MINIREVIEW

Catabolic Hormones and Growth Hormone Resistance in Acquired Immunodeficiency Syndrome and Other Catabolic States

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Nutrient utilization, immune system function and somatic growth are sensitive to changes in the circulating concentrations of insulin and the hormones that antagonize its actions. These processes are impaired in catabolic states including fasting, protein malnutrition, insulin-dependent diabetes mellitus (IDDM), and acquired immunodeficiency syndrome (AIDS), due in part to the consequential changes in the endocrine system. The insulin-antagonizers inhibit these processes directly and indirectly by inducing tissue resistance to anabolic growth promoting hormones. The changes in the circulating concentrations of several of these metabolically active hormones in subjects with AIDS are identical to those occurring in other catabolic states. Therefore, some AIDS-related symptoms may be attributed to secondary changes in the endocrine system rather than to immune system dysfunction *per se*. The purpose of this minireview is not to review all recent advances in the endocrine control of growth, metabolism, and immune function; rather, it is to discuss how these processes are influenced by the changes in the endocrine system that result from catabolic insult.

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Endocrine Regulation of Growth and Metabolism

The endocrine control of growth and metabolism is interrelated. Many of the same endocrine factors involved in the regulation of carbohydrate, lipid, and protein metabolism are also involved in growth regulation. By definition (1), "counterregulatory" hormones antagonize the hypoglycemic and/or lipogenic actions of insulin. These hormones include growth hormone (GH), glucagon, glucocorticoids (cortisol in humans and corticosterone in rodents), thyroid hormones, and catecholamines. However, GH has both insulin-like and antiinsulin-like actions (2); thus, the classification of GH based on its insulin-antagonizing actions may be inappropriate. Although the physiological relevance of some of the insulin-like effects on metabolite regulation are not well understood, GH-stimulated uptake of amino acids and glucose provide necessary substrate for growth processes and are thus somatotropic in nature. Hepatic and local production of insulin-like growth factor–I (IGF-I) is principally, but not exclusively, regulated by GH. In turn, IGF-I mediates the growth-promoting actions of both insulin and GH (3).

The IGFs are anabolic and mitogenic proteins that mediate growth and differentiation in autocrine, paracrine, and endocrine fashions (3). Both IGFs (IGF-I and -II) are single-chain polypeptides and are structurally similar to proinsulin (4). The availability and biological action of both IGFs are modified by relatively high affinity binding proteins (IGFBP-1 through -6) (3). IGFBPs can either augment or inhibit IGF action depending on the specific IGFBP, its concentration, and its location. Although aggregate growth and growth

rate of somatic tissues are highly correlated to circulating IGF-I levels, local rather than hepatic production of IGF-I appears to be more important in some tissues (5).

IGF-I genes have been identified and are fully characterized in several vertebrate species. Protein and cDNA sequence analysis indicates that these genes are highly conserved (4). The human IGF-I gene is organized into six exons and initiation of transcription begins at two different promoter sites upstream of exon 1 and 2, respectively (4). Although few *cis*-acting elements in the IGF-I gene promoter regions have been identified, recent studies suggest that AP-1 activity may mediate transcription through a pathway involving protein kinase-C activation (6). It is generally believed that IGF-I gene expression is regulated at several levels; thus, other *cis*-acting elements may exist. It is unknown how GH, insulin, glucocorticoids, or glucagon regulate IGF-I gene expression.

GH Resistance in Catabolic States

Fasting, Protein Malnutrition, IDDM and Trauma. Reduced growth is commonly associated with catabolic states such as fasting, protein deficiency, and IDDM. Although circulating GH levels may be elevated in these states, growth retardation is accompanied by a reduction in circulating IGF-I concentration and a refractoriness to the anabolic actions of both GH and IGF-I (7–11). GH-stimulated production of IGF-I by the liver is not maintained in these states due to a reduced number of hepatic GH receptors and to a post-receptor defect (12–16). Furthermore, overexpression of bovine GH in transgenic mice with IDDM fails to restore growth or the depressed circulating IGF-I concentrations (17). Scheiwiller *et al.* (18) claim to have restored "normal growth of diabetic rats" with subcutaneous infusions of rhIGF-I. However, they report in the results section that the body weight and tibial growth of those receiving rhIGF-I were approximately half of the control values. In fact, the circulating IGF-I levels were almost twice as high in the treated rats than in the controls. Thus, IGF-I was only minimally effective at overcoming diabetic-growth impairment in these animals. Partial growth restoration can also be accomplished without restoring euglycemia by infusing a low dose of insulin into the hepatic portal vein (19).

