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Review Articles

Insulin-Counteracting Hormones: Their Impact on Glucose Metabolism

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Insulin-counteracting hormones exerting a 'diabetogenic' action include growth hormone, glucagon, adrenaline and cortisol. Well-known clinical syndromes exist (e.g. acromegaly, glucagonoma, phaeochromocytoma and Cushing's syndrome), in which elevated plasma levels of the respective hormones can induce an insulin-resistant state. Furthermore, acute illnesses including trauma, surgical procedures, myocardial infarction and decompensated diabetes mellitus [1–4] may be associated with a stress hormone response and impaired glucose tolerance. In diabetic ketoacidosis the combination of insulin-deficiency, hypovolaemia with dehydration, hyperosmolality, and acidosis impairs glucose metabolism per se [4–6] and via elevation of circulating stress hormones [7]. Among these hormones, plasma glucagon, growth hormone, cortisol, and noradrenaline are frequently increased five- to tenfold, and adrenaline up to fifty times normal [4, 7–9]. In patients with poor metabolic control of their diabetic state, glucagon and growth hormone levels may also be chronically elevated and thereby contribute to the metabolic derangements [10, 11]. On the other hand, insulin-counteracting hormones also increase in response to hypoglycaemia to restore glucose homeostasis by modulating either glucose production, glucose utilization, or both [12–15].

The relative importance of these hormones, and their physiological and pathogenic significance or relation to insulin-counteracting events are still under debate. Evidence has accumulated in recent years which indicates that, under certain experimental conditions, exogenous administration of these hormones adversely affects glucose tolerance and insulin sensitivity [16–19]. Apart from their impact on glucose metabolism they are all known to exert lipolytic and ketogenic actions, particularly when elevated to high physiological concentrations in association with insulin deficiency [19–24]. The various direct metabolic effects of 'anti-insulin' hormones have led to the concept that they may play a major role in the pathogenesis of diabetes mellitus and the development of diabetic ketoacidosis [7, 25, 26]. However, whether elevated plasma concentrations of these hormones are mere associated findings or are causally related to poor metabolic control is still unclear. Their actual role as aggravating factors for diabetic ketoacidosis is, at least, supported by the markedly retarded development of metabolic derangements in some diabetic subjects after insulin withdrawal and after suppression of 'diabetogenic hormone' release or pituitary ablation [4, 26, 27]. Besides the opposing arguments concerning the significance of the 'diabetogenicity' of insulin-counteracting hormones in human pathophysiology, their individual or synergistic impact on carbohydrate metabolism in the normal state is even more controversial and remains only partly elucidated [28].

Growth Hormone

In acromegalic patients with high circulating levels of growth hormone (GH), glucose intolerance and impaired sensitivity to the action of insulin are well recognized [29]. A significant impairment of glucose metabolism has also been observed following the administration of pharmacological doses of GH [17, 30]. There is only limited experimental evidence that physiological changes in GH concentration are an important regulator of glucose homeostasis. GH has been infused in normal subjects in amounts sufficient to raise circulating GH levels to those seen in mild stress, exercise, sleep or in diabetic patients with deranged metabolic control [9, 31–33]. Insulin sensitivity of peripheral tissues decreases within 2 to 12 h [34] after a transient increase [34]. Thus, in contrast to glucagon and adrenaline, which both antagonize the effect of insulin acutely, the insulin antagonistic effect of GH takes several hours to develop. This impairment of glucose metabolism is pre-

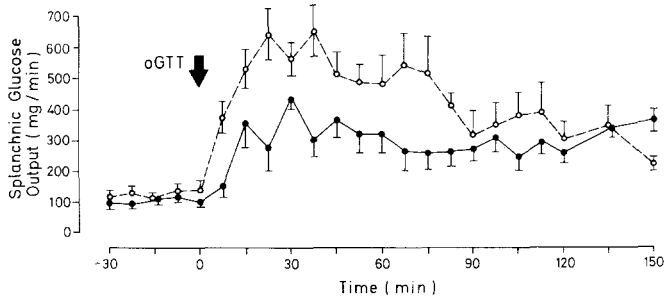

Fig. 1. Effect of short-term exposure to growth hormone (320–550 pmol/l) on the hepatic handling of an oral glucose load (oGTT; 75 g) as estimated in healthy subjects by means of the liver vein catheter technique. Results are presented as mean ± SEM; n = 6. The higher amounts of glucose released into the systemic circulation following growth hormone infusion (○---○, integrated splanchnic glucose output, 64 ± 7 g/150 min) compared with the control study without growth hormone infusion (●—●, 43 ± 3 g/150 min, $p < 0.02$) provides evidence for the major role of the liver in the development of glucose intolerance by moderate elevations in plasma growth hormone

