. 2).

Plasma growth hormone was suppressed and plasma cortisol unaffected during infusion of somatostatin with and without glucagon replacement (Fig. 3). The infusions did not significantly affect heart rate or blood pressure (Fig. 3).

Effects of adrenergic blockade and adrenergic blockade coupled with glucagon deficiency. Infusion of phentolamine with propranolol to produce combined α- and β-adrenergic blockade from 225 through 305 min after glucose ingestion did not significantly affect the plasma glucose concentration (Fig. 4). Infusion of phentolamine and propranolol with somatostatin (with insulin replacement) resulted in decrements in plasma glucose levels significantly below control values from 245 through 305 min (Fig. 4). Although the glucose decrement from the pre-intervention plateau (175–215 min) during these combined infusions (to 62±6% of the pre-intervention plateau) was significantly ($P < 0.05$) greater than that (to 71±4% during somatostatin [with insulin replacement] alone) of the pre-intervention plateau, the mean nadir glucose concentrations at 275 min were not different (62±6 and 62±3 mg/dl, respectively).

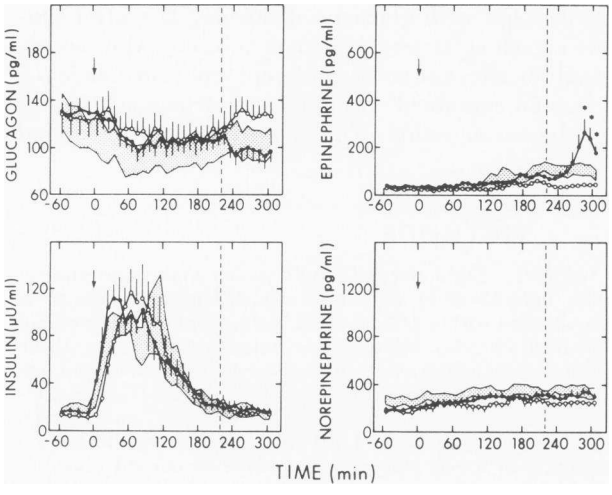

FIGURE 2 Plasma glucagon, insulin, epinephrine, and norepinephrine concentrations before and after ingestion of 75 g of glucose (arrows) in eight normal human subjects. The stippled areas are one SE around the mean when saline was infused from 225 through 305 min, the closed symbols mean (±SE) values when somatostatin (with insulin replacement) was infused from 225 through 305 min (glucagon deficient) and the open symbols mean (±SE) values when somatostatin (with insulin replacement) was infused and glucagon was replaced from 225 through 305 min (glucagon replaced). The asterisks denote data points significantly different from the corresponding points during saline infusion.

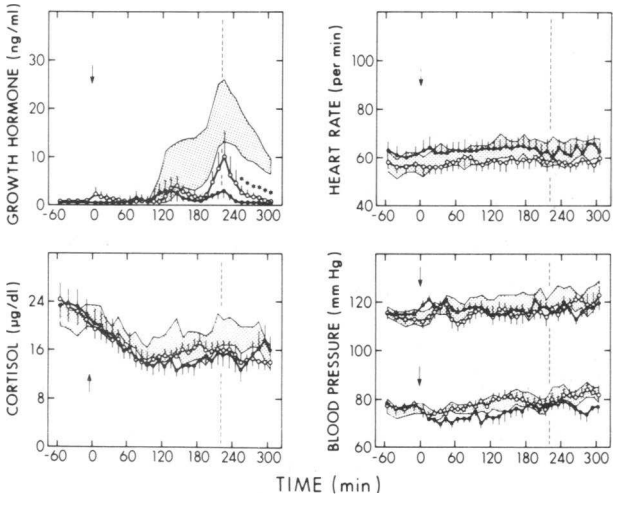

FIGURE 3 Plasma growth hormone concentrations, cortisol concentrations, heart rate, and systolic (above) and diastolic (below) blood pressure before and after ingestion of 75 g of glucose (arrows) in eight normal human subjects. The stippled areas are one SE around the mean when saline was infused from 225 through 305 min, the closed symbols mean (±SE) values when somatostatin (with insulin replacement) was infused from 225 to 305 min (glucagon deficient), and the open symbols mean (±SE) values when somatostatin (with insulin replacement) was infused and glucagon was replaced from 225 through 305 min (glucagon replaced). The asterisks denote data points significantly different from the corresponding points during saline infusion.