Although the circulating concentrations of glucose, fatty acids, and amino acids in fasting, malnourished, and diabetic animals may be quite different depending on the catabolic state, the circulating levels of some insulin-antagonizing hormones are elevated in each condition and those of insulin are depressed (1, 20, 21). Therefore, it is unlikely that blood metabolites are directly responsible for GH and IGF-I resistance.

Injury-induced trauma has been shown to reduce circulating IGF-I and IGF-II despite a 25-fold increase in circulating GH (22). Plasma IGFBP-3 was also reduced, and IGFBP-1 was elevated in the same patients. The latter existing primarily in its phosphorylated form. Administration of rhGH to catabolic trauma patients with multiple injuries elevated plasma IGF-I and IGFBP-3 levels without affecting the total free amino acid concentration in muscle or plasma, nitrogen retention, or urea excretion (23). These results suggest that trauma patients are at least partially, but not completely, resistant to the anabolic actions of GH.

Endocrine Abnormalities Associated with AIDS. Despite their manifold differences in clinical manifestations and pathophysiology, IDDM and AIDS patients share some abnormalities in endocrine function. Circulating levels of insulin and IGF-I are reduced, while those of cortisol and GH are elevated (24–29). Furthermore, the circulating IGFBP-3 level is reduced while that of IGFBP-1 is elevated in fasting subjects and in those with IDDM or AIDS (26, 30). Levels of the former are positively controlled by GH and IGF-I, while those of the latter may be inversely controlled by these anabolic factors (30). These data suggest that wasting associated with AIDS cachexia may by due in part to GH resistance. Fasting elevates circulating glucocorticoids and reduces insulin, which results in increased hepatic gluconeogenesis and the maintenance of normal blood glucose levels. The similar circulating profile of these hormones in subjects with AIDS may explain why they are often euglycemic. Thus, the GH-resistant state associated with AIDS is more similar to that which occurs during fasting conditions than to that which occurs in subjects with IDDM and hyperglycemia. In fact, cachexia typically occurs with chronic infection not associated with AIDS (31) despite elevations in circulating GH concentrations (32).

GH Resistance and AIDS. Recent studies show that subjects with AIDS cachexia are at least partially GH resistant. Thus, insulin deficiency alone is not responsible for the reduction in circulating IGF-I. GH-stimulated levels of circulating IGF-I in AIDS patients are significantly lower than those in age-matched controls (33). In addition, Krentz *et al.* (34) determined that administration of recombinant human (rh) GH at physiological doses for 3 months failed to increase weight gain, lean body mass, or circulating IGF-I levels in AIDS patients. Administration of pharmacological doses of the hormone in the same study significantly increased all of these parameters. Thus, these subjects were resistant to the anabolic actions of physiological doses of exogenous GH, and supraphysiological doses of the hormone were only partially effective

at overcoming the refractoriness. By contrast, Mulligan *et al.* (35) reported anabolic effects of exogenous GH in cachectic subjects with AIDS. Administration of rhGH significantly elevated the total plasma IGF-I levels in both HIV^- and HIV^+ subjects. However, the GH-stimulated IGF-I concentration in the HIV^+ subjects appeared to be approximately 60% ($P < 0.05$) of the level in HIV^- subjects. The resting energy expenditure, protein oxidation rate, and urinary nitrogen excretion before and during rhGH treatment were equal in both groups, which indicates that the HIV^+ subjects were not severely cachectic. These subjects appeared to be partially GH-resistant in a manner similar to those in the study of Krentz *et al.* (34). Unfortunately, it is impossible to determine if the anabolic response to rhGH was due to the treatment or to unaccountable factors because the experimental design failed to include placebo controls.

Pituitary and Adrenal Maintenance of GH and IGF-I Resistance. Research in animals showed that hypophysectomy alleviates the metabolic symptoms of IDDM (36, 37) and partially restores their responsiveness to GH *in vivo* (10, 38) and restores the responsiveness of their cartilage to IGF-I *in vitro* (7). Therefore, the pituitary gland contributes to the metabolic imbalance and growth impairment associated with IDDM.

