HUMAN GROWTH HORMONE AS A REGULATOR OF BLOOD GLUCOSE CONCENTRATION AND AS A DIABETOGENIC SUBSTANCE

By

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The role of the hypophysis in experimental diabetes was discovered in 1930 by Houssay & Biasotti, who demonstrated that the severity of the diabetes decreases following extirpation of the hypophysis, and increases again after implantation or injection of the pars distalis of the pituitary gland. Young, in 1937, was able to produce diabetes in intact dogs by the administration of crude anterior pituitary extracts. In 1949, Cotes et al. and Houssay & Anderson independently demonstrated that growth hormone was the active substance in pituitary extracts which induced diabetes in animals. With the demonstration in 1960 by Ikkos & Luft that human growth hormone (HGH) could induce a transient diabetic state in human subjects similar to the experimental diabetes of animals, the chain of experimental evidence assigning to growth hormone the role of a prominent diabetogenic substance was completed.

This presentation will deal mainly with the ability of HGH to raise the blood glucose concentration. Two aspects of this action will be discussed: 1. the role of HGH in blood glucose homeostasis, and 2. HGH as a diabetogenic substance. The mechanism of action of the hormone will not be discussed.

1. The significance of HGH in blood glucose homeostasis

When HGH became available for studies in man (Li & Papkoff 1956), we had, for the first time, the means to tackle the problem of the role of HGH in blood glucose homeostasis. This action of the hormone is best illustrated by depressing the blood sugar and registering firstly how the administration of HGH influences the blood glucose reaction, and secondly how endogenous HGH production responds to the induced hypoglycaemia. Hypoglycaemia has mostly been induced by giving an intravenous injection
of 0.05—0.1 unit of insulin per kg body weight. By this means the blood sugar in healthy subjects is decreased to about 20 mg per 100 ml, and returns to normal, usually within 90 min.

In a patient with panhypopituitarism, unable to influence any of the factors regulating blood glucose homeostasis except epinephrine, the situation is different. Blood glucose remains low throughout the insulin tolerance test. Administration of cortisone and throxine to one such patient only slightly improved the unresponsiveness to hypoglycaemia, while treatment with HGH brought the blood glucose curve to normal (Luft 1965).

The second approach to the problem is by measuring plasma HGH during the insulin tolerance test. In healthy subjects, plasma HGH increases during such a test. When the pituitary is destroyed, as is so often the case in pituitary dwarfism, the plasma HGH level is not influenced by insulin hypoglycaemia (Luft 1965).

The insulin tolerance test does not stimulate a physiological condition, since it implies the depression of blood sugar to exceptionally low values. This insulin loading better compares with tests used in endocrinology to demonstrate the functional capacity of a gland. Such a test does not necessarily give information on the physiological significance of the product of the gland. We may assume that under normal conditions, and even during prolonged starvation, blood glucose does not fall by more than 10—15 mg per 100 ml. In order to mimic physiological conditions we infused as little as 0.01 unit of insulin per kg body weight over a 60 min period (Luft et al. 1966).

The results obtained in 21 such insulin infusion tests performed in healthy subjects may be summarized as follows: a decrease in blood glucose of at least 10 mg per 100 ml was almost always accompanied by a substantial rise in plasma HGH and, as a rule, the magnitude of the rise in HGH matched the degree of hypoglycaemia obtained.

All these experiments clearly demonstrate the intimate relationship between the blood glucose level and the secretion of HGH. Therefore, it may be concluded with certainty that HGH is of great significance for the maintenance of a normal blood glucose level.

In the above discussion on the effect of HGH on blood sugar homeostasis one of the major properties of the hormone has not been mentioned, i.e. its promoting effect on bodily growth and protein synthesis, the prime characteristics of the normal somatotrophic activity of the anterior pituitary. It may then be questioned what the biological fitness would be of a hormone with the function of stimulating growth which, at the same time, varied markedly with minor changes in blood sugar. The discussion involves the two major biological properties of the hormone: its anabolic and adipokinetic or antitocabolic effects.
The generally accepted view of these effects of GH is presented in Fig. 1. Its aim is to explain these activities as two actions of one and the same hormone (Raben 1965). The adipokinetic effect would serve the purpose of shifting cellular metabolism to the utilization of fat, whenever a shortage of carbohydrate develops. At the same time, through a decrease in glucose disappearance from the blood, the breakdown of protein for the purpose of gluconeogenesis is said to be diminished. Thus, through one mechanism — FFA release — the same hormone would act as an anabolic and anticatabolic agent. The increase in GH in plasma during hypoglycaemia might then be an expression of a feedback mechanism between blood glucose level and GH release. This explanation of GH action actually reduces it to a purely anticatabolic agent.