Phentolamine-propranolol infusion did not alter plasma glucagon, the glucagon response to somatostatin, plasma insulin, or plasma insulin during infusion of somatostatin (with insulin replacement) (Fig. 5). However, phentolamine-propranolol infusion resulted in substantial changes in epinephrine and norepinephrine (Fig. 5). Phentolamine-propranolol infusion alone from 225 through 305 min after glucose ingestion was associated with an increment in mean plasma epinephrine to a peak of 394±79 pg/ml at 275 min, significantly ($P < 0.01$) higher than the corresponding control value of 113±22 pg/ml. This was likely the result of decreased clearance of epinephrine from the circulation produced by propranolol (11) coupled with accelerated epinephrine secretion in response to a decreasing plasma glucose concentration (1, 12) late after glucose ingestion. When the additional secretory stimulus of a sharp fall in plasma glucose to lower levels was added by the superimposition of somatostatin infusion, mean plasma epinephrine rose markedly, reaching a peak of 2,010±803 pg/ml at 295 min. Phentolamine-propranolol infusion late after glucose ingestion was also associated with increments in mean plasma norepinephrine to a peak of 695±64 pg/ml at 305 min, significantly ($P < 0.01$) higher than the corresponding control value of 330±40 pg/ml. This could have been the result of several factors, including decreased norepinephrine clearance from the circulation produced by propranolol (11) and increased norepinephrine release produced by phentolamine (13)—antagonism of presynaptic α-adrenergic receptors that mediate suppression of norepinephrine release, sympathetic reflex activation triggered by a decrease in blood pressure, or both—as well as increased release nonspecifically stimulated by ingestion (1). As with epinephrine, when the additional stimulus of a sharp fall in plasma glucose to lower levels was added by the superimposition of somatostatin infusion, mean plasma norepinephrine rose even higher, reaching a peak of 915±181 pg/ml at 305 min.

Phentolamine-propranolol infusion alone resulted in significant increments in plasma growth hormone but did not impair somatostatin-induced suppression of plasma growth hormone (Fig. 6). Heart rates tended to decrease and systolic and diastolic blood pressures

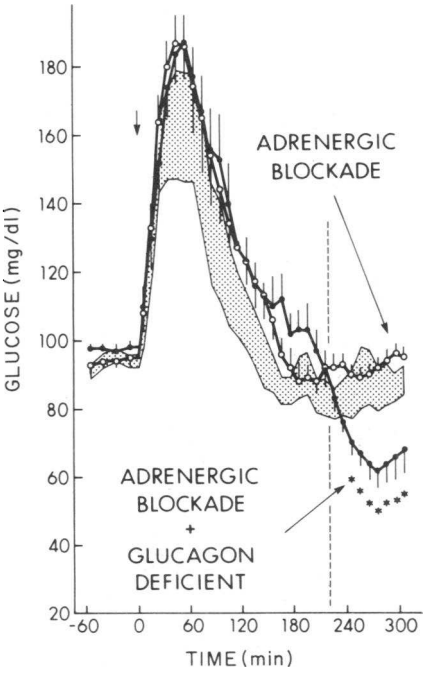

FIGURE 4 Plasma glucose concentrations before and after ingestion of 75 g of glucose (arrow) in eight normal human subjects. The stippled area is one SE around the mean when saline was infused from 225 through 305 min, the open symbols mean (±SE) values when phentolamine-propranolol was infused from 225 through 305 min (adrenergic blockade), and the closed symbols mean (±SE) values when phentolamine-propranolol and somatostatin (with insulin replacement) were infused from 225 through 305 min (adrenergic blockade plus glucagon deficient). The asterisks denote data points significantly different from the corresponding points during saline infusion.