Early studies also showed that GH exacerbates the metabolic symptoms in IDDM (39). In contrast with humans, however, rats with IDDM have reduced GH levels (2) and defective or reduced GH receptors (12). It is therefore unlikely that GH is responsible for the resistance to anabolic hormones in these rodents. However, the reduction in GH receptor concentration and function during IDDM may contribute to GH resistance in both models. Other data indicate that activation of the adrenocorticotropic hormone (ACTH)–adrenocortical axis may be a major counterregulatory mechanism to insulin in rats with IDDM. Streptozotocin (STZ)–induced diabetes in rats increases plasma and urinary corticosterone concentrations, decreases thymus weight, and increases adrenal weight. These responses are accompanied by increased metabolic activity in pituitary corticotropes and decreased sensitivity to glucocorticoid negative feedback (17, 40).

Recent studies suggest that stimulation of glucocorticoid production is responsible for exacerbating the hyperglycemia and GH resistance associated with IDDM (10, 11). GH responsiveness returns and hyperglycemia is reduced when diabetic rats are adrenalectomized, while corticosterone replacement restores the symptoms of IDDM in these animals, including resistance to GH. Corticosterone replacement to adrenalectomized-diabetic and nondiabetic rats impairs the ability of IGF-I to augment tibial growth in a dose-dependent manner (41). These experimental results reemphasize that complications that arise during IDDM may be due to the actions of the insulin-antagonists rather than to insulin deficiency *per se*. Furthermore, glucocorticoids reduce basal IGF-I and -II levels as well as GH-stimulated IGF-I production *in vitro* and *in vivo* (42–49).

Because glucocorticoids, glucagon, and epinephrine act synergistically to regulate glucose homeostasis (1), it is possible that other actions of these hormones involve synergism. Physiological levels of glucagon inhibit basal and GH-stimulated IGF-I production (50, 51). These results suggest that glucagon may also contribute to the maintenance of GH resistance. Circulating levels of IGF-I and insulin are negatively correlated with catecholamine excretion in catabolic posttraumatic adults (52). Restoration of nutritional status had no effect on the elevated cortisol and reduced IGF-I concentrations in these same patients. Elevation of intracellular cAMP levels by glucagon or 8-bromo-cAMP inhibit IGF-I production in primary rat hepatocytes (50, 51, 53); therefore, the inhibitory action of epinephrine on GH action is likely mediated by β-adrenergic receptors. It is unknown whether glucagon or epinephrine are implicated in AIDS cachexia or even if circulating levels of the hormones change throughout the course of this disease.

Mechanisms of Glucocorticoid-Maintained Growth Inhibition and Immunosuppression. In addition to maintaining GH resistance, glucocorticoids can inhibit somatic growth directly (54). Prolonged exposure to glucocorticoids decreases bone mass and induces osteoporosis *in vivo* (55). This effect is mediated by the inhibition of DNA and collagen synthesis (56) and by inhibiting calcium metabolism and bone mineralization (57). In addition, glucocorticoids inhibit the expression of integrins on plasma membranes and consequent osteoblast adhesion to bone extracellular matrix (58).

In rat hepatoma cells, glucocorticoids inhibit growth by arresting the mitotic cell cycle in the early G1 phase, by inhibiting gene expression of the platelet-derived growth factor A chain and by interrupting the transforming growth factor-alpha autocrine loop (59). In addition, the activated glucocorticoid receptor, but not the mineralocorticoid receptor, can inhibit gene expression and cell growth by binding to the c-Jun and c-Fos transcription factors, thereby inhibiting the c-Jun/c-Fos heterodimer binding to AP-1 genomic binding sites (Fig. 1) (60–64). Furthermore, an AP-1 enhancer has been identified in the mouse IGF-II promoter (65) and in the chicken (6) and human (66) IGF-I promoters. Although the exact mechanism of how GH stimulates IGF gene transcription is unknown, GH rapidly induces c-*jun* and c-*fos* transcription (67, 68); an effect shared by insulin and IGF-I (69–72). Activation of protein kinase-C stimulates IGF-I gene tran-

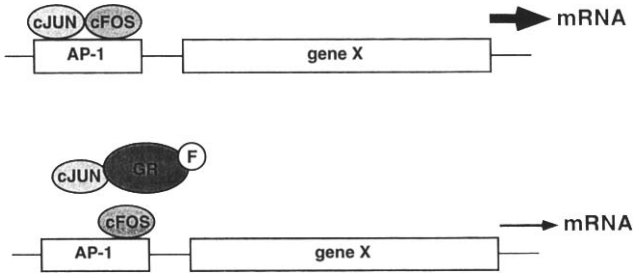

Figure 1. Glucocorticoid inhibition of AP-1 enhancer activation and regulation of gene expression. Once activated by cortisol (F), binding of the glucocorticoid receptor (GR) to the c-Jun transcription factor can suppress gene expression by preventing the binding of the c-Jun/c-Fos heterodimer to AP-1 enhancers (60–64).