A second working hypothesis for GH action, introduced by Levine & Luft (1964), postulates two physiologically distinct hormones which may or may not be secreted together under a variety of circumstances, the somatotrophin proper (STH) and the adipokinetic factor (AK) (Fig. 2). AK then corresponds to the anticatabolic property mentioned above, and its secretion is evoked by the signal of carbohydrate deficiency. STH promotes epiphyseal proliferation and is probably the moiety responsible for the insulinogenic action of GH, thereby enhancing its anabolic effect. The signal for the liberation of STH is not known.

A third explanation of the dual action of GH has been presented by Rabinowitz et al. (1966). According to these authors, the anabolic actions of GH are optimized by the presence of insulin, whereas the diabetogenic actions are dominant in the absence of insulin.
Fig. 2.
The dual-factor theory of the effect of HGH on energy metabolism and growth.

Any of these theories as regards GH action may be correct. We have to await the clarification of the chemistry of the GH molecule before it can be decided whether we are dealing with two hormones or two aspects of the action of one and the same hormone.

The diabetogenic action of HGH

The fact that a hormone operates during hypoglycaemia by counteracting the effect of insulin does not carry the implication that this hormone must be diabetogenic. As a matter of fact, we demonstrated in earlier experiments that HGH in a daily dose as high as 30 mg had no significant effect on fasting blood sugar in 11 normal subjects, nor did it induce glucosuria (Ikkos et al. 1962).

On the other hand, there exist numerous experimental data which demonstrate that a state very similar to diabetes mellitus can be induced in human subjects with HGH (Ikkos & Luft 1960 a). I shall use some of our own data to show this:

1. The intravenous glucose tolerance was decreased in most of 11 normal subjects after three days on 30 mg of HGH daily (Ikkos et al. 1962). It was noticeable, and at that time unexplainable, that a diabetic glucose tolerance, a k-value below 0.95, was obtained in only three of these subjects.

2. In five non-diabetic hypophysectomized patients, given 10—20 mg HGH daily for 3—4 days, the fasting blood sugar increased (Ikkos & Luft 1962). The peripheral uptake of glucose was measured with ¹⁴C-glucose and was found to be unchanged by HGH in all but one case, where it decreased. One must bear in mind, however, that the peripheral uptake of glucose is directly correlated to the blood sugar level. When, as in the present experiment, the blood sugar rise was not accompanied by a similar increase in peripheral glucose utilization, this indicates that HGH in fact induced a relative decrease in glucose uptake.
3. Administration of HGH in a daily dose of 20 mg for 2—3 days to two hypophysectomized non-diabetic patients induced a condition similar to the idiopathic diabetes mellitus of the laboratory animal (Ikkos & Luft 1960).  

4. Some of our older findings clearly showed that HGH, when given to diabetic patients, led to deterioration of the disease. This was most obvious in hypophysectomized juvenile diabetics, in whom as little as 1—2 mg of HGH induced a dramatic response (Luft et al. 1958).

5. In this connection it should be mentioned that diabetes is ten times as common in acromegaly as in the general population (Daughaday 1962).

These and similar data in the literature have urged us and many others to answer the question of the diabetogenic action of HGH in the affirmative. However, our recent work on prediabetes makes it necessary to re-evaluate the concept of the diabetogenicity of HGH, and to consider it in a new context. We should first like to give a brief summary of our findings in pre-diabetes, on which this new view is based.

1. In the majority of healthy subjects the plasma insulin response to a standardized one-hour glucose infusion showed an immediate and substantial rise in plasma insulin and hyperinsulinaemia lasting for the rest of the infusion period (Cerasi & Luft 1967).

2. In diabetic patients the insulin response was either totally absent, or, if present, delayed and sluggish (Cerasi & Luft 1967). This type of response was found both in patients with overt diabetes of varying severity and in subjects with only an abnormal glucose tolerance test.

