EDITORIAL REVIEW

Cortisol and catabolism: a new perspective

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Catabolic hormones

In normal man there is a fine balance between anabolic and catabolic processes. Both are under hormonal control, with insulin acting as the prime anabolic agent and a group of hormones, glucagon, the two catecholamines and glucocorticoids, regulating catabolism. Growth hormone has a mixed anabolic and catabolic function directed primarily at amino acid and protein conservation. Recently there has been considerable interest in the role of these different hormones in pathological catabolic states, such as uncontrolled diabetes, severe burns, trauma and the postoperative state. As accurate methods have appeared for the measurement of these hormones, so each has been spotlighted and their roles have become more clearly defined. Recently glucagon has received much attention, for a period being considered as part of the cause of diabetes (Unger & Orci, 1975), and it has also been considered to be of major importance in determining the degree of catabolism in burns (Wilmore, Lindsey, Moylan, Faloona, Pruitt & Unger, 1974), starvation and other catabolic states (Unger, 1971). The importance of glucagon has undoubtedly been overemphasized and it is perhaps pertinent to re-examine the role of the other catabolic hormones, in particular the glucocorticoids, which have long been ignored and under-emphasized as metabolic regulatory hormones.

Much of the difficulty in ascribing roles to individual hormones has arisen from imprecise usage of the term catabolism. Many early workers equated catabolism with loss of muscle mass or long-term loss of total body nitrogen, which is obviously of clinical importance, but many other processes are involved. These include glycogen breakdown in liver and other tissues, gluconeogenesis, increased mobilization of gluconeogenic precursors (lactate, pyruvate and glycerol, as well as amino acids) from extrahaepatic tissues, and the breakdown of triglyceride stores with the production of alternative fuels such as fatty acids and ketone bodies. These are all directed to provide the increased fuel necessary for the enhanced energy requirement of catabolic states. In addition, the complexity of the hormonal interactions has hampered interpretation of the role of individual hormones.

Glucocorticoids as catabolic hormones

The problem with regard to glucocorticoids stems from a phrase first used by Ingle (1951) more than 20 years ago: that of 'permissive' hormone. Since then it has generally been agreed that cortisol is necessary for the catabolic response to occur, but that cortisol itself has no true regulatory role in catabolism. Many authors have shown an increase in adrenocortical secretion with trauma (Meguid, Brennan, Aoki, Muller, Ball & Moore, 1974), surgery (Moore & Ball, 1952), burns (Wilson, Lovelace & Hardy, 1955) and infection (Beisel, 1975), but is cortisol merely serving a permissive role? It appears profligate to increase secretion of a hormone if this is to have no additional effect.

Ingle's experiments concentrated upon measurement of body weight and urinary excretion of nitrogen in rats and mice after experimental injury. He showed that the expected increase in nitrogen excretion did not occur if animals were adrenalectomized, whereas if they received hormone replacement with
adrenal extract the usual response occurred (Ingle, Ward & Kuizenga, 1947). In another classic paper Campbell, Sharp, Boyne & Cuthbertson (1954) showed that the catabolic response to a long-bone fracture in adrenalectomized rats could be restored by use of so-called 'maintenance' doses of cortisone acetate. Both papers concluded that as a fixed replacement dose of glucocorticoid could yield the same response as the intact adrenal gland then the glucocorticoids had no positive role to play. However, in neither study was corticosterone, the major glucocorticoid in the rat, administered, and the dose and type of steroids used leave interpretation of the data open. The long-term nature of the studies may be more important, as short- or moderate-term changes could well have been masked. Indeed, in the study of Ingle et al. (1947) the adrenalectomized rats with hormone replacement lost less nitrogen than the sham-operated animals in the first 24 h after injury.

