Protein anabolic action of insulin, growth hormone and insulin-like growth factor I

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Insulin, growth hormone (GH), insulin-like growth factor I (IGF-I), thyroid hormones, sex steroids, glucocorticoids, glucagon and catecholamines all influence protein metabolism and the response to physiological or pathological processes. Of these, insulin, IGF-I and GH play a dominant role in the day-to-day regulation of protein metabolism (see Refs 24, 72, 85 and 140). It is clear that these peptide hormones work in a coordinated and interdependent manner that is just beginning to be understood. The outcome in many pathological states is closely related to the balance of anabolic and catabolic processes. With a better understanding of the regulation of these processes, together with the newly available recombinant hormones, it will hopefully be possible to make therapeutic and clinical advances in the near future. The general principles of measuring protein metabolism and the role of each of these hormones in the regulation of protein metabolism are discussed below.

Body protein and composition

All body proteins are made from amino acids and the sequence of these determines both their physical and biological properties. Amino acids may be present free within the body (within the circulation and extra- or intracellular fluid) or bound (as protein). Free amino acids are incorporated into proteins by protein synthesis and released by protein breakdown. Amino acids may therefore enter the free amino acid pool by release from protein, from the dietary amino acids ingested in the gut and by synthesis for non-essential amino acids. It is customary to refer to body composition as consisting of the fat mass (fat) and the lean body mass (consisting of predominantly protein). Lean body mass does not change when protein synthesis and breakdown are in balance. An increase in lean body mass can be achieved by an increase in protein synthesis, a reduction in protein breakdown or a combination of the two (Fig. 1). Conversely, a reduction in lean body mass can be caused by a reduction in protein synthesis, an increase in protein breakdown or a combination of both.

During growth in young animals, protein synthetic rates and protein breakdown rates are higher than in adult animals and the increased protein breakdown may allow the remodelling of muscle, enabling growth to take place (1). During muscle hypertrophy induced by exercise, both protein synthesis and breakdown increase but synthesis exceeds breakdown and there is a net gain of lean body mass (2). Conversely, during starvation the rates of protein synthesis and breakdown decrease but breakdown exceeds synthesis and there is a net loss of lean body mass (3). In acute serious illness, the resultant catabolic state is due predominantly to an increased rate of protein degradation (4).

Assessment of protein metabolism

The measurement of body composition is one way of assessing protein metabolism; however, there are drawbacks because methods are relatively insensitive and long periods of time are usually required to measure differences. A number of methods therefore have been developed to measure protein metabolism over short periods of time. Some have the added advantage of unravelling the relative contribution of synthesis and degradation.

(i) Nitrogen balance techniques where dietary nitrogen intake and urinary output of nitrogen are measured allow an estimate of the net protein balance.
(ii) Urinary release of 3-methylhistidine, usually expressed as the ratio of 3-methylhistidine to creatinine, provides an index of protein breakdown in the whole body (5).
(iii) The dilution of $^{15}$N in metabolism end-products (urea or ammonia) following infusion of a labelled amino acid, usually $^{15}$N glycine, enables an estimate of protein turnover to be made (6, 7).
(iv) Use of a single dose (8) or continuous infusion (9) of a labelled amino acid, e.g. $^{13}$C leucine, to assess turnover or flux in the free amino acid pool enables calculations of protein turnover to be made.
(v) The incorporation of labelled free amino acid into the bound amino acid pool within tissue (muscle) or within plasma proteins provides a measure of the synthesis rate of specific proteins (10).
(vi) The "flooding dose" technique also provides a measure of protein synthesis. In this method an isotopically labelled amino acid is given with a large amount of unlabelled amino acid to create a similar isotopic enrichment in the extra- and intracellular...
Insulin

The importance of insulin in the control of body protein is demonstrated by the loss of protein in uncontrolled insulin-dependent diabetes mellitus (IDDM) and the reversal of this following treatment with insulin. However, the mechanism of insulin's action on protein metabolism is uncertain and there is an apparent conflict between studies in isolated tissues and studies in man. At the molecular level insulin has been shown to increase the transcription and translation of specific proteins and in isolated tissues from rats to stimulate protein synthesis. However, studies of whole-body protein metabolism in man, using isotopic tracer techniques, have shown that insulin inhibits protein breakdown with no effect on protein synthesis.

