SPECIAL ARTICLE

The Relation Between the Growth and Diabetogenic Effects of the So-Called Growth Hormone of the Anterior Pituitary

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SUMMARY

The accumulated evidence in the literature since 1930 reveals that pituitary extracts rich in "growth hormone" exert powerful diabetogenic effects. It has not been possible thus far to separate these two activities as belonging to two distinct molecular species. However, an analysis on broad biological principles makes it most probable that two hormonal entities compose the so-called growth hormone fraction. The somatotrophic component (STH) would be expected to exert the following actions: (1) promote protein synthesis (together with insulin); (2) cause orderly proliferation of epiphyseal cartilage; (3) lead to increased insulin liberation from B cells. The total effect would consist of growth in bodily length and enhanced protein synthesis. The diabetogenic component (here called adipokinetic -AK) would play its role in: (1) liberating fatty acids from adipose tissue, thus shifting cellular metabolism to the utilization of fat, whenever there develops a relative scarcity of carbohydrate. This shift would inhibit glucose use and lead to insulin resistance, ketone production, etc.

This analysis is presented in order to stimulate experimental approaches for testing the validity of either the "one" or "two" factor hypothesis of the pituitary growth hormone fraction. Available experimental evidence is not adequate nor sufficiently convincing for unequivocal decision.

The close association between pituitary growth function and the occurrence of diabetes derives, in the first place, from the classic clinical observation of the frequency of disturbed glucose tolerance and overt hyperglycemia in acromegaly. Indeed, it is this observation which gave rise to the enormous literature on pituitary function in the animal kingdom.

In the decade between 1930 and 1940 the work of Evans,[1] Houssay,[2] Young,[3] Campbell[4] and Lukens[5] established that alkaline extracts of the anterior pituitary could produce the phenomenon of diabetes, especially in the dog and in the cat. In these carnivorous species such extracts, at first, produced an insulin-resistant diabetic state which reverted to normal on cessation of treatment. However, if administration of large amounts continued for weeks on end, the β-cells of the islets of Langerhans were irreversibly destroyed with the production of what has been known as metahypophyseal or permanent diabetes. In the early phase of the administration of pituitary extract, there was increased activity of the insulin apparatus of the β-cell observed by degranulation,[6,7] and in some species, hyperplasia (the rat).[8] It was postulated that the consequent destruction of the β-cell was due to overwork, atrophy and exhaustion.

The extracts contained the somatic growth principle (GH) of the anterior pituitary. Although these preparations were not pure they were reasonably free of the other known trophic factors of the gland. It thus became a matter of great interest whether the somatotrophic and the diabetogenic properties of alkaline pituitary extracts were due to the same or to different hormonal materials. Two of the trophic hormones of the hypophysis, namely ACTH and TSH, do exhibit diabetogenic properties via the production of glucocorticoids and thyroxins, respectively. However, the diabetogenic activity of the growth fraction could not be ascribed to contamination by either ACTH or TSH.[7]

Purification of the crude extract with respect to the characteristics specific for growth (tibial epiphyses) increased the diabetogenic effect parallel to somatotrophic activity.[4] Immunological and electrophoretic studies have shown several fractions. However, these seem to be very closely related.[9]

From time to time work has appeared concerning

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fractions possessing diabetogenic and/or adipokinetic properties, and free of somatotrophic activity.[10] Thus far, however, this separation has not been consistently and firmly established.[11]

The work of the last ten years on various effects of GH preparations administered in vivo, or added to isolated tissues in vitro, has produced a large variety of results which are difficult to correlate and ascribe to the action of one material.[11-14] The initial observation of Raben[15] that GH preparations raise the blood NEFA level has been amply confirmed and elaborated.[16-19] It is not clear how this material acts on the fat cell, and what the exact relationships are between it, catecholamines, thyroid, the glucocorticoids and ACTH.[20] However, it is an old established fact that the hypophysectomized animal or man mobilizes depot fat with difficulty.[2] The recent observations from Berson's laboratory indicate that lack of available carbohydrate (fasting and hypoglycemia) is followed by a rise in the NEFA level accompanied by an increase in immunologically determined serum GH values.[21,22] The pituitary is thus seen to respond promptly to metabolic situations, and it can be argued that this may be the pathway of regulation by which the tissues are presented with easily oxidizable fatty acids in the face of carbohydrate lack. It has also been shown that the secretion of this principle is equally promptly inhibited by carbohydrate in the presence of insulin. The shift to fatty acids as a fuel may account at least in part for the inhibition of glucose uptake and the fall in sensitivity to insulin which occurs in experimental and clinical states of hyperactivity of the pituitary. This is supported by Randle[23] on the basis of his own work and the earlier data of Mirsky et al.[24] and of Wick and Drury.[25] It is consistent with the work of Russell[26,27] which showed that the rise in cardiac glycogen in the fasting animal did not occur in the absence of the hypophysis. The rise in cardiac glycogen after fasting and after pancreatic and phlorrhizin diabetes is probably due to inhibition of the downward glycolytic pathway making available glucose-6-phosphate for glycogen synthesis.[23] The adipokinetic effect of the pituitary may also account for the earlier observations of lowering of the RQ[28] and preservation of the glycogen stores (myoglycostatic effect).[29]