Much more detailed studies of metabolism have now delineated the overall role and functions of glucocorticoids more clearly. Cortisol appears to exert its main metabolic effects in muscle, liver and adipose tissue. Administration of glucocorticoids results in a marked increase in the free amino acid pool in muscle and in the release of amino acids, in particular alanine, the main gluconeogenic amino acid, into the circulation (Kaplin & Shimizu, 1963; Wise, Hendler & Felig, 1973). In addition we have shown that chronic administration of adrenocorticotropic hormone to normal subjects results in a striking elevation in blood lactate and pyruvate (D. G. Johnston, A. Gill, G. F. Batstone, K. G. M. M. Alberti & H. Ørskov, unpublished work). There is also an increase in activity of hepatic aminotransferases, which will facilitate the entry of amino acids into hepatic carbohydrate pathways, and an increase in the activity of key gluconeogenic enzymes (Weber, 1968). In the short term this results in an increase in hepatic glycogen formation (Ashmore, Stricker, Love & Kilshheimer, 1961), and in the long term in an increase in hepatic glucose output and hyperglycaemia (Lecocq, Mebane & Madison, 1964). In normal subjects there is hyperinsulinaemia, probably as a result of hyperglycaemia, although there may be a direct effect on pancreatic insulin secretion. There is simultaneous insulin resistance due to an inhibition of extrahepatic glucose uptake, at least in adipose tissue, skin and lymphoid tissue (Munck, 1962; David, Grieco & Cushman, 1970). The release of non-esterified fatty acids from adipose tissue is moderately increased, from failure of glucose entry into adipocytes, with consequent lack of the α-glycerophosphate required for re-esterification, and also from a depression in the activity of lipogenic enzymes (Diamant & Shafrir, 1975). However, ketone-body concentrations are unaltered (Henneman & Bloom, 1957) with the non-esterified fatty acids being diverted in the liver to triglyceride synthesis rather than to ketogenesis.

Catabolic action of cortisol in man

These observations are obviously relevant to the catabolic role of cortisol in man. In a recent study of the hormonal and metabolic response to severe burns strong correlations were found between the circulating plasma cortisol concentration and those of several metabolites during the first 5 days after burn injury (Batstone, Alberti, Hinks, Smythe, Laing, Ward, Ely & Bloom, 1976). Cortisol concentrations were strikingly elevated on the day after the burn, particularly in the severely burned group (mean, 1093 nmol/l) and were still elevated a week later (815 nmol/l). The cortisol concentration correlated positively with the blood concentrations of lactate, alanine, the sum of the gluconeogenic substrates, total ketone bodies, and plasma non-esterified fatty acids and urea, suggesting, but not proving a causal relationship. The other major candidate as an important catabolic hormone, glucagon, showed a different pattern with peak concentrations not being reached for several days. Glucagon then correlated with urea and the lipid metabolites, but the correlations were either absent or much weaker during the early phase of injury.

It is therefore possible that cortisol may have a major and positive role in fuel mobilization in the first phase after injury. Cortisol concentrations are known to rise immediately after injury or surgery (Moore & Ball, 1952; Meguid et al., 1974; Madsen, Engquist, Badawi & Kehlet, 1976) as do those of catecholamines. Indeed Moore (1953) clearly labelled the first post-operative phase as the adrenergic–corticoid phase. He emphasized that the first few minutes or hours of this phase are dominated by adrena-
line but ‘as this wanes the corticoid picture is unmasked and persists much longer’.

**Ketogenic role of cortisol**

This concept explains well our observations in the patients with burn injury. However, cortisol correlated not only with gluconeogenic precursors and urea but also with ketone bodies. This suggests a ketogenic role for cortisol, which has been denied in normal man, although there have been reports of a possible ketogenic role of the adrenal in animals. In 1936 Long & Lukens showed that the adrenal glands had to be present for ketoacidosis to develop in diabetic rats. In the early experiments hypophysectomy was performed simultaneously and it was believed that growth hormone had to be given as well as glucocorticoids. However, experiments on pancratexactomized rats after adrenalectomy and/or hypophysectomy demonstrated that of cortisone, growth hormone, adrenocorticotropic hormone, thyroid-stimulating hormone and proactin, only cortisone was necessary for the development of ketosis (Scow, Chernick & Guarco, 1958). L’Age, Fechner, Langholz & Salzmann (1974) have shown that normal ketogenesis can be restored after adrenalectomy of alloxan-diabetic rats simply by corticosterone replacement. More important, they have also shown a progressive rise in plasma corticosterone concentration with insulin withdrawal in diabetic animals. A rise in cortisol has also been shown after insulin deprivation in diabetic man (Alberti, Christiansen, Iversen & Ørskov, 1975).