In vitro studies

Protein synthesis involves numerous steps, many of which may be controlled by insulin. Following the transcription of DNA into mRNA, there is an association of mRNA with ribosomes and subsequent translation into a peptide or protein. Insulin has been shown to increase the mRNA content for albumin in rat liver (15) and for myosin heavy-chain α in skeletal muscle (16) but to decrease the mRNA for some proteins (17, 18). These studies suggest that insulin can increase the capacity for protein synthesis by increasing mRNA for certain proteins. In insulin deficiency there is a decrease in total RNA concentration in rat muscle, heart and liver (19, 20) and reduced ribosomal synthesis in heart muscle (20). There is decreased peptide chain initiation in muscle, which is restored following treatment with insulin, suggesting that insulin also controls the translation process (21). In studies of skeletal muscle, heart and perfused livers, diabetes has been shown to reduce the incorporation of labelled amino acids into protein (19, 22–24) whereas insulin increased this measurement of protein synthesis (20, 22, 23).

Insulin has been shown to inhibit protein degradation in rat heart (25, 26), skeletal muscle (25, 27) and liver (28). It is not clear whether insulin has an effect on muscle myofibrillar protein breakdown because one study has shown no effect in vitro (29) while another study has reported a restraining effect of insulin on myofibrillar protein breakdown in vivo (30). There has recently been considerable progress in elucidating the mechanisms for protein breakdown. Three systems for protein breakdown have been described: a lysosomal system that contains ATP-independent acid proteases (cathepsins) and hydrolases; a cytosolic ATP-dependent system that may require ubiquitin; and a cytosolic Ca-dependent system (involving the proteases, calpains I and II). The lysosomal system in rat liver, which is involved in the degradation of extracellular and membrane-associated proteins, has been shown to be

Fig. 1. Diagrammatic representation of the effect of changes in rates of protein synthesis and degradation on whole-body protein.

(vii) The simultaneous employment of arteriovenous phenylalanine tracer exchange and amino acid balance techniques across muscle beds allows the assessment of skeletal muscle protein breakdown and synthesis (12).

(viii) The measurement of tissue ribosome content to assess the capacity for protein synthesis (13) and the measurement of the polyribosomal profile in tissue biopsy samples provide an assessment of translational activity (14).
sensitive to insulin (31). In rat muscle, insulin stabilizes lysosomes reducing free cathepsin D activity and thus limiting protein breakdown (32). In cultured muscle cells, insulin also has been shown to inhibit the degradation of membrane-bound receptors by lysosomes (33). However, myofibrillar protein degradation is not mediated by lysosomes (34). The ATP-dependent system was generally believed to be important in the rapid breakdown of abnormal proteins and of short-lived normal proteins (35). Recent studies suggest that this system may have a role in the degradation of normal muscle proteins, including long-lived myofibrillar protein, in fasting and in response to denervation (36). However, there is at present no evidence for an effect of insulin on this system.

In vivo studies in animals

Using an infusion of a $^{14}$C-labelled amino acid, studies in young streptozotocin diabetic rats have shown a small decrease in whole-body protein synthesis (37), a 70% decrease in protein synthesis in skeletal muscle and a 40% decrease in heart muscle (38). Insulin treatment of the diabetic rats in the latter study restored the protein synthetic rate to normal, whereas insulin treatment of normal animals had no effect on synthesis (38). More recently, similar results have been found using the flooding dose technique in streptozotocin diabetic rats (39). In this study protein synthesis was shown to be decreased in muscle (gastrocnemius, diaphragm, soleus, EDL and heart) and liver, while protein degradation estimated from the rate of protein synthesis and growth was increased in gastrocnemius, diaphragm and heart.

Whole body studies in man

Using isotopic tracers, many studies have shown that in uncontrolled IDDM there is an increase in whole-body protein degradation while whole-body protein synthesis is either unchanged or increased (8, 40, 41). Administration of insulin decreases protein degradation in these patients (8, 41) (Fig. 2). Studies in normal subjects, which have investigated the effect of different infusion doses of insulin on protein metabolism, have demonstrated a clear dose-response effect of insulin on whole-body proteolysis with no effect on protein synthesis (42). At physiological insulin concentrations, protein breakdown was suppressed by 20–30%. Associated with the decrease in proteolysis was a large decrease in amino acid levels. At insulin concentrations of 75 mU/l, the leucine concentration was decreased by 50% from postabsorptive values (43).