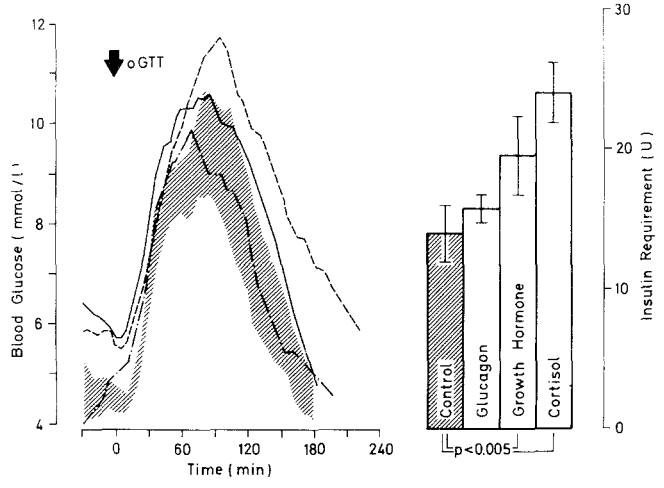

Fig. 2. Effect of long-term (12 h) exposure to 'diabetogenic' hormones upon mean blood glucose and insulin requirement following an oral glucose load (oGTT; 50 g) in insulin-dependent diabetic patients controlled by an automated glucose-controlled insulin infusion system. Plasma hormone concentrations were raised by intravenous administration of glucagon (—·—), growth hormone (---) or cortisol (–·–) to levels seen in diabetic patients with severe derangements of metabolic control (121 ± 18 pmol/l, 605 ± 50 pmol/l, and 718 ± 55 nmol/l, respectively). Shaded areas represent mean ± SD blood glucose concentration and amount of insulin required to utilize the given glucose load in intra-individual control studies without hormone administration. Exposure to growth hormone and cortisol caused a 40% and 90% increase in insulin requirement respectively [37]

dominantly caused by a post-receptor defect in insulin action, whereas insulin binding to its receptor is only slightly diminished after prolonged exposure to GH [34]. Little information is yet available regarding the effect of GH on hepatic glucose metabolism. Besides an early 'insulin-like' effect of GH on hepatic glucose metabolism [34, 35], the suppressibility of hepatic glucose production by insulin is diminished [34]. This delayed development of GH-induced insulin resistance at the level of the liver is also demonstrated by the reduced capacity of the liver to dispose of orally administered glucose. Estimating splanchnic glucose metabolism by means of the hepatic venous catheter technique [36], a significantly higher proportion of a given glucose load is released into the systemic circulation when serum GH levels are raised within the physiological range (Fig. 1). Whereas B cell responsiveness to an identical glycaemic stimulus is unaltered by GH [34], the augmented hyperglycaemic response to glucose loading is responsible for the observed enhancement of pancreatic insulin secretion. Also insulin-dependent diabetic patients, when tightly controlled by a glucose-controlled insulin infusion system, exhibit marked alterations in the disposal of an oral glucose load following prolonged exposure to moderate elevations of plasma GH concentrations (Fig. 2; [37]). However, since the attenuated development of hyperglycaemia during pharmacological suppression of GH secretion is not reversed by simultaneous GH replacement in diabetic patients after insulin withdrawal [21], elevated GH levels in diabetic ketoacidosis do not seem to contribute to insulin resistance in this state.

In insulin-induced hypoglycaemia, the rise in GH concentration does not seem to be essential for the counter-regulatory response to hypoglycaemia [38]. However, because of the characteristic delay in the effect of GH on glucose utilization, the increase in GH secretion may be an important factor in the genesis of post-hypoglycaemic glucose intolerance [39].

Glucagon

The impact of glucagon on carbohydrate metabolism is a matter of great controversy [40]. In normal man basal hepatic glucose production is augmented by either exogenous glucagon or stimulated endogenous glucagon [41, 42]. This effect is short-lived due to feedback inhibition via hyperglycaemia and stimulated insulin secretion. Any physiological effect of glucagon on glucose tolerance [16] has been questioned on the basis of various experimental approaches with exogenous glucagon administration and suppression of endogenous glucagon secretion [43, 44]. Thus, in normal man [45] and insulin-treated diabetic patients [37, 46], even significant hyperglucagonaemia fails to impair the disposal of an oral glucose load (Fig. 2). In diabetic patients with absolute or relative insulin deficiency, however, glucagon may actually cause metabolic deterioration [16]. This is especially important, as glucagon secretion is abnormal in diabetic patients and is particularly high during diabetic ketoacidosis or in periods of very poor control [8, 10, 47]. Since pharmacological suppression of glucagon markedly attenuates the development of hyperglycaemia and hyperketonaemia in diabetic subjects after acute insulin withdrawal [21, 26], this hormone may be a major factor in the initiation of metabolic derangement.

