Section of Endocrinology

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Hormonal Interrelations and their Clinical Significance

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Growth Hormone and Insulin

When talking about growth hormone/insulin interrelations it is important to differentiate fact from speculation. Both polypeptides are 'growth hormones', in the sense that they are anabolic and share several metabolic actions. Before epiphyseal fusion growth hormone is largely responsible for linear skeletal growth but it requires the presence of adequate amounts of insulin to fulfil this function; in the absence of adequate amounts of insulin the role of growth hormone is reversed and its action becomes primarily catabolic. On the other hand, in the absence of growth hormone linear growth is severely restricted but circumferential growth tends to be exaggerated under the unopposed action of insulin.

In the adult, both hormones remain anabolic but growth hormone is apparently no longer essential. There can be little doubt that even in the absolute absence of growth hormone normal health can be maintained. This does not mean that growth hormone has no physiological role in the adult; it simply implies that endocrine 'redundancy' is capable of readjustment to compensate for the lack of growth hormone. In the absence of growth hormone there are several well recognized metabolic defects.

It is well known that there is a tendency to fasting hypoglycæmia and to 'hypoglycæmia unresponsiveness' following insulin administration. Indeed, it is this latter phenomenon that has proved to be the major long-term threat to the insulin-treated hypophysectomized diabetic. These clinical observations fit well with experimental data in animals that show that hepatic gluconeogenesis is impaired after hypophysectomy and cannot be restored to normal unless the animals are treated with cortisone, thyroxine and growth hormone.

A normal glomerular filtration rate is also dependent upon adequate secretion of growth hormone and a fall in glomerular filtration rate is responsible for the further impairment in renal function that commonly occurs in diabetics following hypophysectomy, even when they are on full replacement therapy with cortisone and thyroxine. It is not yet clear whether or not these changes are due directly to a lack of growth hormone or to a secondary lack of somatomedin.

Possible interaction between the hormones can take place at three main levels – synthesis, secretion, and metabolic actions at the tissues. We must also consider the effects of insulin on growth hormone and the effects of growth hormone on insulin.

Effects of Insulin on Growth Hormone

Growth hormone synthesis in the pituitary gland is to some extent insulin dependent. The energy required for the synthetic processes in the anterior pituitary arises mainly from glucose metabolism. The uptake and oxidation of glucose by the anterior pituitary is insulin dependent (Goodner & Freinkel 1961). It has been demonstrated that insulin will stimulate growth hormone synthesis *in vitro* but we have no evidence that growth hormone synthesis is deficient in diabetes mellitus.

One of the most widely used tests of growth hormone secretion is the insulin tolerance test. Insulin does not normally stimulate growth hormone secretion directly; it is the hypoglycæmia induced by insulin that does so. The magnitude of the growth hormone response is directly proportional to the extent of the hypoglycæmia (Sönksen *et al.* 1973). The mechanism by which hypoglycæmia acts is probably by inducing neuroglycopenia since it can be readily reproduced by infusions of 2-deoxy-D-glucose which inhibits the oxidation of glucose (Wegienka

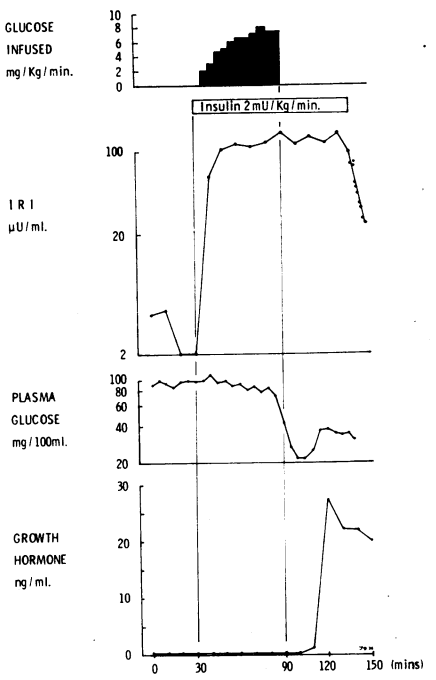

Fig 1 *Hyperinsulinæmia in the absence of hypoglycæmia does not stimulate growth hormone secretion*

et al. 1967). It is thought that inhibition of glucose oxidation in the central nervous system triggers the release of growth hormone releasing factor from the hypothalamus, but we should now consider the alternative explanation – that 2-deoxy-D-glucose inhibits somatostatin release and thus leads to an increase in growth hormone secretion.

That insulin itself does not release growth hormone in normal subjects can be demonstrated readily by infusing insulin and glucose simultaneously, maintaining blood glucose constant (Fig 1). It can be seen that growth hormone secretion does not occur until blood glucose has been allowed to fall.

There is evidence that insulin may stimulate growth hormone secretion directly in uncontrolled diabetes mellitus (Sönksen *et al.* 1972) and possibly also in some patients with acromegaly (Sönksen 1974). The infusion of small amounts of insulin into untreated diabetics was followed by a rapid increase in growth hormone secretion before there had been an appreciable change in blood glucose. We postulated that this was directly related to increased glucose metabolism and energy production in the anterior pituitary.

The effects of insulin on the action of growth hormone at the tissue level are much less clear and probably should not be mentioned since they come into the field of speculation rather than fact. It is known that both hormones have a primarily anabolic action but that insulin is by far the more potent. It is possible to demonstrate a direct effect of growth hormone and insulin on uptake of amino acids and protein synthesis in many tissues and they appear to act synergistically. In some tissues, for example cartilage, growth hormone has no demonstrable effect on protein synthesis while insulin has a marked stimulatory action. It was this observation that led to the description of somatomedin (or sulphation-factor), a constituent of plasma that stimulates protein synthesis in cartilage. Somatomedin synthesis appears to be dependent on growth hormone secretion, in that its plasma concentration is high in acromegaly and falls after hypophysectomy (Daughaday 1971).