The intense insulin resistance produced after prolonged administration of growth extracts can probably not be explained simply by the inhibitory effect of fatty acids on glucose turnover. Evidence has been adduced of the appearance of insulin inhibitory protein fractions after GH preparations have been given for some days (e.g., Krahl,[12] Park and Bornstein,[30,31] etc.). Of interest in this connection is the observation of Vallance-Owen and Lukens[32] that the albumin-linked insulin antagonist disappears from the blood after hypophysectomy. The exact connection between fat mobilization and the appearance of insulin antagonists is not understood.

For the sake of brevity let us call the just described effects by the term adipokinetic or AK activity. Viewed from a biological standpoint these effects serve an animal well indeed by enabling him to use his fat stores for the expenditure of energy, by keeping in check the action of insulin, and by conserving carbohydrate for the use of the central nervous system which cannot readily use fat derivatives, and which does not require insulin for glucose uptake. However, the AK-insulin-inhibiting activity does not seem to go hand in hand with bodily growth and increased protein synthesis, the prime characteristics of the normal somatotrophic activity of the anterior pituitary. The work of Lukens,[33,34] Gaebler,[35] Mirsky[36] and Scow[37] had shown some years ago that the enhancement of protein synthesis by growth hormone required the presence of endogenous (pancreas) or exogenous insulin. It is, indeed, difficult to see a sense of biological fitness in having the AK-insulin-antagonistic activity reside in the same molecule with the purely growth and protein synthetic properties.

It has been argued that the liberation of fatty acids provides a *needed* source of energy for bodily growth, as if available carbohydrate would not suffice for this purpose. We know that two moles of ATP are needed for the activation of one mole of an amino acid of average molecular weight of 150. Let us suppose that for the other reactions in protein biosynthesis (messenger-RNA, s-RNA and peptide-bond formation) a comfortable total of eight additional moles of ATP per mole of amino acid are needed. It can be calculated that in order to synthesize 25 gm. of protein per day (which would be a very large gain during growth in man) the energy requirement would be met by the ATP produced in the dissimilation of about 10 gm. of glucose. It is therefore not necessary to invoke the need for a large supply of fatty acids as an unequivocal prerequisite for this purpose. It must also not be forgotten that carbohydrate utilization spares protein. It would seem therefore more logical to connect growth promotion and protein biosynthesis with a

situation which allows for insulin liberation and the enhancement of carbohydrate uptake. Indeed, many such effects of somatotrophic preparations have been known to occur in the intact animal and in some isolated tissues.

Thus, soon after the administration of purified GH there occurs a short period of hypoglycemia combined with some fall in the NEFA level of the blood.[11,14,20] The addition of such preparations to isolated tissues in vitro enhances their glucose uptake.[12] It is not clear whether this hypoglycemic action is mediated by the release of insulin from the pancreas or from attachment to tissues. That GH preparations can and do release insulin from the β-cells has again been shown by Campbell[38] in the intact dog and by Pfeiffer[39] in the semi-isolated dog pancreas. Luft et al.[40,41] demonstrated that in some active acromegalics, infusion of glucose leads to a very exaggerated insulin release as compared to the control subjects, and that the administration of human GH to normal and hypopituitary man gives rise to very high insulin levels in blood on glucose infusion. The insulin evoking property of GH is consistent with the lower than normal insulin levels in the blood found after hypophysectomy.[39]

The destruction of the islets found in metahypophyseal diabetes is the result of the long-continued injection of *very large amounts* of GH. This need not argue against a healthy physiological trophic effect of normally secreted amounts of this hormone, even though the islands may be completely protected by normoglycemia in the presence of such doses of GH.[5]

When GH extracts are administered one obtains the contradictory situation in which high insulin liberation is accompanied by insulin resistance and decreased glucose tolerance. However, during periods of rapid bodily growth in animals or in man, carbohydrate tolerance is not impaired, nor does insulin resistance develop. Conversely, during fasting when carbohydrate utilization diminishes, and the NEFA level is increased, there is no evidence of insulin release.

