

GROWTH HORMONE SECRETION: ITS REGULATION AND THE INFLUENCE OF NUTRITIONAL FACTORS

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INTRODUCTION

Growth hormone (GH) has direct and indirect actions through which it stimulates growth of skeletal and other tissues, and influences the availability of metabolic fuels (Davidson, 1987; Isaksson *et al.* 1987). The growth promoting actions of GH are 'indirect' and are largely mediated through generation of the insulin-like growth factor, IGF-1, which may act both as an endocrine and paracrine hormone (Isaksson *et al.* 1987). The 'direct' actions of GH are predominantly antagonistic to insulin, although there are acute insulin-like effects of uncertain physiological significance (Fig. 1). Thus, there is an important interrelationship between the actions of GH, nutrition and growth.

GH is released from the human pituitary in a pulsatile manner. The pituitary has a unique anatomical relationship with the hypothalamus, such that the only blood supply to

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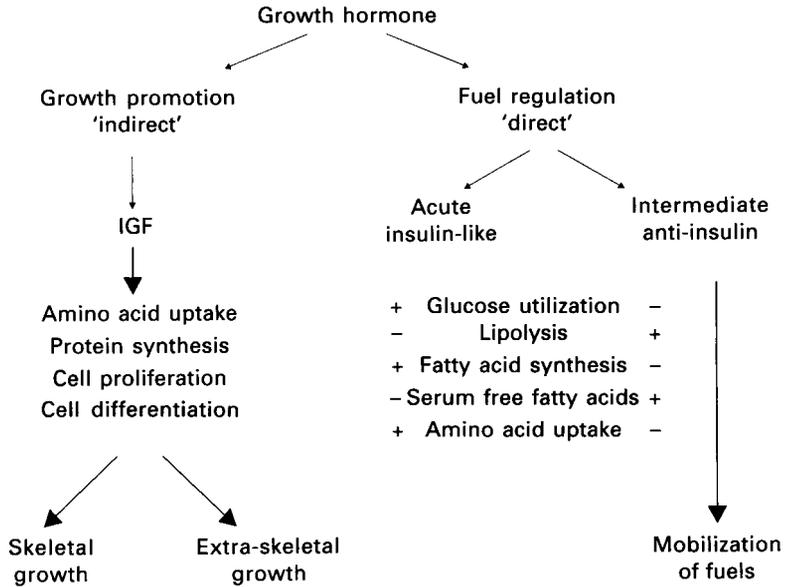


Fig. 1. Actions of growth hormone (GH). The growth-promoting effects are mediated predominantly through local tissue generation of insulin-like growth factor (IGF-1). Acute insulin-like effects have been demonstrated within 2 h of GH administration, before tissues become refractory to further GH exposure. The major impact of GH on fat and carbohydrate metabolism is, however, to antagonize the actions of insulin.

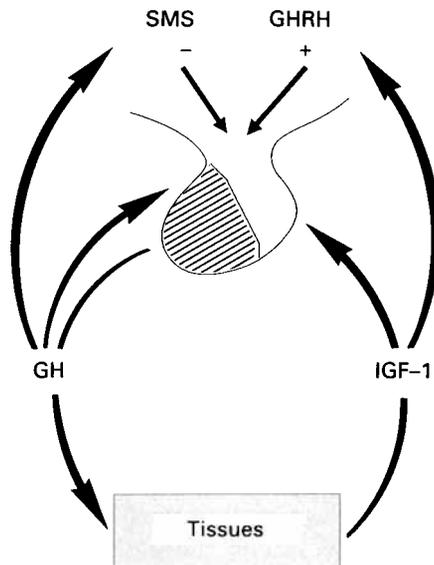


Fig. 2. Diagrammatic representation of feedback mechanisms on the hypothalamus and pituitary which regulate growth hormone (GH) and insulin-like growth factor (IGF) secretion. SMS, somatostatin; GHRH, growth hormone-releasing hormone.

the anterior pituitary is derived from a portal venous system draining the hypothalamus. Thus, the hypothalamus can modulate release of anterior pituitary hormones by secreting various factors into this portal circulation. GH release is determined by a dynamic equilibrium between the inhibitory and stimulatory hypothalamic peptides, somatostatin (SMS) and growth hormone-releasing hormone (GHRH) (Fig. 2). The hypothalamic release of GHRH and somatostatin is, in turn, controlled through a complex network of neurotransmitters, and the hypothalamo-pituitary response may be influenced by age, sex, GH feedback, insulin, thyroid and steroid hormones, and nutritional status.

The GH-IGF-1 axis, therefore, includes the hypothalamic peptides, GH and IGF-1, and a complex network of feedback between the various hormones (Fig. 2). We will discuss the factors involved in the neuroendocrine regulation of GH secretion in man and how the influence of nutrition may modulate this system.