The failure to demonstrate a stimulatory effect of insulin on protein synthesis in these studies may be due to the lack of substrate for protein synthesis. Studies have therefore been performed with amino acids either maintained at basal levels or at high levels during an insulin infusion. In the studies in normal subjects in which the amino acid levels were “clamped” at basal levels (44, 45), insulin had no effect on whole-body protein synthesis (Fig. 3) and the inhibition of proteolysis by insulin was greater than in the absence of an amino acid infusion (44). In hyperaminoacidemia hyperinsulinaemia studies in IDDM patients, no effect of insulin on whole-body protein synthesis could be demonstrated (46). In hyperaminoacidemia hyperinsulinaemia studies in normal subjects a stimulation of protein synthesis was found but the same stimulation of protein synthesis was found in the absence of insulin.
Fasting adult rats only affects protein synthesis in one of these muscles (epitrochlearis) (49, 50). Infusing insulin in these rats increased protein synthesis in young rats but had no effect in the adult rat, except in the epitrochlearis muscle. This suggests that in young growing rats the sensitivity of protein synthesis to insulin may be related to the growth process, whereas in adults the control of muscle protein turnover may be by the control of protein degradation.

Effects of insulin on different tissues and plasma proteins

Because whole-body protein metabolism is a composite measure, it is possible that insulin may increase the synthesis of some proteins but this may be masked by the lack of effect on other proteins. To investigate this, the effect of insulin on protein turnover has been examined in skeletal muscle and the splanchnic bed, the two major regions of protein turnover in the body. Two main methods have been used to determine the effect of insulin on skeletal muscle protein metabolism: using limb catheterization combined with an isotopic technique, and using an infusion of [1-13C]leucine followed by measurement of the incorporation of labelled amino acid into a muscle biopsy. In normal subjects the former technique has demonstrated that local physiological hyperinsulinaemia in the forearm inhibits proteolysis with no effect on protein synthesis (51). An investigation of the dose response of proteolysis to insulin has shown that a local infusion that produced concentrations of only 30 mU/l insulin in the forearm maximally decreased protein degradation (52). Systemic infusion of insulin in IDDM also decreased proteolysis in the forearm with no effect on protein synthesis, but resulted in a marked decrease in amino acid concentrations (53). Concomitant infusion of amino acids to maintain basal levels or to produce hyperaminoacidemia inhibited proteolysis but there was no effect on protein synthesis (54, 55).

Further evidence for a lack of effect of insulin on muscle protein synthesis comes from muscle biopsy studies. Muscle fractional protein synthesis was shown to be normal in insulin-withdrawn IDDM and was not different following an insulin infusion (56). When an amino acid infusion was administered with the insulin infusion to prevent hypoaminoacidemia in IDDM patients, muscle fractional protein synthesis was unchanged (46). An infusion of amino acids to produce hyperaminoacidemia increased muscle fractional protein synthesis in normal subjects but this effect was independent of insulin (57, 58).

The effect of insulin on protein metabolism in the splanchnic bed has been studied in man using a multi-isotope technique in which one isotopically labelled amino acid is infused intravenously and a second labelled amino acid is added to a meal (59). These
studies have shown that the splanchnic utilization of dietary amino acids is not affected by diabetes or by an insulin infusion (60, 61). The fractional synthetic rates of the liver proteins albumin, fibrinogen, apolipoprotein B and antithrombin III have been studied using isotopic tracers. In these studies a constant infusion of [1-13C]- or [1-14C]leucine was administered and the incorporation of the isotopically labelled amino acid into specific proteins was determined over 4–8 h. In normal subjects a euglycaemic hyperinsulinaemic clamp (0.4 mU·kg⁻¹·min⁻¹) was shown to increase the fractional synthetic rate of albumin. decrease the fractional synthetic rate of fibrinogen and antithrombin III but to have no effect on total apolipoprotein B synthesis (62, 63). In IDDM, however, insulin deficiency was found to have no effect on the albumin synthesis rate (64). Other studies that have measured VLDL apolipoprotein B synthesis have shown this to be increased in non-insulin-dependent diabetic patients compared to normal subjects (65), while a euglycaemic hyperinsulinaemic clamp (1 mU·kg⁻¹·min⁻¹) decreased the fractional synthetic rate of VLDL apolipoprotein B in both normal and diabetic subjects (66, 67).