It has been suggested that the rise in growth hormone that consistently occurs post-prandially or 3–4 hours after a glucose load acts synergistically with the still elevated plasma insulin to stimulate protein synthesis; although largely speculative this hypothesis is soundly based (Rabinowitz *et al.* 1966).

Effects of Growth Hormone on Insulin

There is evidence that growth hormone is capable of regulating the rate of insulin release from isolated pancreatic tissue but I know of no direct evidence that it regulates insulin synthesis. It appears that growth hormone has little effect when added *in vitro* to pancreatic tissue from hypophysectomized animals but that it is capable of restoring insulin secretion to normal when these animals are treated with growth hormone *in vivo* (Bouman & Bosboom 1965).

There is a wealth of evidence that demonstrates unequivocally that growth hormone positively affects insulin secretion *in vivo*. Acute growth hormone administration does not stimulate insulin secretion (Owens *et al.* 1973). However, basal plasma insulin concentration is increased in acromegaly, even when blood glucose is normal (Table 1) (West *et al.* 1975). Insulin secretion in response to glucose and other stimuli is increased in acromegaly and falls when growth hormone concentration is lowered by hypophysectomy (Sönksen *et al.* 1967). Growth

Table 1

Basal plasma insulin concentrations in various conditions

Diagnosis	*Fasting insulin* (μu/ml)	*Insulin/glucose ratio* (μu/mg)
Normal	3.75	5.6
Obesity	4.70	5.67
Thyrotoxicosis	5.02	6.15
Myxœdema	6.46	9.3
Oral contraception	11	12.95
Acromegaly	14.63	18.2
Liver disease	16.26	21.8

hormone administration to animals has a similar effect, demonstrable within a few days (Campbell & Rastogi 1966). Prolonged administration of growth hormone leads to diabetes in animals and man. When symptomatic diabetes developed in a patient with acromegaly, the previously elevated plasma insulin values fell to diabetic levels (Sönksen *et al.* 1967). It would seem therefore, that after initially stimulating insulin synthesis and secretion, probably indirectly by inducing insulin resistance (West *et al.* 1975), excess growth hormone induces pancreatic endocrine failure. It is not clear whether this is a direct or indirect effect but morphological changes suggesting degeneration are readily demonstrable within the B cells (Young 1963). It has been suggested that insulin secretion is reduced in patients with growth hormone deficiency and this is commensurate with their known insulin sensitivity. Treatment of panhypopituitary patients with growth hormone increases insulin secretion and improves glucose tolerance (Luft & Cerasi 1964, Frohman *et al.* 1967).

What are the effects of growth hormone on insulin action at the tissue level? It has been known for a long while that when injected into humans and experimental animals growth hormone has an early insulin-like action lasting about an hour, followed by a diabetogenic action lasting much longer (Frohman *et al.* 1967). The insulin-like action is not due to insulin secretion. Growth hormone also has insulin-like actions *in vitro*; for example it inhibits lipolysis in adipose tissue from hypophysectomized rats (Goodman 1970), possibly by inhibiting the formation of cyclic AMP.

The more characteristic diabetogenic action of growth hormone follows the early insulin-like action and can be demonstrated by about 3 hours after growth hormone administration *in vivo* and *in vitro*. On adipose tissue *in vitro* this diabetogenic action is characterized by decreased glucose uptake and reduced fatty acid synthesis. *In vivo*, the repeated administration of canine growth hormone to dogs (1 mg/kg per day) results in hyperglycæmia and elevated plasma glucose. Glucose production and utilization are both increased and there is also a threefold increase in free fatty acid turnover (Rathgeb *et al.* 1970).

Growth hormone administration to human subjects can induce a similar diabetes-like metabolic state (Luft & Cerasi 1964), again characterized by hyperglycæmia and high plasma insulin concentrations. This metabolic situation is readily reversible in man and animals following cessation of growth hormone treatment similar to the improvement in glucose tolerance seen in acromegalics following successful treatment (Sönksen *et al.* 1967, Sönksen 1974).

One of the characteristic features of acromegaly is resistance to the action of exogenous insulin (West *et al.* 1975). This is probably the mechanism that leads to the stage of impaired glucose tolerance with greater than normal plasma insulin concentrations that is so common in acromegaly. So long as the B cells are capable of responding to this state of insulin resistance, a stage of 'compensated chemical diabetes' exists, with hyperglycæmia but no ketosis or tissue catabolism. If the B cells can no longer keep pace with the increased insulin requirements uncompensated clinical diabetes develops which may progress to diabetic ketoacidosis. At this stage insulin production is maximal in the fasting state and no longer increases after glucose administration. In other metabolic states where insulin secretion is limited, namely insulin-dependent diabetes mellitus and obese subjects after prolonged fasting (Drenick *et al.* 1970), injections of growth hormone lead to the rapid development of ketoacidosis.

It would thus seem that growth hormone induces diabetes first by producing a metabolic state characterized by increased glucose production and extreme insulin resistance which may then progress to a stage of 'B cell exhaustion'. Whether this is entirely secondary to insulin resistance or involves a direct toxic action of growth hormone on the B cells is not clear. It is, however, known that with withdrawal of growth hormone treatment or reduction in plasma growth hormone concentration, the situation is reversible and both glucose tolerance and insulin secretion can return to normal (Sönksen 1972).

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