Review
Glucose Counterregulation in Man

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The central nervous system requires a continuous supply of glucose, its metabolic fuel under most physiologic conditions, and cannot extract glucose from the circulation against a concentration gradient. Thus, maintenance of the plasma glucose concentration is crucial to survival. It has long been appreciated that insulin is the glucose regulatory hormone; it suppresses glucose production and accelerates glucose utilization and, thus, lowers the plasma glucose concentration. In contrast, despite a plethora of candidates, the precise physiologic mechanisms that raise the plasma glucose concentration have not been clearly defined. What are the mechanisms that promote recovery from hypoglycemia and that prevent the occurrence of hypoglycemia?

Theoretically, glucose counterregulation could be accomplished by hormonal signals, neural signals, glucose autoregulation, or a combination of these mechanisms. Hormonal signals could include a decrement in circulating insulin or increments in circulating counterregulatory hormones such as glucagon, epinephrine, cortisol, or growth hormone. Neural signals could include norepinephrine released from sympathetic postganglionic neurons. Lastly, evidence that hepatic glucose release is an inverse function of the circulating glucose concentration, independent of hormonal and perhaps neural signals,[1–4] raises the possibility that glucose autoregulation may play a role in glucose counterregulation.

The rise in plasma glucose following hypoglycemia produced by the i.v. injection of insulin has been the model used most extensively to dissect the mechanisms of acute glucose counterregulation. Since the onset of glucose counterregulation can clearly occur while plasma insulin concentrations are still substantially elevated,[5] a decrease in plasma insulin cannot be the sole explanation for glucose recovery in this model. Furthermore, this observation indicates that glucose recovery can occur in the presence of elevated insulin levels. On the other hand, insulin-induced hypoglycemia stimulates the release of glucagon, epinephrine, cortisol, growth hormone, and norepinephrine,[5] all potentially important glucose counterregulatory factors.

In a series of studies[6–8] summarized in Figure 1, we have examined the effect of isolated deficiencies of the secretion or action of potentially important glucose counterregulatory factors on recovery from insulin-induced hypoglycemia in normal subjects. These studies demonstrate that recovery from insulin-induced hypoglycemia is essentially normal when glucagon secretion is intact, and is partially impaired (by approximately 40%) when glucagon secretion is inhibited. Glucose recovery from moderate hypoglycemia is impaired little, if at all, during pharmacologic adrenergic blockade and in the total absence of epinephrine. However, when glucagon secretion is inhibited, glucose recovery is markedly impaired during adrenergic blockade and fails to occur in the absence of epinephrine. Thus, glucagon normally plays a primary role in recovery from insulin-induced hypoglycemia, and glucagon deficiency is largely compensated for by enhanced adrenomedullary epinephrine secretion. Glucose recovery fails to occur only in the absence of both glucagon and epinephrine. The acute release of cortisol and/or growth hormone is not critical. Lastly, neither the release of sympathetic neural norepinephrine nor glucose autoregulation is sufficiently potent to promote glucose recovery, and neither of these need to be invoked to explain glucose recovery from insulin-induced hypoglycemia.

My earlier statement that glucose recovery from moderate hypoglycemia is impaired little, if not at all, during adrenergic blockade requires further comment. The effects of β-adrenergic antagonists on insulin-induced hypoglycemia have been examined in at least 13 studies;[6,8–19] these are summarized in Table 1. β-Adrenergic blockade was associated with a significantly lower plasma glucose nadir after insulin injection in only one[11] of these 13 studies. Indeed, in the 12 studies showing data, the mean (± SE) nadir plasma

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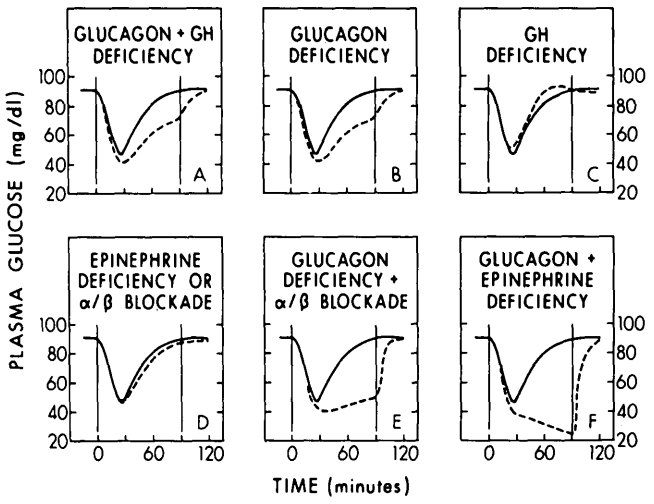