**Growth hormone**

In 1910 hypophysectomy was shown to arrest growth (68), and in 1912 Ashner demonstrated that the main action of GH was to promote longitudinal bone growth (69). Growth hormone is essential for body growth but as normal growth occurs over a relatively short time period and GH secretion continues throughout life, it is not surprising that GH has many other functions, including both acute and chronic effects on protein metabolism and body composition. Many of the actions of GH are mediated both directly and indirectly through IGF-I acting in an endocrine or paracrine manner.

**In vitro metabolic actions**

The early observations of the effects of GH in hypophysectomized animals led several groups to study the effect of GH on protein metabolism in vitro. Kostyo performed a number of experiments using amino acid tracers that demonstrated the GH-stimulated uptake of amino acids into rat diaphragm (70–72). Growth hormone also stimulated the uptake of labelled glycine into protein, an effect that was independent of amino acid uptake (73, 74). These findings have been repeated more recently, together with a time course of action (75).

**In vivo metabolic actions**

Growth hormone produces both acute and chronic metabolic effects in vivo, which in some cases are paradoxical.

**Acute effects.** Acute insulin-like effects of GH on protein, glucose and fat metabolism have been described (76–78). These insulin-like effects are transient and in the continued presence of GH the tissues become refractory (79). The physiological relevance of these acute actions is uncertain and not fully understood.

**Chronic effects.** Growth hormone is the classical anabolic hormone. It increases both growth and muscle mass in GH-deficient children (80, 81). Growth hormone is associated with a decrease in nitrogen excretion and an increase in the number of ribosomes in tissues (82, 83). In acute short-lived studies of GH administration, the metabolic effects of GH are unlikely to be modulated by changes in circulating levels of either insulin-like growth factors or insulin. However, in more long-term studies, administration of GH is associated with both rising circulating levels of insulin-like growth factors and insulin and it is therefore difficult to be certain that the measured effects are directly mediated by GH. Interestingly, Milman et al. (84) failed to increase nitrogen retention with GH in diabetic cats unless insulin was also given. Early studies investigating the effects of GH were performed in hypophysectomized animals and it was shown that hypophysectomy was associated with a loss of body protein and that GH administration to these animals restored the amount of body protein (85).

There has been recent interest in the effect of a lack of GH on lean body mass (LBM) and protein metabolism in adult GH-deficient patients (86). An initial study demonstrated a reduction in LBM of 7–8%, corresponding to approximately 4 kg of lean tissues (86). Measurement of the cross-sectional area of the dominant quadriceps muscle demonstrated that GH-deficient patients had a 15.5% lower area than controls matched for age, sex and physical activity (87). In all reported studies of GH replacement in adult GH-deficient patients, there has been an increase in LBM after 6 months despite the use of a range of different measurement techniques (86, 88, 89). Open studies conducted over longer periods of GH treatment (up to 3 years) suggest that the restoration of LBM is maintained over longer periods (90).

Isotopic studies investigating the mechanism of action of GH in normal subjects showed that GH had a direct effect on whole-body protein synthesis at pharmacological doses (91, 92). In forearm studies in normal subjects, intra-arterial GH stimulated protein synthesis acutely without altering proteolysis but these measurements were highly dependent on forearm blood flow, which altered during the GH infusion (92). Adult GH-deficient patients have also been used as a model to investigate the actions of GH on protein metabolism. In an uncontrolled study of GH replacement in adult GH-deficient adults, Binnerts et al. (93) reported an increase in protein synthesis and nitrogen balance, determined using 15N-glycine, after 1 month of treatment but not at
other time points. However, they were unable to demonstrate any differences when the results were corrected for the change in LBM. Using whole-body leucine turnover studies the anabolic action of GH through direct stimulation of protein synthesis has been demonstrated (Fig. 4) (94). Growth hormone treatment for 2 months caused an increase in non-oxidative leucine disappearance rate, expressed in terms of LBM (a measure of protein synthesis), and had an additional effect to reduce leucine oxidation rate. Although proteolysis per kilogram of body weight was increased, there was no significant effect on the rate of proteolysis when expressed in terms of LBM. Thus, GH seems to produce its anabolic effect by stimulating protein synthesis without affecting proteolysis, in contrast to insulin (8), which predominantly inhibits proteolysis. These effects of GH on protein metabolism provide a mechanism for the changes in body composition and increased LBM and muscle mass observed in all studies of GH replacement in adult GH-deficient adults (85, 95).