REGULATION OF GH SECRETION

PHYSIOLOGICAL GH RELEASE

GH is released in a pulsatile fashion with pulses occurring every 3–4 h with the greatest release during sleep (Quabbe *et al.* 1966). The amplitude and frequency of GH pulses is dependent on age, being greatest during puberty and declining with age (Finkelstein *et al.* 1972; Rudman *et al.* 1981; Martha *et al.* 1989). Sleep, stress, exercise, and post-prandial decline in blood glucose concentration act as stimuli to GH secretion, although it is likely that most episodes of release are spontaneous (Martin, 1976). The greatest secretion of GH occurs at night during sleep (Takahashi *et al.* 1968). Slow-wave sleep is frequently associated with GH release, but individual patterns of GH secretion during sleep show considerable heterogeneity (Adlard *et al.* 1987) and the time of sleep onset, rather than of slow-wave sleep, is more closely related to the nocturnal rise in GH secretion (Born *et al.* 1988). Martin (1976) concluded that GH release was a sleep-related event which probably should not be considered as closely linked to, or caused by, the neural process that subserves slow-wave sleep. A more specific basis for the association between sleep mechanisms and GH release has yet to be determined.

GROWTH HORMONE-RELEASING HORMONE

GHRH was the most recent of the hypothalamic regulatory peptides to be characterized (Guillemin *et al.* 1982; Rivier *et al.* 1982). Its existence had been proposed much earlier (Reichlin, 1961), but attempts to isolate it from animal hypothalami were unsuccessful because of the small quantities present and the coexistence of SMS, which interfered with the bioassays. GH-releasing factors were finally extracted from the pancreatic tumours of two patients in whom the ectopic production of GHRH had resulted in acromegaly (a condition arising from hypersecretion of GH). Three homologous peptides varying in length from thirty-seven to forty-four amino acid residues were characterized: GHRH(1–37)NH₂, GHRH(1–40)OH, GHRH(1–44)NH₂ (Fig. 4).

Peptides of both forty and forty-four residues have been extracted from human hypothalamic fragments and are identical to the pancreatic peptides (Ling *et al.* 1984). There has been considerable debate as to which is the native hormone, although it is likely that both the forty-four and forty residue peptides are important (Frohman & Jansson, 1986). GHRH immunostaining has been demonstrated in the arcuate nucleus of the hypothalamus with fibres projecting to the median eminence and ending in contact with the portal vessels (Bloch *et al.* 1983). The human GHRH gene has been characterized and

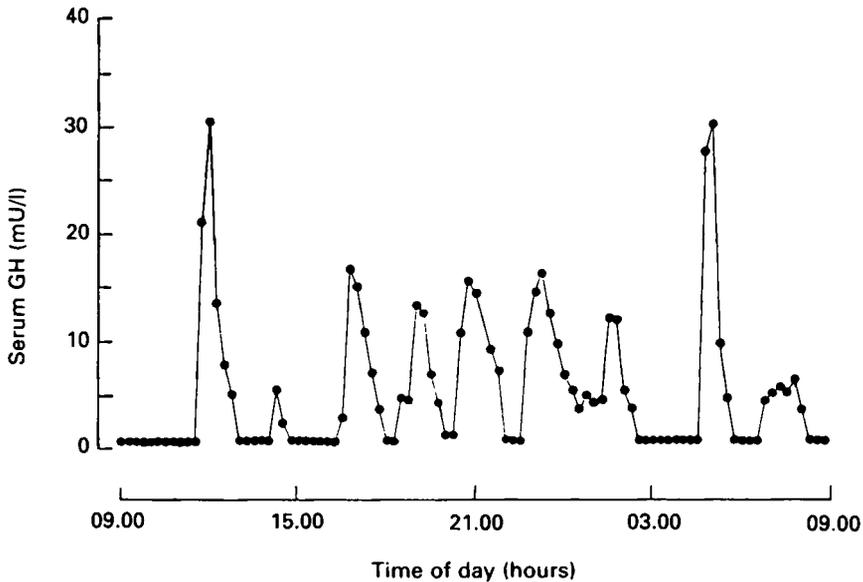


Fig. 3. Serum growth hormone (GH) levels over a 24 h period in a prepubertal boy. Blood samples were collected intermittently via an indwelling venous cannula at 15 min intervals.

mapped on chromosome 20 (Mayo *et al.* 1985). It has been demonstrated in vitro that GHRH stimulates not only GH secretion but also transcription of the GH gene (Barinaga *et al.* 1985). Transgenic transfer of the GHRH gene in mice results in enhanced growth (Hammer *et al.* 1985).

Specific receptors for GHRH have been demonstrated on rat pituitary cells in culture, and the GHRH receptor activates the adenylate cyclase-cAMP system (Frohman & Jansson, 1986). GHRH given as an intravenous bolus selectively promotes GH release in normal subjects (Gelato *et al.* 1983; Grossman *et al.* 1983; Rosenthal *et al.* 1983), and anti-GHRH antiserum blocks pulsatile GH release in the rat (Wehrenberg *et al.* 1982*a*). Studies in rats given GHRH after pretreatment with anti-somatostatin antiserum suggest that there is tonic secretion of both GHRH and somatostatin into hypophyseal portal blood. Superimposed on this are three- to four-hourly pulses of GHRH release which, in association with trough levels of SMS, generate pulses of GH (Tannenbaum & Ling, 1984). Sampling of blood from the hypophyseal portal circulation of the rat confirms that SMS is continuously secreted but reaches trough levels at the time of GH release (Plotsky & Vale, 1985).