There is no doubt that elevated glucagon concentrations, when unaccompanied by appropriate increases in insulin secretion, can result in sustained hyperglycaemia [48]. Excessive elevations in plasma glucagon, such as those seen in the glucagonoma syndrome, may however cause mild glucose intolerance even when sufficient endogenous insulin is available.

One argument for the diabetogenic action of glucagon and, to a lesser extent, of growth hormone in insulin-dependent diabetic patients [49] has been the blood glucose lowering effect of somatostatin which suppresses these hormones. For this reason, the inhibitory action of somatostatin upon the release of glucagon has been advocated as being potentially useful in the treatment of insulin-dependent diabetic subjects [7, 49]. However accumulating evidence suggests that, apart from the suppression of 'diabetogenic' hormone release, slowing of intestinal nutrient absorption contributes considerably to the diminished insulin requirements and the delayed rise in blood glucose concentration during somatostatin administration [28, 50, 51]. It must not be overlooked that, in healthy men as well as in diabetic patients with a limited insulin reserve, the concomitant suppression of insulin secretion characterizes somatostatin as a further, potentially 'diabetogenic' hormone [52].

In insulin-induced hypoglycaemia the increased hepatic glucose production precedes augmented glucagon secretion, which may therefore not be essential for the restoration of glucose homeostasis [53]. Moreover, the action of glucagon is short-lived and its contribution to impaired glucose tolerance in response to insulin-induced hypoglycaemia ('Somogyi effect', [39]) is therefore of no pathogenic relevance.

Catecholamines

Adrenaline affects carbohydrate homeostasis not only by its effect on the liver and on peripheral tissues but also by altering insulin secretion [54, 55]. It is well established that the intravenous administration of adrenaline causes a deterioration in glucose tolerance in healthy man by inducing peripheral and hepatic insulin resistance. These effects, which are indicated by a transient increase in hepatic glucose production but a fall in glucose clearance, are mediated by β-adrenergic mechanisms [54, 56]. Furthermore, adrenaline inhibits insulin secretion via an α-adrenergic action [55] so that the expected rise in plasma insulin concentration during hyperglycaemia fails to occur. After glucose ingestion the inhibitory effect of adrenaline on insulin secretion, and its insulin-counteracting effect on hepatic glucose disposal, are largely counter-balanced by significant hyperglycaemia resulting in unchanged insulin secretion and near-normal glucose extraction by the liver [57]. In contrast to adrenaline, noradrenaline is only weakly hyperglycaemic in normal and insulin-deficient man [58].

Much of the present knowledge about the action of catecholamines on carbohydrate metabolism has been gained from studies in diabetic patients. Elevations of adrenaline and noradrenaline have been reported in insulin-dependent diabetic patients at the time of diagnosis, during ketoacidosis or periods of poor metabolic control [12]. This catecholamine excess, which can be rapidly corrected by rehydration and insulin treatment [4, 12], may in turn exaggerate and maintain the metabolic abnormality of diabetic ketoacidosis. Our own observations made in diabetic man emphasize the role of adrenaline as the hormone exerting the most pronounced insulin-opposing action [46]. The potency of adrenaline in producing a deterioration in glucose metabolism may explain the known positive relationship between 'stress' of various causes and the onset of deranged control of the diabetic state [59]. Even emotional factors, which can be accompanied by catecholamine release, may aggravate the metabolic state of diabetic patients who are otherwise well controlled by insulin therapy [60].

The importance of adrenergic mechanisms in the initiation of the counter-regulatory response to hypoglycaemia has been underlined by the observation that, of all the hormones studied, only the increment in plasma catecholamines precedes the increase in hepatic glucose production [53]. However, since adrenergic receptor blockade does not modify glucose counter-regulation following insulin-induced hypoglycaemia [61], catecholamines may not be essential to glucose homeostasis which may be equally well restored by glucagon alone [62]. Adrenaline becomes critical, however, when glucagon secretion is impaired [61].