The powerful anabolic action of GH on protein metabolism has led to the use of this hormone in the treatment of catabolic diseases that cause loss of LBM. Thus, GH has been shown to promote a positive nitrogen balance in post-operative patients (96, 97) and in burn and trauma patients (98, 99). In a study of burns patients, whole-body protein synthesis measured with an infusion of $^{15}$N-lysine was increased in four patients receiving GH (0.4 U·kg$^{-1}$·day$^{-1}$) compared to a placebo group (100). This resulted in a net reduction in protein loss of 50%. In a study of 12 surgical patients receiving total parenteral nutrition, GH treatment (0.3 U·kg$^{-1}$·day$^{-1}$) for 3 days decreased urea production but had no effect on protein degradation measured isotopically (101). Septic patients have not been studied extensively and doubt exists as to the effectiveness of GH in these patients. However, in one study of 20 patients with severe sepsis nitrogen balance improved following intravenous administration of GH (0.2U·kg$^{-1}$·day$^{-1}$) for 3 days (102). Wasting is a common complication of AIDS and GH has been shown to reduce nitrogen excretion and protein oxidation in a study of six HIV positive patients (103). Growth hormone may therefore be a promising therapy for HIV-associated wasting. The anabolic effects of GH treatment may also be enhanced by the concomitant infusion of insulin. The combination of GH treatment (3 days) and an exogenous insulin infusion in normal subjects has been shown to result in a higher whole-body and skeletal muscle protein balance than with either hormone alone (104). This combination therapy also has been examined in cancer patients. In a placebo-controlled study of 28 patients, the effect of insulin to reduce protein breakdown was greater in GH-treated patients than in the placebo-controlled group (105).

**Insulin-like growth factor I**

In 1957 Salmon and Daughaday suggested that the growth effect of GH was mediated by another factor that was initially called sulphation factor and subsequently fully characterized and called IGF-I (106). It was thought until recently that IGF-I was in effect a second messenger for GH and exclusively produced by the liver. This endocrine hypothesis was compelling because the liver possesses a large number of GH receptors (107). Because GH is secreted in pulses and IGF-I turnover in the circulation is slow, owing to it being almost entirely protein bound, this provides a mechanism by which the amount of GH secreted can be...
integrated. However, with the discovery that IGF-I was produced by many cell types for local autocrine and paracrine action, it was clear that its mechanism of action was altogether more complex (108, 109). Although GH is the prime regulator of IGF-I production, both from the liver and from the majority of other IGF-I producing tissues, insulin and nutrition also play important regulatory roles (110). The biological actions of IGF-I can be classified as either anabolic (growth promoting) or insulin-like.

**In vitro metabolic actions**

Insulin-like growth factor I has been shown to stimulate DNA synthesis and cell replication in muscle cell cultures (111), cardiac muscle (112), organ explants and established cell lines (113). It may act as a progression factor and act synergistically with other growth factors, such as platelet-derived growth factor (114). Insulin-like growth factor I may also be involved with cell differentiation, especially in myoblasts (115), osteoblasts (116), granulosa cells and oligodendrocytes (117), and has been shown to stimulate cell cycle progression (113, 118, 119) and oncogene mRNA (119). Many of these in vitro actions can be modulated by the presence of binding proteins and are assumed to be mediated through the type I IGF-I receptor.