SOMATOSTATIN

SMS was discovered when a substance that inhibited GH release was unexpectedly detected in rat hypothalami during the search for a growth hormone-releasing factor (Krulich *et al.* 1968). This factor was subsequently extracted from ovine hypothalamic fragments and proved to be a tetradecapeptide which was called 'somatostatin' (Brazeau *et al.* 1973) (Fig. 4). This name is perhaps inadequate; SMS possesses many physiological and pharmacological functions beyond the regulation of GH secretion. It is widely distributed within the nervous system, gut and both endocrine and exocrine glands, and it acts as a neurotransmitter as well as an endocrine hormone; for example, SMS is synthesized in the

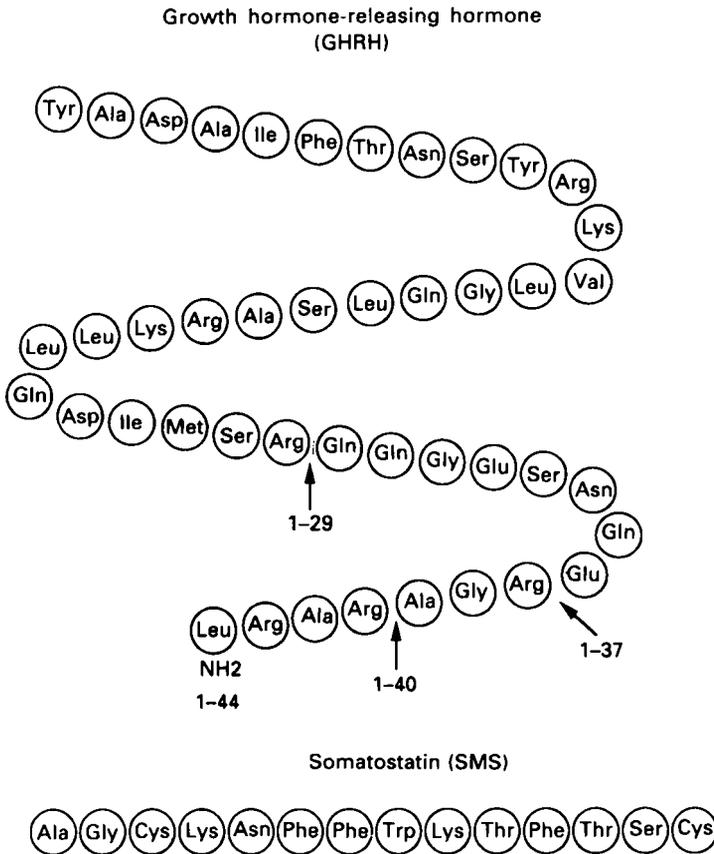


Fig. 4. Amino acid sequences of the various forms of growth hormone-releasing hormone and somatostatin.

pancreas and inhibits secretion of insulin, glucagon, and the exocrine secretions of the gut (for a full review, see Reichlin, 1983 *a, b*).

There is now ample evidence for a physiological role of SMS in the control of GH secretion. The administration of anti-somatostatin antiserum increases trough levels of GH and, in rats, reverses the inhibitory effect on GH release of stress and starvation (Arimura *et al.* 1976; Terry & Martin, 1981; Wehrenberg *et al.* 1982 *b*). The simultaneous administration of SMS with GHRH blocks the GH response to GHRH in man (Davies *et al.* 1985 *b*).

Both GHRH and SMS are found in the peripheral circulation. Some authors have suggested that these circulating plasma levels reflect hypothalamic secretion (Argente *et al.* 1987) but this seems unlikely, as circulating levels of GHRH and SMS are normal in GH-deficient children, show no relationship to GH levels, and are modulated by food intake (Sopwith *et al.* 1985, 1986, 1987; Roskamp *et al.* 1987 *a*). It is probable that peripheral levels of these hormones are largely derived from the gut.

INSULIN-LIKE GROWTH FACTORS (IGF/SOMATOMEDINS)

The 'somatomedin hypothesis' arose from the observation that cartilage from hypophysectomized rats was unresponsive to GH added in vitro, but incorporated sulphate in

response to normal rat serum and serum from GH-treated hypophysectomized rats (Salmon & Daughaday, 1957). It was suggested that there was a 'sulphation factor' or 'somatomedin' which mediated the effects of GH. The GH-dependency of this factor was confirmed by subsequent studies showing low levels of sulphation factor activity in hypopituitary patients, high levels in acromegalic patients, and raised levels in hypopituitary patients given human-GH (Hall, 1971).