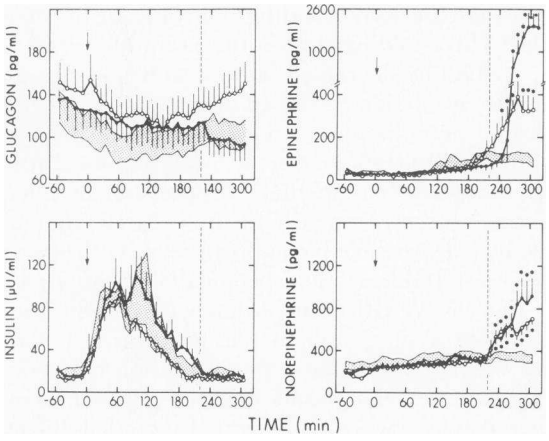

FIGURE 5 Plasma glucagon, insulin, epinephrine, and norepinephrine concentrations before and after ingestion of 75 g of glucose (arrows) in eight normal human subjects. The stippled areas are one SE around the mean when saline was infused from 225 through 305 min, the open symbols mean (±SE) values when phentolamine-propranolol was infused from 225 through 305 min (adrenergic blockade), and the closed mean (±SE) values when phentolamine-propranolol and somatostatin (with insulin replacement) were infused from 225 through 305 min (adrenergic blockade plus glucagon deficient). The asterisks denote data points significantly different from the corresponding points during saline infusion.

decreased significantly during phentolamine-propranolol infusion; these were unaffected by the superimposition of somatostatin (Fig. 6).

Effects of epinephrine deficiency and combined epinephrine and glucagon deficiency. Although nadir glucose concentrations late after glucose ingestion tended to be lower in epinephrine-deficient (bilaterally adrenalectomized) patients compared with normal subjects, mean plasma glucose levels were not significantly different (Fig. 7). In contrast, somatostatin infusion (with insulin replacement) from 225 through 305 min after glucose ingestion led to a progressive decline in plasma glucose in epinephrine-deficient patients (Fig. 7). From a mean pre-intervention value of 98±10 mg/dl, plasma glucose fell to 47±9 mg/dl at 305 min, the final sampling point. The latter value was significantly ($P < 0.02$) lower than the 305 min value of 78±10 mg/dl during the control study (saline infusion) in these patients and also lower than the final values of 88±4 mg/dl in normal individuals infused with saline ($P < 0.001$) (Fig. 1) and 68±3 mg/dl in normal individuals infused with somatostatin ($P < 0.05$) (Fig. 1). Nonspecific symptoms occurred in four of the five patients. In one patient, lethargy, interpreted as evidence of neuroglycopenia, occurred at 285 min; the study was discontinued and intravenous glucose given. This patient's final plasma glucose value (35 mg/dl) was used in calculating the mean values at 295 and 305 min shown in Fig. 7. The final mean would have likely been lower had the study been continued with this patient.

Plasma glucagon levels in epinephrine-deficient patients were not significantly different from those of normal subjects. As in normal subjects, the somatostatin-induced decrements in measured immunoreactive glucagon were small (Fig. 8). The patients exhibited mild hyperinsulinemia at baseline and marked hyperinsulinemia after glucose ingestion, which was probably the result of the inclusion of obese patients. However, plasma insulin levels during somatostatin infusion with insulin replacement were not higher than those during saline infusion (Fig. 8). In the adrenalectomized patients, plasma epinephrine levels did not rise above baseline values (18±4 pg/ml) after glucose ingestion, despite the production of hypoglycemia during late somatostatin infusion (Fig. 8). Plasma norepinephrine concentrations were not significantly different from those of normal subjects; again, an apparent rise followed glucose ingestion. Interestingly, plasma norepinephrine did not rise despite hypoglycemia during somatostatin infusion late after glucose ingestion.