**In vivo metabolic actions**

Initial studies were performed with IGF-I purified from plasma, but with the advent of recombinant IGF-I more studies have been possible. Studies have been able to confirm the biological actions in vivo, demonstrating both growth promoting and insulin-like actions. Zapf et al. (120) demonstrated that intravenous IGF-I induced hypoglycaemia in hypophysectomized and normal rats. Only minor effects were reported on fat metabolism. Infusion of IGF-I has been shown to have an insulin-like action with suppression of hepatic glucose output and stimulation of peripheral glucose utilization in rats (121), pancreatectomized dogs (122) and normal dogs (123). These findings have been confirmed with detailed isotopic metabolic studies examining glucose and fat metabolism in man and animals (124–129).

Although IGF-I mediates some of the growth-promoting effects of GH, there is controversy as to whether all GH actions are mediated by IGF-I. Expression of an IGF transgene in GH-deficient transgenic mice restores normal weight and linear growth, as does expression of a GH transgene (130). Growth has been stimulated by IGF-I in hypophysectomized rats (131, 132). Snell dwarf mice (133), diabetic rats (134) and humans with GH insensitivity syndrome (135). Although IGF-I stimulates growth, some studies have suggested that this is less effective than GH itself (132, 134, 136). Other studies have also suggested that IGF alone leads to differential and disproportionate growth of some internal organs, such as kidney and spleen (136, 137).

The mechanism of action of IGF-I on protein metabolism has been investigated in both animal and human studies (128, 129, 138, 139). The mechanism by which IGF-I mediates its anabolic effects in vivo has been demonstrated only recently. Initial isotopic studies of protein metabolism in both animals and humans examined acute infusions of IGF-I. Without exception, these showed that IGF-I had insulin-like effects with a reduction in proteolysis and no effect on protein synthesis (Fig. 5). This was somewhat surprising, as
IGF-I is anabolic and stimulates growth and protein synthesis in vitro and is thought to mediate many of the anabolic actions of GH, which clearly acts by stimulating protein synthesis. All of these studies, however, had methodological problems because fasted subjects were used and the insulin-like metabolic effects reduced plasma amino acids from low (fasting) to unphysiologically low levels, thus reducing the substrate availability for active protein synthesis. Thus, lack of substrate may have inhibited protein synthesis. Using an amino acid clamp protocol (45) in which circulating substrate levels of amino acids were maintained, it has been demonstrated that IGF-I acts to promote protein synthesis directly (Fig. 3). These studies subsequently have been confirmed by other groups using intraarterial infusions of IGF-I (140). Thus it appears that the major anabolic action of IGF-I is to promote protein synthesis, but only during conditions of adequate amino acid substrate supply.

Malnutrition and severe infection are associated with GH resistance. Because IGF-I may overcome this and directly stimulate protein anabolism, IGF-I may have a role in the treatment of catabolic states. Administration of IGF-I for 6 days to normal human volunteers has been shown to reverse diet-induced catabolism (141). Treatment of AIDS patients with either low- or high-dose intravenous IGF-I (4 or 12 µg·kg⁻¹·h⁻¹ for 12 h each day) for 10 days was shown to increase cumulative nitrogen retention with both doses. However, treatment had no effect on protein turnover measured with an infusion of [¹³C]leucine (142). Because administration of both GH and IGF-I above certain doses can lead to complications, the combination of GH and IGF-I treatment may be beneficial. Insulin-like growth factor I has been shown to have a synergistic action with GH on nitrogen balance in diet-induced catabolism in normal subjects (143). In AIDS patients, combined GH and IGF-I treatment for 1 week resulted in a marked change to a positive nitrogen balance that was substantially greater than treatment with either hormone alone (144).

Conclusion

Insulin, GH and IGF-I all play a major role in the control of protein metabolism. In man, insulin appears to act primarily to inhibit proteolysis while GH stimulates protein synthesis. In the postabsorptive state IGF-I has acute insulin-like effects on proteolysis, but in the fed state or when substrate is provided for protein synthesis in the form of an amino acid infusion, IGF-I has been shown to stimulate protein synthesis. All three hormones have a role in the treatment of catabolic states, either alone or in combination. Growth hormone combined with insulin has been shown to improve whole-body and skeletal muscle kinetics, while GH combined with IGF-I has a greater positive effect on protein metabolism in catabolic states than either hormone alone. Thus, these hormones have enormous potential in the treatment of catabolic states associated with loss of LBM.

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