The somatomedin peptides were first purified from human plasma and have a molecular weight of approximately 750000 and show marked structural homology with pro-insulin (Rinderknecht & Humbel, 1978*a, b*). They possess a number of insulin-like properties, notably a potent hypoglycaemic effect, and, therefore, have been named 'insulin-like growth factors (IGF)'. In man, there are two distinct somatomedins; somatomedin-C or (IGF-1) and IGF-2. A recent consensus has suggested that the term 'somatomedin' should be used as a generic designation with the specific growth factors referred to as IGF-1 and IGF-2 (Daughaday *et al.* 1987). IGF-1 is highly GH-dependent, has potent mitogenic activity *in vitro*, and its serum levels generally reflect GH activity, being high in acromegaly and low in GH deficiency (Hall & Sara, 1984).

The IGF, unlike most other peptide hormones, are associated in serum with specific binding proteins. The two major species of binding protein are the predominant GH-dependent protein (IGFBP-3) of approximately 150000 molecular weight, and a GH-independent protein of approximately 30000 (IGFBP-1) (Letter, 1990). Whereas levels of IGFBP-3 show little, if any, diurnal variation, IGFBP-1 appears to be metabolically regulated. Serum levels of IGFBP-1 show a diurnal rhythm with an inverse relationship to insulin and may have a critical role in maintaining glucose homeostasis (Baxter & Cowell, 1987; Yeoh & Baxter, 1988). A rise in IGFBP-1, through increasing the bound fraction of IGF, could be protective against the hypoglycaemic, insulin-like effects of IGF-1, and inhibit the growth-promoting effects, when insulin levels and fuel substrate are low (Taylor *et al.* 1990).

There is considerable debate as to whether the somatomedins act in an endocrine, paracrine or autocrine fashion. The role of circulating IGF-1, which derives mainly from the liver, remains unclear, but as discussed below it may be important in GH feedback. Studies in which GH and IGF-1 have been infused into the hindlimb of rats have demonstrated a local growth-promoting effect which is abolished by antiserum to IGF-1 (Schlechter *et al.* 1986; Isaksson *et al.* 1987). These results are generally consistent with the 'somatomedin hypothesis' that the growth-promoting action of GH is mediated through IGF-1, but shift the emphasis away from circulating IGF-1 produced in the liver and towards locally generated IGF-1.

GH FEEDBACK

There is good evidence that GH modulates its own secretion, but whether by a direct or indirect effect remains unclear. The GH response to pharmacological stimuli such as insulin-induced hypoglycaemia and arginine, and to physiological stimuli such as sleep and exercise is attenuated by pretreatment with human GH (Abrams *et al.* 1971; Hagen *et al.* 1972; Mendelson *et al.* 1983). This inhibition of response to both pharmacological and physiological stimuli could be a direct action of GH, or be mediated indirectly by GH-induced IGF-1 production or by other metabolic factors under the influence of GH, such as a rise in free fatty acid (FFA) levels. Both GH and IGF-1 may exert feedback at either the hypothalamic or pituitary level; at the hypothalamus, control of GH release could, in turn, be mediated either through altered GHRH or SMS secretion.

GH pretreatment blocks the response to GHRH, both when given acutely before a rise

in serum IGF-1 can be generated (Ross *et al.* 1987a) and after prolonged treatment associated with a rise in IGF-1 levels (Nakamoto *et al.* 1986; Rosenthal *et al.* 1986). GH can therefore regulate its own secretion independently of circulating IGF-1, although the mechanism for this may require local generation of IGF-1 in the hypothalamus or pituitary. Circulating IGF-1 may offer a further regulatory influence on GH secretion. There is evidence in man to suggest that GH feedback occurs under hypothalamic control, through SMS, since pyridostigmine, an acetylcholinesterase inhibitor that reduces SMS release, blocks GH feedback (Ross *et al.* 1987c). In addition, there is good evidence from both in vivo and in vitro studies in the rat that GH and IGF-1 induce release of hypothalamic SMS (Sheppard *et al.* 1978; Tannenbaum, 1980; Tannenbaum *et al.* 1983; Berelowitz *et al.* 1981) and that IGF-1 but not SMS will suppress pituitary GH mRNA (Namba *et al.* 1989). Receptors for IGF-1 and IGF-2 are widely distributed within the central nervous system of rats, particularly in the pituitary gland and the median eminence of the hypothalamus (Lesniak *et al.* 1988; Ocrant *et al.* 1989). Notably, reduced energy intake sufficient to lower plasma IGF-1 levels is associated with an increase in IGF-1 receptors in the median eminence (Bohannon *et al.* 1988).

In man, repetitive administration of GHRH at two-hourly intervals is accompanied by attenuation of the GH response, but with a continuous infusion of GHRH there is augmentation of the amplitude of endogenous GH secretory pulses (Shibasaki *et al.* 1985; Vance *et al.* 1985). The likely explanation for these findings is that the *frequency* of GH pulses is determined by variations in background SMS activity and the *amplitude* by a pulse of GHRH coincident with trough levels of SMS. The pulse of GH contributes in turn to inhibition of further GH release through the feedback loop, provoking an increase in SMS release. A further level of control is suggested by the observation that GHRH may itself exert feedback stimulation of SMS release (Lumpkin *et al.* 1985).