FIGURE 1. Plasma glucose curves during insulin-induced hypoglycemia in normal subjects during control studies (solid lines) and as modified (dashed lines) by: (A) somatostatin infusion; (B) somatostatin plus growth hormone infusion; (C) somatostatin plus glucagon infusion; (D) phentolamine plus propranolol infusion or studies in bilaterally adrenalectomized patients; (E) somatostatin plus phentolamine and propranolol infusion; and (F) somatostatin infusion in bilaterally adrenalectomized patients. These idealized curves were derived from data in refs. 6–8.

glucose concentration was identical (34 ± 3 mg/dl) during control studies and during administration of antagonist. Significant impairment of plasma glucose recovery was reported in 6 of these 13 investigations but not in the remaining 7. A plausible explanation for this apparent discrepancy comes from the observation that plasma glucose concentrations at nadir tended to be lower in those studies reporting an effect of β-adrenergic antagonist. Thus, more severe hypoglycemia may have unmasked an adrenergic component to glucose recovery. Supporting this interpretation is the fact that glucose recovery during administration of β-adrenergic antagonists, expressed as percent of recovery during the corresponding control study, was significantly correlated with the plasma glucose nadir (r = 0.657, P ~ 0.02) in the 12 evaluable studies.

The critical point, in my judgment, is that major glucose recovery occurs during β-adrenergic blockade (as it does during suppression of glucagon secretion). Glucose recovery at 120 min averaged 88% of control in all studies and 74% of control in the six studies reporting impaired glucose recovery during β-adrenergic blockade. Clearly, some counterregulatory factor in addition to the catecholamines makes an important contribution to recovery from insulin-induced hypoglycemia. For reasons developed earlier, that factor is glucagon. To repeat, glucose recovery from hypoglycemia fails to occur only in the absence of both glucagon and epinephrine.[7,8]

The precise mechanisms of nonhypoglycemic glucose counterregulation, i.e., those that reverse physiologic decrements in the plasma glucose concentration and prevent hypoglycemia, have not been determined. It seems likely that suppression of insulin secretion is a factor. Several groups of investigators[20–22] have begun to examine the effect of more physiologic, nonhypoglycemic decrements in plasma glucose, again produced by i.v. insulin, on plasma concentrations of potentially important glucose counterregulatory factors. Our experience[22] in human subjects is summarized in Figure 2. Controlled reductions of the plasma glucose concentration from 95 to 60 mg/dl stimulated significant early increments in plasma epinephrine, norepinephrine, and glucagon and later increments in plasma cortisol and growth hormone. Interestingly, plasma glucose reductions from 200 to 100 mg/dl were also associated with small increments in circulating epinephrine, norepinephrine, glucagon, and growth hormone.

These findings[20–22] indicate that there is no absolute plasma glucose concentration threshold for activation of hormonal glucose counterregulatory systems and that nei-

TABLE 1
Effect of β-adrenergic antagonists on insulin-induced hypoglycemia

Reference	Year	N	β-Adrenergic antagonist	Insulin dose (U/kg)	Glucose nadir (mg/dl) Control	Glucose nadir (mg/dl) Antagonist	Glucose nadir Significantly decreased	Glucose recovery Significantly decreased	Glucose recovery % of control (120 min)
9	1976	6	Propranolol	0.15	~39	~36	No	Yes	~72
10	1976	8	Propranolol*	0.10	23	23	No	Yes	58
11	1976	11	Propranolol†	0.10	~36	~32	Yes	Yes	~78
12‡	1979	7	Propranolol§	0.15–0.25	29	23	No	Yes	~22¶
13	1979	8	Propranolol	0.10	—‖	—‖	No	Yes	—‖
14	1979	7	Propranolol	0.15	25	25	No	Yes	61
15**	1974	5	Propranolol	0.15	~30	~30	No	No	~110
16	1975	12	Propranolol	0.15	~33	~33	No	No	~93
17	1976	5	Penbutolol	0.10	30	35	No	No	90
18	1978	8	Metoprolol	0.10	~29	~29	No	No	~92
19††	1978	4	Propranolol	0.06	~56	~52	No	No	~128‡‡
6	1979	4	Propranolol	0.05	35	40	No	No	~90
8	1979	6	Propranolol§§	0.04	48	51	No	No	~86
							r = 0.657, P ~ 0.02		
							r = 0.607, P < 0.05		

* Altenolol had no effect. † Metoprolol also exerted an effect; acebutolol decreased the glucose nadir only. ‡ Patients with insulin-dependent diabetes. § Metoprolol had no effect. ¶ At 190 min (~100% at 120 min). ‖ Data not shown. ** After 84 h of fasting. †† Dogs. ‡‡ At 80 min. §§ With phentolamine.