Thus when insulin is deficient increased ketone-body concentrations occur simultaneously with increases in glucocorticoid. Treatment of normal subjects with adrenocorticotropic hormone, although causing mobilization of non-lipid fuels, had no effects on circulating ketone-body concentration. However, if after 3 days of this treatment, insulin secretion (and that of glucagon and growth hormone) was suppressed by infusion of somatostatin, there was an immediate sharp rise in ketone-body concentration. This effect was not seen without pretreatment with adrenocorticotropic hormone. Similar results were reported by Schade & Eaton (1976) in insulin-dependent diabetic man, although in their studies concentrations of non-esterified fatty acids were artificially elevated. This effect of cortisol is very similar to that with glucagon, where insulin deficiency is required for the ketogenic effects to be apparent.

A possible mechanism for the ketogenic action of cortisol comes from the work of Diamant & Shafrir (1975). In normal rats given glucocorticoids the normal increase in peripheral fatty acid mobilization was associated with an increase in hepatic lipogenesis, which was almost certainly due to activation of the rate-limiting enzyme of lipogenesis, acetyl-CoA carboxylase. However, in diabetic rats this activation did not occur, acetyl-CoA presumably being diverted to ketone-body formation.

This ketogenic effect of cortisol is important in the genesis of diabetic ketoacidosis. Most cases arise as a secondary result of precipitating factors such as infection, trauma and myocardial infarction, all of which increase the concentrations of catabolic hormones, particularly of cortisol and glucagon (Alberti, Barnes, Bloom, Holloway, Johnston & Ørskov, 1977). These hormones, presumably working in concert, will then tend to drive metabolism towards enhanced gluconeogenesis and ketogenesis. How relevant are these findings to other catabolic states? In the first phase after injury there is an increase in catecholamine secretion which will suppress insulin secretion (Porte, Graber, Kuzuya & Williams, 1966), whereas glucocorticoid administration by itself causes marked hyperinsulinism. Thus the ketogenic effect of glucocorticoids will be unmasked, which explains the correlation between cortisol and ketone body concentrations found in the first phase after severe burn injury.

**Conclusions**

But what of the original statement that cortisol is permissive rather than regulatory? In long-term post-injury homeostasis glucocorticoids may be permissive, but their role appears more important in the early stages. The sequence of events after injury would suggest an intricately interwoven but interdependent series of hormonal events. Initial stimulation of secretion of adrenocorticotropic hormone results in hypercortisolism, and catecholamine secretion is enhanced at the same time. These events combine to cause an increased flux of amino acids, lactate, pyruvate, glycerol and non-esterified fatty acids to the liver, thus increasing hepatic...
gluconeogenesis and ketogenesis, with suppression of insulin secretion and peripheral insulin resistance. The evidence available so far suggests an active role for cortisol in these events, with preliminary evidence suggesting that this is true in milder injury as well as in burns. Catecholamine concentrations then fall, and in this second phase glucagon rises. The combined effects of cortisol and glucagon will be to drive amino acids towards gluconeogenesis, with a marked increase in ureagenesis and loss of nitrogen in the urine. The duration of the cortisol effects is not known. In our own studies the plasma cortisol concentrations were still raised 2 weeks after injury. We have also found that insulin resistance persists for several weeks, if not for months, after injury. This may again be related to cortisol.

It thus seems probable from critical examination that cortisol has a regulatory role in catabolism, when this is defined carefully. However, it is erroneous to take this out of context, and to regard cortisol in an inflated role as the catabolic hormone. It is one of a group of hormones which act together and all of which have roles to play. In the catabolic scenario there are no stars, just players.

References