scription and is mediated by an AP-1 enhancer (6). Therefore, it is possible that one mode of GH-induced IGF gene transcription occurs by c-Jun/c-Fos binding to an AP-1 motif. Glucocorticoids also downregulate mRNA and protein levels of insulin receptor substrate–1 (IRS-1) (73). Insulin and IGF-I receptor signaling are dependent on the phosphorylation and activation of IRS-1 (74, 75). Interestingly, GH receptor activation in turn phosphorylates IRS-1 (76–78). Thus, glucocorticoids could maintain GH, IGF-I, and insulin resistance by binding to the AP-1 complex in addition to downregulating IRS-1. King and Cart-Su (79) have recently shown the synthetic glucocorticoid dexamethasone to interfere with GH receptor signaling events independent from IRS-1. GH-stimulated phosphorylation of mitogen-activated protein (MAP) kinases (ERK1 & ERK2), the Stat3 transcription factor, and a Janus kinase (JAK2) were all reduced by the steroid. These effects appear to be mediated by a significant loss in GH receptors.

Endogenous glucocorticoids are physiological immune system modulators that suppress immune responses during stress (80). Furthermore, synthetic glucocorticoids are used pharmacologically to induce immunosuppression and to promote transplant tolerance (81). The GH-resistant state that occurs during chronic infection may be due to a concurrent rise in circulating cortisol concentrations due to cytokine stimulation of the hypothalamo-pituitary-adrenal (HPA) axis (82). The HPA axis is stimulated by several cytokines including interleukin-1 (IL-1), IL-6, and tumor necrosis factor/cachectin. Glucocorticoids suppress the production of cytokines that support cell-mediated immune reactions (type 1) and promote the production of humoral immune-stimulating cytokines (type 2) (83, 84). Concentrations of the former are reduced in AIDS subjects, and those of the latter are elevated (85, 86). However, not all of the immunosuppressive actions of glucocorticoids are due to the modulation of cytokine production. Glucocorticoids have been shown to inhibit directly phorbol ester and Ca^{++} ionophore induction of T cell–specific IL-2 gene expression (87). IL-2 is primarily responsible for $CD4^+$ T cell proliferation (Fig. 2) (88), and the promoter region of the IL-2 gene contains two AP-1 enhancers as well as many other *cis*-regulatory elements. In fact, glucocorticoids inhibit IL-2 gene expression through interactions between the activated glucocorticoid receptor and the nuclear factor of activated T cells (NFAT) and the AP-1 motifs (84). Glucocorticoids also promote IκBα synthesis. This regulatory protein sequesters the transcription factor NF-κB in the cytoplasm, rendering it inactive and ultimately suppressing the expression many cytokine genes, including IL-2 (89–91). Therefore, it is possible that the elevated circulating levels of cortisol in AIDS patients contribute in part to the loss in $CD4^+$ T cell number and activity, by inhibiting IL-2 gene expression through interactions with these *cis*-regulatory elements and by promoting the production of type 2 cytokines.

GH Resistance and Immunosuppression. The immune-enhancing properties of prolactin (PRL), GH, and IGF-I have recently been reviewed by Gala (30) and Murphy *et al.* (92). Both humoral and cell-mediated immune responses are compromised in hypophysectomized animals or in Snell mice which lack the cells that synthesize PRL and GH. Replacement of these pituitary hormones corrects the immune deficiencies associated with pituitary hypofunction. Proliferation and antigen responses of T cells are augmented by GH both *in vitro* and *in vivo*. GH also promotes proliferation of B and natural killer cells. Many