THYROID AND STEROID HORMONES

Thyroid hormones, glucocorticoids and sex steroids all influence GH secretion. Hypothyroidism in man is associated with decreased GH release on provocative testing and spontaneous nocturnal GH secretion shows a reduction of GH pulse amplitude in children with severe hypothyroidism, with recovery over 3–6 months after thyroxine replacement (Iwatsubo *et al.* 1967; Buchanan *et al.* 1988). Regulation of GH secretion has been more clearly defined in animal models or in vitro systems. The rat GH gene contains thyroid- and glucocorticoid hormone-responsive elements and these may independently promote increased GH synthesis (Gick & Bancroft, 1987; Wight *et al.* 1987). Glucocorticoids may have net positive or negative influences on GH secretion according to whether the predominant effect is on hypothalamic SMS and GHRH release, or directly on the pituitary somatotroph (Nakagawa *et al.* 1987). Dexamethasone (a potent glucocorticoid) will ablate the inhibitory effect of IGF-1 on GH release by rat pituitary cells in vitro (Lamberts *et al.* 1989). In man, short-term steroid treatment augments GH release but long-term treatment suppresses GH release (Burguera *et al.* 1990).

Oestrogens are probably responsible for the differences in GH release between men and women, in particular with regard to the rise in GH secretion seen during puberty, and may account for the sexual dimorphism of GH secretion in other species (Conway *et al.* 1989). It is not clear whether the effects of androgens are mediated through oestrogens or act independently. Oestrogens, both endogenous and administered, are known to enhance basal and stimulated GH release. Women have higher basal levels of GH than men (Unger *et al.* 1965), especially during the high oestrogenic phase of the menstrual cycle (Frantz & Rabkin, 1965), and oestrogen pretreatment of normal men increases both basal and

stimulated GH secretion (Frantz & Rabkin, 1965; Merimee *et al.* 1966). Androgens increase the GH response to provocative stimuli in prepubertal children (Laron *et al.* 1972), but have no effect on either the basal or stimulated GH secretion of adult women (Merimee *et al.* 1969, Merimee & Fineberg, 1971). Ho *et al.* (1987) have demonstrated a close correlation between oestradiol levels and GH pulse amplitude. Oestradiol appeared to increase GH pulse amplitude and duration rather than frequency. Oestrogen pretreatment does not alter the GH response to exogenous GHRH, suggesting that its effects are to augment endogenous GHRH release (Ross *et al.* 1987*b*).

NEUROTRANSMITTERS AND GH RELEASE

Neurons containing catecholamines, acetylcholine, the amino-acid neurotransmitter γ -aminobutyric acid (GABA), and the opioid peptides are found in the hypothalamus. There is a complex interaction between the various neurotransmitters and both SMS and GHRH, but as yet, which neurotransmitters have the most important role in physiological GH secretion remains unclear.

Studies with α -adrenergic agonists and antagonists suggest that α -2 adrenergic receptor stimulation is important in GH release stimulated by hypoglycaemia (Tatár & Vigaš, 1984). The α -2 agonist, clonidine, stimulates GH release in man and is used as a test of GH secretion (Lanes & Hurtado, 1982). α -2 adrenergic stimulation may cause GH release through increased GHRH secretion, as rats depleted in GHRH fail to respond to clonidine (Katakami *et al.* 1984). Propranolol, a β -adrenergic blocker, enhances the GH response to insulin-induced hypoglycaemia and GHRH in man, an effect that may be mediated through inhibition of SMS release (Chihara *et al.* 1985). Dopamine stimulates transient GH release in man and augments the GH response to GHRH (Bansal *et al.* 1981; Delitala *et al.* 1987).

The cholinergic nervous system is important in the regulation of GH secretion. Atropine and pirenzepine, both cholinergic muscarinic antagonists, block the GH response to physiological stimuli of GH secretion such as sleep and the GH response to GHRH (Casanueva *et al.* 1984; Jordan *et al.* 1986; Massara *et al.* 1986; Peters *et al.* 1986; Delitala *et al.* 1987). Similarly, drugs which act by enhancing cholinergic tone, such as the acetylcholinesterase inhibitors, increase GH secretion and augment the GH response to GHRH (Leveston & Cryer, 1980; Massara *et al.* 1986; Ross *et al.* 1987*c*). Acetylcholine inhibits SMS release from the rat hypothalamus (Richardson *et al.* 1980), while the effects of cholinergic manipulation on GH secretion in rats were abolished by depletion of hypothalamic SMS (Locatelli *et al.* 1986). Thus, findings in animals suggest that the effect of cholinergic manipulation on GH secretion is mediated through hypothalamic SMS secretion. However, in man the mechanism of action is less clear (Freeman *et al.* 1990).

Basal GH secretion is stimulated by GABA and by a number of GABA-ergic drugs such as muscimol, baclofen, and diazepam. In contrast, GABA is able to reduce the GH response to insulin-induced hypoglycaemia. A dualistic role of GABA on dopamine secretion and GH release has been suggested (Bercu & Diamond, 1986). The opioid peptides also stimulate GH release, an effect blocked by low doses of naloxone (Stubbs *et al.* 1978; Grossman, 1983). The GH response to maximal doses of GHRH is augmented by the opioids, suggesting that they act independently of GHRH (Delitala *et al.* 1987).