Cortisol

As observed in Cushing's syndrome, excess glucocorticoid adversely affects glucose tolerance and may cause fasting hyperglycaemia [63]. In healthy man, in whom circulating cortisol levels are increased to those seen in major stress by an infusion of cortisol, glucose clearance decreases after 2 h of hormone exposure [64], whereas the insulin antagonizing effect of cortisol upon hepatic glucose production takes several hours to occur [65]. Recent studies by Rizza et al. on the mechanism by which cortisol affects glucose metabolism have shown that it exerts its insulin-antagonistic effect by affecting post-receptor actions of insulin [65]. Moreover, glucocorticoids induce a rapid and persistent reduction in binding of insulin to its receptor, indicating that receptor alterations are also operative [66]. In insulin-dependent diabetic subjects a more rapid and exaggerated hyperglycaemic effect of cortisol has been shown to be due to an early stimulation of hepatic glucose production [67], which probably results from the failure of compensatory portal hyperinsulinaemia in these patients. This explanation may also apply to the pheno-

menon of apparent hyper-responsiveness of insulin-dependent patients to the other 'anti-insulin' hormones [67]. When insulin *is* sufficiently available in these subjects, elevation of plasma cortisol concentrations to the range usually observed in severe derangements of diabetic control [4] does not materially affect glucose tolerance [46]. After prolonged exposure to cortisol, however, its insulin-counteracting effect on glucose disposal becomes manifest (Fig. 2; [37]).

With respect to the role of cortisol in the restoration of blood glucose concentration after insulin-induced hypoglycaemia, it appears that augmented hormone secretion plays no essential, but rather a permissive, role for this response [38]. This is explained by the protracted time-course of cortisol secretion following hypoglycaemia and the delayed tissue response to elevated plasma levels.

Thyroid Hormones, Prolactin and Calcitonin

Interference of these hormones with carbohydrate metabolism has been advocated in man. Insulin resistance with an increased incidence of impaired glucose tolerance is observed in thyrotoxic patients [68–70]. Inadequate B cell responsiveness may contribute to the development of glucose intolerance in hyperthyroidism [68, 70]. A diabetogenic effect has also been proposed for prolactin, as a decrease in glucose tolerance with subsequent improvement following pharmacological prolactin suppression has been described in hyperprolactinaemic patients [71]. However, there is no clinical evidence that prolactin is involved in producing impaired glucose metabolism in diabetic man [72]. Calcitonin in pharmacological doses has also been accused of being diabetogenic in man as it inhibits basal and glucose-stimulated insulin secretion [73, 74]. On present evidence however, neither calcitonin nor prolactin appear to be of physiological or pathological relevance to the regulation of carbohydrate metabolism in man.

In Summary

'Diabetogenic' hormones may impair carbohydrate metabolism directly (growth hormone, cortisol, glucagon, and adrenaline) or indirectly by reducing insulin secretion (adrenaline, thyroid hormones and somatostatin). The overall picture emerges that, among these hormones, adrenaline is the most potent factor in inducing peripheral and hepatic insulin resistance. This may explain the fact, well-known to the practicing physician, that stress of various forms may cause acute deterioration of diabetic control. Growth hormone and cortisol, even in high physiological concentrations, impair the hepatic uptake and peripheral utilization of glucose. Whereas the action of adrenaline is of rapid onset, growth hormone and cortisol do not affect glucose disposal for several hours. Elevated plasma glucagon concentrations do not alter glucose tolerance acutely nor after long-term exposure, as long as insulin is sufficiently available. In insulin-deficient diabetic patients however, glucagon may become a potent glucogenic hormone and cause deterioration of glucose tolerance. Furthermore, the insulin-antagonistic effect of 'diabetogenic' hormones on glucose turnover is also reflected in a potent stimulation of both lipolysis and ketogenesis in insulin-deficient man. These metabolic effects are antagonized by appropriate insulin availability [46, 75]. Since, after acute insulin deprivation in insulin-dependent diabetic patients, glucagon is the only hormone that rises during the initial period of progressive hyperglycaemia and hyperketonaemia [76, 77], excess of the other counter-regulatory hormones may not be essential for the initiation but rather for the perpetuation of metabolic disturbances seen in diabetic ketoacidosis. Since elevated plasma levels of counter-regulatory hormones appear to be secondary to insulin deficiency and volume depletion, sufficient insulin and fluid replacement remain the corner-stone of adequate treatment of the decomposed diabetic state [78, 79]. Pharmacological modification of the counter-regulatory hormones by the use of blocking agents as a form of therapeutic intervention does not appear to be either feasible or theoretically correct.

Regarding the role of insulin-counteracting hormones in hypoglycaemia, adrenaline (and possibly, alternatively, glucagon) appear to constitute the major hormonal mediators of the acute counter-regulatory response in restoring euglycaemia, while growth hormone exerts its anti-insulin effect in the post-hypoglycaemic period only.

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