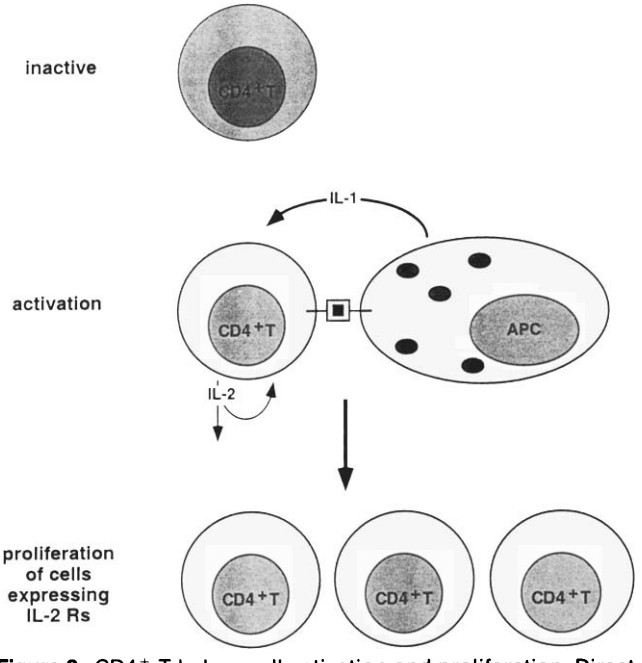

Figure 2. $CD4^+$ T helper cell activation and proliferation. Direct interactions between $CD4^+$ T helper and antigen presenting cells (APC) result in the release of IL-1. Activation of the IL-1 receptor and the $CD4^+$ T cell receptor complex stimulates IL-2 and IL-2 receptor production which drives proliferation (60).

of these actions may be mediated by IGF-I, which is capable of independently reproducing some of these proliferative effects. Although GH receptors are known to be expressed in B and T cells, GH may also exert its effects through interactions with PRL receptors. Thus, glucocorticoid-induced GH and IGF-I resistance may also contribute to immunosuppression in AIDS as well as to the cachexia that accompanies secondary infection. In fact, coadministration of GH and adrenocorticotropic hormone (ACTH) to hypophysectomized rats inhibits GH/PRL restoration of antibody formation.

Summary and Conclusions

The classification of metabolically active hormones as either regulatory or counterregulatory is inappropriate; all of these hormones regulate metabolic and growth processes. In fact, some "counterregulators" elicit insulin-like effects including the aforementioned actions of GH and the glycogenic action of glucocorticoids. By contrast, the proposed reclassification of these hormones based on their somatotropic actions in anabolic and catabolic conditions is free from contradiction (Table I). In anabolic states, insulin and the insulin-antagonists participate in the homeostatic control of metabolism and stimulate growth. Preliminary studies in our laboratory suggest that, like glucagon, glucocorticoids and catecholamines maintain GH resistance in primary hepatocytes as well. Thus, in catabolic states, elevated circulating levels of the catabolic growth inhibitors (Table I) may help to maintain GH resistance and growth suppression. Although thyroid hormones stimulate GH receptor gene expression, they inhibit chondrocyte clonal expansion and cartilage formation (4). However, in catabolic states, circulating thyroid hormone concentrations and tissue sensitivity are reduced (93); thus, they should be classified as anabolic growth promoters.

Adrenal insufficiency may develop in some AIDS patients. Altered steroidogenesis can impair glucocorticoid, mineralocorticoid and androgen secretion (94–102). However, long-term studies suggest that circulating concentrations of basal and ACTH-stimulated cortisol are generally normal or elevated in HIV^+ men (96, 103). Opportunistic infections of cytomegalovirus, mycobacteria, and fungi, as well as the development of Kaposi's sarcoma and lymphoma in the glands themselves, are likely responsible for the development of adrenal insufficiency (104, 105).

Although the metabolic rate increases throughout the progression of AIDS, it does not correlate with cachexia, which often occurs only after secondary infection (106). Because cachexia, hypercortisolism, and opportunistic infections occur within the terminal stages of the disease, it is possible that host reaction to the opportunistic infections activates the HPA axis, which contributes to wasting and immunosuppression. Thus, it is also possible that the prevention of hypercortisolism could revive immune function by partially restoring circulating $CD4^+$ T cell numbers in addition to GH responsiveness and restored body composition. The glucocorticoid synthesis inhibitors metyrapone and aminoglutethimide, which are typically used to treat patients with Cushing's syndrome, or the glucocorticoid receptor antagonist mifeprisone (RU486) could be administered orally to counteract the effects of hypercortisolism. Administration of these agents in combination with GH would likely prove to be even more effective. Circulating cortisol levels may change dramatically in AIDS patients depending on the presence or absence of opportunistic infections. The possible development of adrenal insufficiency in a small percentage of subjects may complicate data interpretation further. Therefore, future intervention studies regarding the endocrine abnormalities associated with AIDS should take into account symptom variability. Such variability could be avoided if HIV^+ study subjects met the Center for Disease Control's criteria for Group IV AIDS and had $CD4^+$ T cell counts of 0 to 200 cells/mm^3.

Table I. Reclassification of Endocrine Regulators of Metabolism Based on Their Somatotropic Actions in Anabolic and Catabolic States

Anabolic growth stimulators	Catabolic growth inhibitors
Growth hormone	Catecholamines
Insulin	Glucagon
Thyroid hormones	Glucocorticoids

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