The contribution of serotonin remains controversial as both stimulatory and inhibitory influences have been reported in man. The role of histamine is also difficult to establish because of the poor neuropharmacological specificity of its antagonists, which frequently also possess anti-cholinergic and anti-dopaminergic properties. Most evidence favours an inhibitory role for histamine on both basal and stimulated GH release (Netti *et al.* 1981).

	Glucose	Insulin	FFA	GH	IGF-1	Catabolism
Fasting	N	↓	↑	↑	↓	↑
Malnutrition	N	↓	↑	↑	↓	↑
Sepsis	N / ↑	↑	↑	↑	↓	↑
Diabetes mellitus	↑	↓	N	↑	↓	↑
Obesity	N	↑	N	↓	N / ↑	↓

Fig. 5. Metabolic effects on the growth hormone (GH)-insulin-like growth factor (IGF) axis in varying nutritional states. FFA, free fatty acids; N, within normal limits.

THE INFLUENCE OF NUTRITION ON GH SECRETION

The nutritional state of subjects and patients has a profound effect on GH secretion and IGF-1 levels. As discussed below, metabolic factors, obesity, fasting, anorexia, diabetes mellitus, malnutrition and catabolic states interact with the GH-IGF axis, resulting in differing profiles of GH and IGF secretion (Fig. 5). Serum IGF-1 shows a close correlation with nitrogen balance in sick or malnourished patients and is a sensitive indicator of nutritional status (Clemmons *et al.* 1985; Minuto *et al.* 1989).

METABOLIC FACTORS

Several metabolic factors influence GH secretion, in particular glucose, insulin, FFA and amino acids.

Acute hypoglycaemia is a potent stimulus to GH secretion, and it is likely that GH normally functions as a counter-regulator of glucose levels through effects on glucose production, glucose utilization and lipolysis, although this role is not entirely clear (Davidson, 1987; De Feo *et al.* 1989). Insulin-induced hypoglycaemia is well established as a clinical test for evaluating the integrity of the hypothalamo-pituitary axis through provocation of GH release (Frasier, 1974).

In contrast, an acute rise in glucose after oral or intravenous administration to normal individuals will inhibit GH release and the GH response to GHRH (Davies *et al.* 1984; Sharp *et al.* 1984; Garrel *et al.* 1989). Enhanced cholinergic tone, using pyridostigmine, will counteract this suppressive effect of glucose on GH release probably through effects on SMS secretion (Balzano *et al.* 1989). However, neither acute nor sustained hyperglycaemia has a consistent suppressive effect on GH secretion in the rat (Imaki *et al.* 1986; King *et al.* 1986).

In addition to the indirect stimulatory effect of insulin through hypoglycaemia on GH release, it has a direct suppressive effect on GH synthesis by pituitary cells *in vitro* through inhibition of GH gene transcription (Yamashita & Melmed, 1986), suggesting a mechanism for increased GH production during periods of reduced nutrition and the reverse with hyperinsulinaemia and obesity (Ahmad *et al.* 1989). Insulin may, however, exert both

positive and negative effects on GH gene expression according to the presence of other regulatory factors (e.g. dexamethasone and triiodothyronine) (Isaacs *et al.* 1987).

The fatty acids will, like glucose, inhibit GH release and the GH response to GHRH (Imaki *et al.* 1985, 1986; Sartin *et al.* 1988), and there is evidence in vitro that the effect of FFA is exerted at the pituitary level (Casanueva *et al.* 1987). It has been suggested that GH feedback is in part mediated by FFA (Rosenbaum *et al.* 1989), but this seems unlikely as FFA levels rise during a prolonged fast in association with augmented GH release (Ho *et al.* 1988).

Intravenous infusion of essential amino acids, the fundamental requirements for protein metabolism, will stimulate GH release in humans and non-primate species (Knopf *et al.* 1965; Davis, 1972). Arginine, histidine and lysine are particularly potent. This may explain the post-prandial rise in plasma GH after a protein meal (Sukkar *et al.* 1967) and has formed the basis of a standard provocation test for GH secretion (Merimee *et al.* 1965, 1969). The mechanism whereby GH release is stimulated has not been studied for many amino acids, but arginine appears to act via the hypothalamus; sex-steroid status will influence the response to arginine (Merimee *et al.* 1966), arginine pretreatment will enhance GHRH-stimulated GH release, probably by suppression of endogenous SMS (Alba-Roth *et al.* 1988), and antimuscarinic agents such as atropine suppress arginine-induced GH secretion (Casanueva *et al.* 1984). Obesity and high plasma levels of phenylalanine in children with phenylketonuria have been reported to impair the GH response to arginine infusion (El-Khodary *et al.* 1971; Rosskamp *et al.* 1987c).