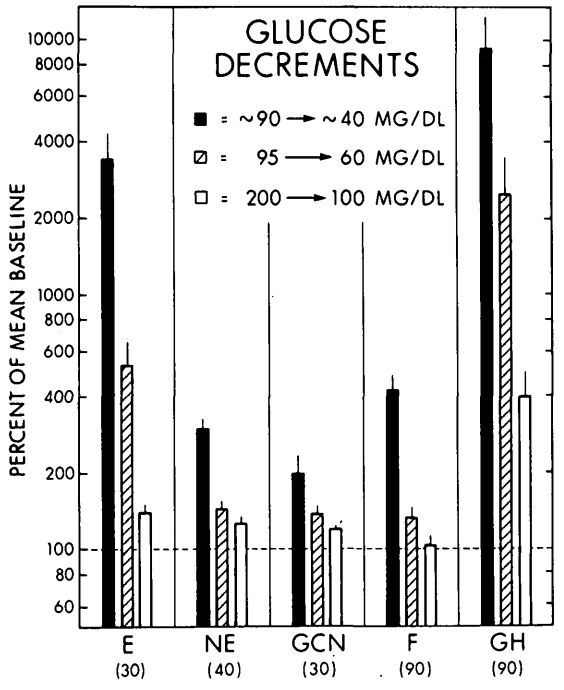

FIGURE 2. Mean (±SE) maximal plasma concentrations of epinephrine (E), norepinephrine (NE), glucagon (GCN), cortisol (F), and growth hormone (GH) resulting from insulin-induced hypoglycemia (solid columns), plasma glucose decrements from 95 to 60 mg/dl (cross hatched columns), and plasma glucose decrements from 200 to 100 mg/dl (open columns). The numbers in parentheses indicate the time, in minutes, after initiation of the change in plasma glucose. These data were derived from refs. 5 and 22.

ther the absolute glucose decrement nor the rate of glucose decline are primary determinants of the magnitude of the counterregulatory response. Rather, the magnitude of the counterregulatory response is primarily an inverse function of the absolute plasma glucose concentration. Thus, glucose decrements to hypoglycemic levels trigger a large hormonal response, decrements from high to low physiologic levels trigger an intermediate response, and decrements from hyperglycemic to normal levels trigger a small hormonal response.

The fact that studies employing a broad range of nadir glucose concentrations[22] (Figure 2) indicate that the absolute plasma glucose concentration achieved is the primary determinant does not exclude the logical possibility that the absolute glucose decrement, the rate of glucose decline, or both, are secondary determinants of the magnitude of the counterregulatory response. It is only reasonable to expect that very small or very slow plasma glucose decrements would not be associated with measurable increments in the circulating concentrations of counterregulatory factors. Whether the absence of significant increments in the plasma concentrations of these factors in studies employing smaller and/or slower plasma glucose decrements[4,20] reflects no stimulation of release or release too small to significantly elevate the mean absolute plasma levels, the magnitude of the counterregulatory response would appear to be less than that occurring when similar plasma glucose levels are achieved more rapidly from higher baseline levels. Thus, although this hypothesis remains to be rigorously tested, it is reasonable to conclude that the absolute glucose decrement and the rate of glucose decline are secondary determinants of the magnitude of the counterregulatory response.

Although clearly important to an understanding of the physiologic mechanisms of activation of the counterregulatory systems, the relevance of these findings to nonhypoglycemic glucose counterregulation and the prevention of hypoglycemia remains to be established. The plasma epinephrine concentrations achieved in association with the 95–60-mg/dl plasma glucose decrements averaged 230 pg/ml,[22] clearly high enough to produce biologic effects.[23] Particularly in view of the experience with hypoglycemic glucose counterregulation discussed earlier, it is reasonable to postulate a biologic role for the increase, albeit small, in glucagon secretion associated with this more physiologic decrement in plasma glucose. Indeed, the recent report of Gauthier, Vranic, and Hetenyi[24] that the small decrement in plasma glucose caused by phlorizin-induced glycosuria in dogs is markedly enhanced by concomitant suppression of glucagon secretion indicates that glucagon may well play a physiologic role in nonhypoglycemic glucose counterregulation.

In conclusion, hormonal signals, specifically glucagon and epinephrine, are the critical factors in recovery from hypoglycemia, and available evidence is compatible with a central role for these hormones in nonhypoglycemic glucose counterregulation (the prevention of hypoglycemia) as well, although the latter has not been fully defined. Obviously, this does not exclude permissive roles for other hormones, such as cortisol and growth hormone, nor does it exclude facilitative roles for neural and/or autoregulatory mechanisms. It should be emphasized that the quantitative contribution of each of these mechanisms to maintenance of the fasting plasma glucose concentration remains to be determined.

The mechanisms of hypoglycemic glucose counterregulation in patients with diabetes mellitus have not been systematically defined. However, increments in plasma epinephrine, norepinephrine, growth hormone, and cortisol occur with physiologic as well as hypoglycemic decrements in plasma glucose in such patients.[20,22] The model of normal hypoglycemic glucose counterregulation discussed in this review provides a conceptual basis for plausible, testable hypotheses concerning the mechanisms of hypoglycemic glucose counterregulation in patients with diabetes and those of nonhypoglycemic glucose counterregulation in diabetics and nondiabetics.

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