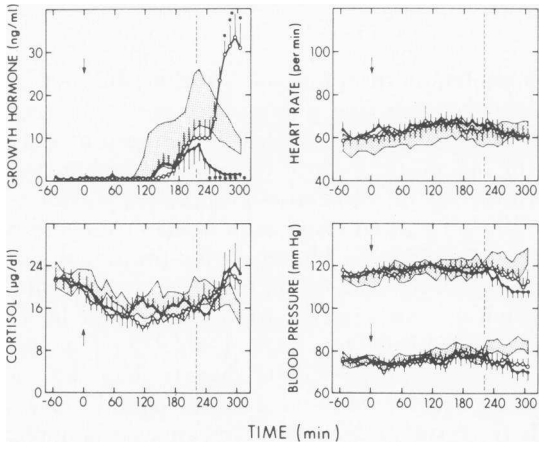

FIGURE 6 Plasma growth hormone concentrations, cortisol concentrations, heart rate, and systolic (above) and diastolic (below) blood pressure before and after ingestion of 75 g of glucose (arrows) in eight normal human subjects. The stippled areas are one SE around the mean when saline was infused from 225 through 305 min, the open symbols mean (±SE) values when phentolamine-propranolol was infused from 225 through 305 min (adrenergic blockade), and the closed symbols mean (±SE) values when phentolamine-propranolol and somatostatin (with insulin replacement) were infused from 225 through 305 min (adrenergic blockade plus glucagon deficient). The asterisks denote data points significantly different from the corresponding points during saline infusion.

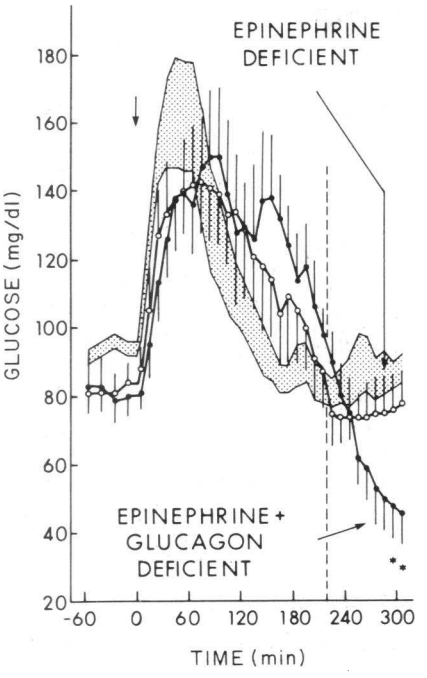

FIGURE 7 Plasma glucose concentrations before and after ingestion of 75 g of glucose (arrow) in five bilaterally adrenalectomized human subjects. The stippled area is one SE around the mean for normal subjects when saline was infused from 225 through 305 min. The open symbols are mean (±SE) values when saline was infused from 225 through 305 min in adrenalectomized subjects (epinephrine deficient) and the closed symbols are mean (±SE) values when somatostatin (with insulin replacement) was infused from 225 through 305 min in adrenalectomized subjects (epinephrine plus glucagon deficient). The asterisks denote data points significantly different from the corresponding points during saline infusion in the adrenalectomized subjects.

Following glucose ingestion, plasma growth hormone levels did not differ from normal in the epinephrine-deficient patients. Growth hormone concentrations were suppressed by somatostatin (Fig. 9). Plasma cortisol was, of course, unmeasurable in the patients (Fig. 9). Heart rates were higher and blood pressures tended to be lower than those of the normal subjects in these patients (Fig. 9). However, it should be noted again that these patients were not matched to the normal subjects in this study.

DISCUSSION

These data demonstrate that, in human subjects, glucagon actively supports the plasma glucose concentration late after glucose ingestion and that epinephrine is not critical to this counterregulatory process when glucagon secretion is intact, but becomes critical when glucagon secretion is suppressed.

Glucagon deficiency, produced by infusion of somatostatin during the glucose counterregulatory phase, resulted in nadir plasma glucose concentrations that were ~30% lower than control values late after glucose ingestion. This was not due to hyperinsulinemia resulting from the replacement dose of insulin infused with somatostatin. Peripheral venous plasma insulin concentrations were not different from those during saline infusion. Furthermore, since the hepatic portal venous to peripheral venous insulin ratio is normally ~2.5:1 (14–16) and since the portal and peripheral insulin concentrations would be identical if insulin secretion were totally suppressed by somatostatin, there must have been portal hypoinsulinemia during the somatostatin-insulin infusions. It is notable, although not unique to this study, that somatostatin produced a clear effect on the plasma glucose concentration but only a small decrease in measured immunoreactive glucagon. This may have been due, in part, to the fact that glucagon was measured in peripheral venous plasma rather than the more biologically relevant portal venous system. More important, perhaps, is the fact that a large proportion of the immunoassayable material measured with the antiserum used is not biologically active, 3,500-D glucagon (17). Thus, the somatostatin-induced suppression of biologically active glucagon was probably substantial and perhaps complete.