OBESITY

Obese subjects show attenuated GH responses to most stimuli including insulin-induced hypoglycaemia and GHRH (Williams *et al.* 1984; Kopelman *et al.* 1985). Despite this, obese children tend to grow at an above-average rate. Circulating IGF-1 levels are higher in obese patients and have been reported to show a negative correlation with the GH response to GHRH (Loche *et al.* 1987), although not all groups have found this relationship (Davies *et al.* 1985a; Rosskamp *et al.* 1987b). The reduced response to GHRH returns to normal after weight loss and it is likely that it is a consequence rather than a cause of obesity (Williams *et al.* 1984; Csizmadi *et al.* 1989). The obese rat, which is hyperinsulinaemic, shows low pituitary GH mRNA levels (Ahmad *et al.* 1989). The suppressed GH secretion in obesity may, therefore, be a consequence of the hyperinsulinaemia or increased IGF-1 levels sometimes seen in this state.

Since GH has nitrogen-preserving and lipolytic actions (Davidson, 1987), it may be of benefit in obese patients attempting to lose weight (Thorner & Vance, 1988). Short-term GH administration was effective in decreasing the loss of lean body mass in individuals on restricted dietary intake, but fat loss was not accelerated (Clemmons *et al.* 1987). The same group have also demonstrated that the dietary carbohydrate content determines responsiveness to GH in obese patients on an energy-restricted diet (Snyder *et al.* 1989). The higher the carbohydrate content of the restricted diet the lower the N excretion of the patients. Interestingly in this second study patients showed increased body fat loss on GH treatment.

FASTING AND ANOREXIA

Fasted normal subjects have marked changes in their pattern of GH release. In a comprehensive study Ho *et al.* (1988) demonstrated that a 5 d fast in normal adult males resulted in increased GH pulse frequency, amplitude, and interpulse GH levels. The increase in pulse frequency and amplitude was evident on the first day of the fast. Serum

IGF-1 levels declined gradually over the 5 d. The GH response to GHRH was the same at the end of the fast as the beginning, suggesting that the changes in GH secretion were not due to changes in the pituitary sensitivity to GHRH. Similar elevation of GH secretion on food restriction has been observed in most species studied (Atinmo *et al.* 1978; Driver & Forbes, 1981; Scanes *et al.* 1981; Breier *et al.* 1988; Cella *et al.* 1989; Foster *et al.* 1989). A notable exception is the rat, in which GH levels fell on fasting, in response to increased SMS release, and catch-up growth on refeeding was associated with enhanced GH secretion through increased GH pulse amplitude (Tannenbaum *et al.* 1979; Mosier *et al.* 1985).

It is well recognized that fasting and malnutrition are associated with low IGF-1 levels. From refeeding studies in both man and the rat it appears that both energy and protein are required for the normal production of IGF-1 (Phillips & Unterman, 1984). Anorexia nervosa is associated with elevated basal GH levels similar to that seen in fasted subjects, and again the GH response to GHRH is the same as control subjects (Casanueva *et al.* 1987; De Marinis *et al.* 1988). The findings in fasting and anorexia are the converse of obesity; greater GH secretion and low IGF-1 levels. Possibly the lack of IGF-1 feedback results in greater GH release.

DIABETES

In contrast to normal subjects, the hyperglycaemia of diabetes mellitus and sick patients with insulin resistance is associated with augmented rather than depressed GH secretion (Asplin *et al.* 1989; Ross *et al.* 1990). Patients with insulin-dependent diabetes have greater amplitude and frequency of GH pulses and higher interpulse GH levels compared with controls (Asplin *et al.* 1989), yet they have lower IGF-1 levels than controls. The GH response to GHRH in diabetes has been reported to be greater than, or similar to, that of controls (Press *et al.* 1984). A 'normal' response to GHRH, however, would be inappropriate in the presence of hyperglycaemia. The abnormality of GH secretion seen in diabetics appears to correlate inversely with their diabetic control. In diabetics and children with kwashiorkor, oral glucose does not provoke the usual suppression of GH secretion (Press *et al.* 1984; Pimstone *et al.* 1967). Thus, the pattern of GH secretion seen in diabetics is similar to that seen in fasted subjects and may well reflect the consequences of intracellular starvation under conditions of insulin deficiency.

MALNUTRITION AND CATABOLIC STATES

Early observations on GH secretion in malnourished states were mainly in children with protein and/or energy deficiency of kwashiorkor and marasmus (Becker, 1983). Plasma GH levels were high in the presence of low insulin, albumin and amino acid levels and returned to normal within days of refeeding with protein (Pimstone *et al.* 1966, 1968). Oral feeding of such children with essential amino acids, but not an intravenous glucose load, provoked a fall in GH within just 30 min (Milner, 1971 *a, b*), and the acute rise in GH after arginine infusion was obtunded (Graham *et al.* 1969; Soliman *et al.* 1986). This reversal of the normal pattern of GH response to metabolic cues was clearly an adaptive phenomenon in nutritional deprivation, although the mechanism and purpose were unclear.

A paradox existed, as depressed amino acid levels were associated with high GH levels when the supply of substrate for growth was deficient. Infusions of amino acids singly or in combination failed to identify an individual amino acid capable of reversing these changes in GH secretion and a similar pattern of GH release could not be reproduced by manipulation of, in particular, the branched-chain amino acids released during starvation and gluconeogenesis.