3. In genetically prediabetic subjects, i.e. the healthy identical twin sibs of diabetic patients, the plasma insulin response to glucose infusion was of the same type as in diabetic patients (Cerasi & Luft 1967 b). Therefore, it was concluded that a decreased and delayed insulin response to glucose is characteristic of the prediabetic state as well as of diabetes.

4. In 15—20 per cent of healthy, non-obese subjects with a normal glucose tolerance test, the insulin response was repeatedly found to be of the diabetic type. On the basis of the type of insulin response they gave, these healthy subjects were presumed to be prediabetics (Cerasi & Luft 1967 a).

5. In patients with acromegaly, the insulin response to glucose infusion was found to be one of two types, depending on whether the patients has a normal or decreased glucose tolerance (Luft et al. 1968). In acromegalic subjects with normal glucose tolerance, plasma insulin showed an immediate and, when compared to normal, grossly exaggerated rise in response to glucose administration. The degree of hyperinsulinism in these patients was correlated to the degree of activity of the acromegaly, the insulin response being highest in the group of patients with very active acromegaly. Successful treatment of the acromegaly was always accompanied by normalization of the insulin response in these patients.
In acromegalic patients with decreased glucose tolerance the plasma insulin response to glucose infusion, regardless of the degree of activity of the acromegaly, was of the type seen in non-acromegalic diabetic patients. After successful treatment of the disease the low and delayed insulin response remained unaltered even in those instances where the glucose tolerance was normalized.

Analysis of these results obtained in acromegalic patients with normal glucose tolerance affords insight into the complex effect of HGH. Insulin release was enhanced much more than could be explained by the hyperglycaemia induced. This is in accordance with the work showing that HGH has a direct insulinogenic effect (Pfeiffer 1965; Bouman & Bosboom 1965; Martin & Gagliardino 1967). On the other hand, HGH decreased the peripheral uptake of glucose — otherwise the hyperinsulinism would have been followed by hypoglycaemia.

The net result of this dual effect was a normal glucose tolerance. When diabetes appears in acromegaly, this must be attributed either to an exceptionally active state of the disease where the peripheral or diabetogenic action of HGH exceeds the secretory capacity of the $\beta$-cells, or to inability of the $\beta$-cells to respond to the insulinogenic effect of HGH. The first alternative is unlikely, since in acromegalic patients with diabetes the acromegaly is not more severe or of longer duration than in those with a normal glucose tolerance. Our findings in acromegalic patients support the second suggestion, i.e. an incapacity of the $\beta$-cells to produce insulin in an adequate manner.

Another finding indirectly supports this suggestion. HGH was administered to normal subjects with a normal glucose tolerance, some of whom had a normal and others an impaired insulin response to glucose infusion (Cerasi & Luft 1968). HGH markedly enhanced the insulin response in the former group, while the prediabetic responded to a much lesser degree. This finding elucidates the sequence of events when a prediabetic subject becomes acromegalic: the $\beta$-cells are here unable to respond to the insulinogenic action of HGH, while the peripheral or diabetogenic effect of the hormone remains unaltered. The net result in such an instance will be diabetes.

These new studies seem to give a more diversified picture of the diabetogenic action of HGH (Fig. 3). The hormone probably invariably decreases the peripheral utilization of glucose. In the presence of pancreas capable of responding to the insulinogenic effect of the hormone, HGH — within a reasonable dose range — is not diabetogenic. In prediabetic subjects, where compensatory hyperinsulinism cannot occur, HGH appears as a diabetogenic substance.

We have demonstrated that about 20 per cent of a group of healthy subjects were prediabetics (Cerasi & Luft 1967 a). This finding all of a sudden clarifies some results with HGH obtained earlier which were at that time
difficult to explain. For instance, that a diabetic glucose tolerance was obtained in only three out of 11 healthy subjects receiving high doses of HGH (see above). Furthermore, it becomes understandable why only about 25% of acromegalic patients develop diabetes.

From this discussion it appears that HGH as such cannot be considered a primary diabetogenic factor. At present, HGH in large doses may be regarded as an additional factor contributing to the development of diabetes, the major prerequisite being a pre-existing prediabetic state.

It should be emphasized that we have here only been discussing a diabetic state connected with overproduction of HGH or with the administration of rather large doses of the hormone. It remains to be shown whether the normal secretion of HGH with its daily fluctuations is of any significance in the precipitation of diabetes in prediabetic individuals.
REFERENCES


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