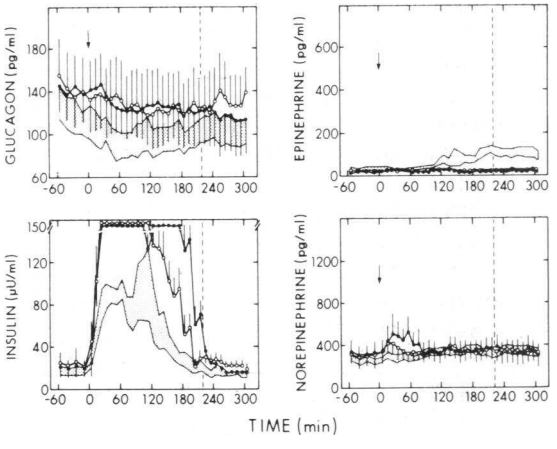

FIGURE 8 Plasma glucagon, insulin, epinephrine, and norepinephrine concentrations before and after ingestion of 75 g of glucose (arrows) in five bilaterally adrenalectomized human subjects. The stippled areas are one SE around the mean for normal subjects when saline was infused from 225 through 305 min. The open symbols are mean (±SE) values when saline was infused from 225 through 305 min in adrenalectomized subjects (epinephrine deficient) and the closed symbols are mean (±SE) values when somatostatin (with insulin replacement) was infused from 220 through 305 min in adrenalectomized subjects (epinephrine plus glucagon deficient).

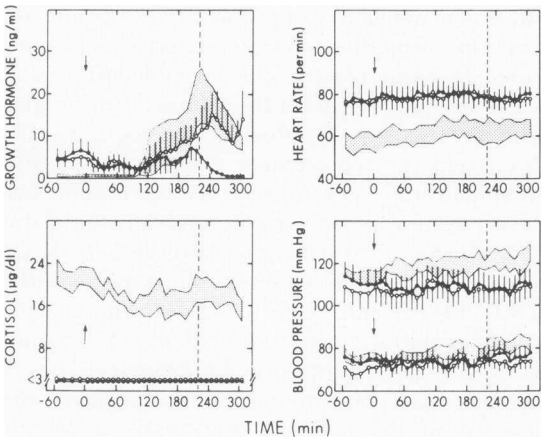

FIGURE 9 Plasma growth hormone concentrations cortisol concentrations, heart rate, and systolic (above) and diastolic (below) blood pressure before and after ingestion of 75 g of glucose (arrows) in five bilaterally adrenalectomized human subjects. The stippled areas are one SE around the mean for normal subjects when saline was infused from 225 through 305 min. The open symbols are mean (±SE) values when saline was infused from 225 through 305 min in adrenalectomized subjects (epinephrine deficient) and the closed symbols are mean (±SE) values when somatostatin (with insulin replacement) was infused from 225 through 305 min in adrenalectomized subjects (epinephrine plus glucagon deficient).

The lower nadir plasma glucose concentrations late after glucose ingestion were the result of glucagon deficiency and this is evidenced by the fact that this effect on plasma glucose was prevented by glucagon replacement. This was not due to failure to administer somatostatin, since plasma growth hormone was suppressed. Furthermore, this was not the result of excessive glucagon administration. The portal venous to peripheral venous plasma glucagon ratio is ~1.5:1 in humans (14–16) and 3,500-D glucagon is preferentially extracted by the liver (18, 19). Since somatostatin preferentially suppresses the secretion of 3,500-D glucagon in dogs (20, 21), a glucagonoma patient (22), and normal humans[1], and since peripheral venous plasma glucagon increased only 18% during glucagon replacement, portal glucagon was underreplaced. If so, why was the decrement in plasma glucose prevented and why did plasma glucose levels tend to be higher than control values during partial glucagon replacement? The likely explanation is the concomitant portal venous hypoinsulinemia discussed earlier.

To avoid possible effects on glucose absorption, we deferred pharmacologic interventions until 225 min after glucose ingestion. The isotopic measurements of glucose absorption of Radziuk et al. (23) indicate that, for a 75-g glucose dose, glucose absorption is complete before that time. Prevention of lower glucose levels by glucagon replacement provides further evidence that the reduction in glucose levels produced by somatostatin was the result of glucagon deficiency per se, and not of an inhibitory effect of somatostatin on glucose absorption.