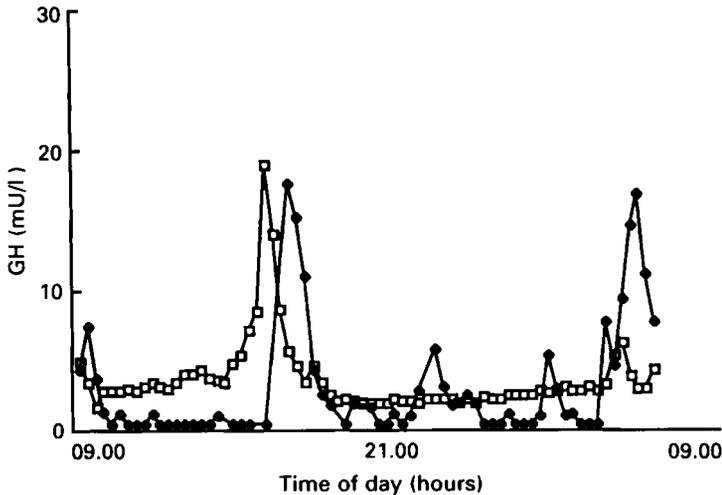


Fig. 6. 24 h growth hormone (GH) profile (20 min sampling) in a 53-year-old patient suffering from sepsis and catabolism following bowel surgery (\square), compared with an age- and sex-matched control (\blacklozenge). Baseline GH levels are consistently elevated in the patient, failing to return to undetectable levels between pulses (R. J. M. Ross & C. R. Buchanan, unpublished results).

Realization that sulphation (somatomedin, IGF) activity was reduced in protein malnutrition helped focus attention on how GH might be diverted from its growth-promoting effects to acquire a more important role in the regulation of available metabolic fuels (Grant *et al.* 1973; Shapiro *et al.* 1978; Phillips, 1986). This response is not restricted to the malnourished child, but occurs similarly in fasted healthy or obese adults (see p. 10), and particularly in undernourished critically ill patients (Phillips & Unterman, 1984; Freeman *et al.* 1989; R. J. M. Ross, unpublished results).

Critically ill, septic patients show an increase in interpulse GH levels compared with fasted controls, yet have similar GH pulse frequency and mean GH levels throughout 24 h (Freeman *et al.* 1989) (Fig. 6). There has been no detailed analysis of the pattern of GH secretion in protein-energy malnourished children, with single basal GH levels having formed the basis of most published studies. The elevated circulating levels of GH in protein-energy malnutrition have, however, been shown to result from enhanced secretion, rather than impaired clearance, by demonstration of a normal GH disappearance time during SMS infusion (Pimstone *et al.* 1975).

Overall, the findings suggest that catabolic states and malnutrition are associated with low serum IGF-1 levels and enhancement of GH secretion. This occurs through an increase in interpulse GH levels and possibly in GH pulse amplitude rather than increased pulse frequency. An explanation may be that circulating or centrally generated IGF-1 is important in GH feedback and that low levels of IGF-1 lead to decreased hypothalamic SMS release and thus an increase in basal GH release. The low IGF-1 levels suggest these patients have a 'GH-resistant' state.

In normal or diabetic rats, this effect of protein restriction appears to be achieved through a post-receptor defect in the GH-tissue axis since GH binding to liver is normal but IGF-1 production reduced (Maes *et al.* 1986; Maiter *et al.* 1989). Insulin deficiency, however, may additionally result in reduced GH binding to its liver receptors (Maiter *et al.* 1989).

With increased understanding of the pathophysiology of malnutrition and catabolic states, it is hoped that advances may be achieved in the clinical management of such disorders through manipulation of one or more components of the GH-IGF axis. It remains to be seen whether GH or IGF-1 has a therapeutic role to improve the nutritional state of sick patients. There is already good evidence that treatment with GH can improve N balance in fasted normal subjects and patients following gastrointestinal surgery and thus potentially accelerate recovery (Manson & Wilmore, 1986; Ward *et al.* 1987; Ziegler *et al.* 1988). In these patients metabolic regulatory mechanisms are so adapted that the GH levels necessary for such effects are only obtained with relatively 'high' doses of exogenous GH. A recent exciting observation is that fasted mice treated with IGF-1 showed less weight loss than untreated mice (O'Sullivan *et al.* 1989).

In the malnourished patient the altered relationship between GH and IGF-1 may represent a protective response. In the fasted state, hypoglycaemia is a persistent danger and appropriate substrates are required for the liver to synthesize essential proteins. The fall in IGF-1 may be an essential permissive event to allow muscle catabolism to yield metabolic fuels and avoid the hazards of hypoglycaemia. Similarly, the accompanying rise in GH levels promotes insulin resistance and lipolysis, both protective metabolic changes during acute and prolonged dietary restriction.

Considerable advances have been made in recent years in our understanding of the factors regulating GH secretion, and its effects on growth and intermediary metabolism. The recent availability of recombinant GH and IGF, characterization of the GH receptor (Waters *et al.* 1990) and the GH- and IGF-binding proteins will greatly enhance our knowledge of this field and may provide new therapies for some nutritional disorders.

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