In contrast to the clear, albeit partial, effect of glucagon deficiency, neither combined α- and β-adrenergic blockade nor the epinephrine-deficient state (bilaterally adrenalectomized, glucocorticoid-replaced, mineralocorticoid-replaced subjects) impaired the glucose counterregulatory process late after glucose ingestion.

To summarize, these data support our hypothesis that the transition from exogenous glucose delivery to endogenous glucose production late after glucose ingestion is the result of coordinated diminution of insulin secretion and resumption of glucagon secretion, and that epinephrine does not normally play a critical role. Yet, glucagon does not appear to be the sole counterregulatory factor since the lower plasma glucose concentrations plateaued and began to rise despite glucagon deficiency late after glucose ingestion.

That epinephrine might compensate partially for deficient glucagon secretion and prevent hypoglycemia is supported by the observed enhanced epinephrine secretory response, but is not convincingly supported by the data from intervention with the adrenergic antagonists, phentolamine and propranolol, during glucagon deficiency. However, these are competitive antagonists that, through a variety of mechanisms (11, 13), result in markedly elevated plasma catecholamine concentrations as demonstrated by the present data. It is quite possible that at least some of the effects of these antagonists might be overcome by massively elevated, endogenous catecholamine levels. Clearly, it would be inappropriate to draw a negative conclusion from these data alone. Thus, the data from epinephrine-deficient (bilaterally adrenalectomized) subjects are particularly relevant.

When coupled with glucagon deficiency, epinephrine deficiency resulted in a progressive fall in mean plasma glucose to a hypoglycemic level late after glucose ingestion. The mean glucose concentration at the final sampling point was 40% lower than the control value in those patients (epinephrine deficiency alone), nearly 50% lower than the control values in normal subjects, and ~30% lower than the glucagon-deficient value in normal subjects. These findings support our second hypothesis that epinephrine normally compensates largely for deficient glucagon secretion and prevents hypoglycemia late after glucose ingestion when glucagon secretion is deficient. This counterregulatory

[1] Jaspan, J. B. Personal communication.

redundancy plausibly explains the rarity of postprandial hypoglycemia even after ingestion of a large carbohydrate load.

These findings underscore the limitations of the use of phentolamine and propranolol in physiologic studies. Although positive findings can be readily interpreted, negative findings must be interpreted cautiously. Furthermore, positive findings may underestimate the magnitude of the normal adrenergic effect.

It is reasonable to assume that dissipation of insulin is important to the glucose counterregulatory process late after glucose ingestion. The present data do not refute this assumption, although the question was not addressed directly. However, the finding that the counterregulatory process is disrupted by combined glucagon and epinephrine deficiencies, despite normal peripheral insulin levels and probable portal hypoinsulinemia, indicates that the counterregulatory factors are normally of critical importance. In their absence, the glucose counterregulatory process fails to occur despite dissipation of insulin.

These data document the critical roles of glucagon and epinephrine in the glucose counterregulatory process late after glucose ingestion. They do not support, but do not exclude, the possibility that other hormones, neural mechanisms, or an autoregulatory process may be involved. Clearly, one need not invoke these and if they are involved, they are not sufficiently potent to prevent hypoglycemia when secretion of the critical counterregulatory hormones—glucagon and epinephrine—is deficient.

The parallels between the physiology of hypoglycemic glucose counterregulation (8–10)—the mechanisms that promote recovery from hypoglycemia—and the presently demonstrated physiology of nonhypoglycemic glucose counterregulation—the mechanisms that blunt decrements in plasma glucose, prevent hypoglycemia, and restore euglycemia—are striking. Neither are solely explicable on the basis of dissipation of insulin; glucagon plays a primary counterregulatory role in both, epinephrine compensates largely for deficient glucagon secretion in both, and counterregulation fails to occur only in the absence of both glucagon and epinephrine in both. It should be noted, however, that both of the models studied in detail involve rapid glucose counterregulation. The mechanisms of more gradual glucose counterregulation may or may not differ.

From the data presented we conclude that the transition from exogenous glucose delivery to endogenous glucose production late after glucose ingestion is the result of coordinated diminution of insulin secretion and resumption of glucagon secretion, and that epinephrine does not normally play a critical role. However, enhanced epinephrine secretion compensates largely and prevents hypoglycemia when glucagon secretion is deficient.

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