We should like therefore to put forward the working hypothesis that even the present purified GH preparations contain two physiologically distinct hormones which may or may not be secreted together under varying circumstances. The somatotrophin proper (STH) would promote epiphyseal proliferation, insulin secretion (liberation?) and glucose uptake. The other, closely related factor, called here the adipokinetic factor (AK), results in mobilization of fat, inhibition of glucose uptake and insulin resistance. The AK, but not the STH, is evoked by the signal of carbohydrate lack. It is not known at present what the physiological signal is for the liberation of STH. We would assume that in acromegaly both factors are liberated in excess, and that the variation in the metabolic parameters would depend on the ratio of the two materials in a particular patient.

One has to assume, in addition, that the immunological assay measures both factors since the levels are high in acromegaly and can be raised by hypoglycemia and starvation as well. It would, of course, be of great advantage to be able to measure STH and AK separately. The only available technics for the STH property are the tibia of the hypophysectomized rat and the so-called sulfation factor activity of Daughaday.[42] There are as yet no studies available as to whether a rise in immunologically determined GH during fasting or hypoglycemia is accompanied by an increase in tibial epiphyseal activity. However, we have data from the work of Almquist et al.[43] showing that sulfation factor activity of serum does not increase during prolonged fasting and insulin hypoglycemia nor is it decreased by glucose administration. Sulfation factor activity is, however, increased in acromegaly, late pregnancy, lactation and during growth. If, indeed, sulfation factor activity mirrors the pure somatotrophic factor, while immunologically determined GH includes it and AK, then the assay data by these various technics could be taken as further confirmation of the presence of two factors in pituitary growth hormone.

It has been shown by Reid[44] that at an acid *p*H the diabetogenic activity of a GH preparation is markedly inhibited while its somatotrophic property is not depressed. Such a finding does suggest the presence of separate factors even though it does not prove it.

We realize, of course, that many difficulties and inconsistencies exist which may not be readily explained at present by the concepts here proposed. Thus, no light is thrown on the intriguing difference between the ability to produce metahypophyseal diabetes in the grown dog versus the resistance of puppies.[45] However, the concept of one factor is equally obscure regarding this difference. The hypothesis now presented seems to us biological advantageous, and suggests a large variety of experimental approaches for testing its validity. It will have served its purpose if it does nothing more than stimulate interest in this field with the proposed point of view in mind.

SUMMARIO IN INTERLINGUA

Le Relation Inter le Crescentia e le Effectos Diabetogene del Si-Appellate Hormon de Crescentia del Pituitario Anterior

Evidentia accumulate in le litteratura depost 1930 indica que extractos pituitari ric in hormon de crescentia exerce un potente effecto diabetogene. Usque al tempore presente il ha non essite possibile separar le duo mentionate activitates e attribuer los a duo distincte species molecular. Tamen, un analyse a base de general principios biologic rende probabile que duo entitates hormonal compone le si-appellate fraction del hormon de crescentia. Il pare plausibile postular que le componente somatotrophic debe exercer le sequente actiones: (1) Promover le synthese de proteina (insimul con insulina); (2) causar un appropriate proliferation de cartilagine epiphysee; (3) causar un augmentate liberation de insulina per le cellulas beta. Le effecto total consisterea alora de un crescentia del longor del corpore e de un promovite synthese de proteina. Le componente diabetogene (denominate adipocinetic in le presente communication) haberea su rolo in: (1) liberar acidos grasse ab tissu adipose, con le resultato que le metabolismo cellular es transponite al utilisation de grassia quandocunque il occurre un manco relative de hydrato de carbon. Iste transposition inhibi le uso de glucosa e resulta in resistentia contra insulina, le production de cetones, etc.

Le presentation de iste analyse ha le objectivo de stimular le disveloppamento de methodos experimental pro testar le validitate del hypothese a un o a duo factores con respecto al fraction de hormon de crescentia in le pituitario. Le existente evidentia experimental non es adequate e non sufficientemente convincente pro supportar un decision inequivoc.

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LETTER TO THE EDITOR

DEAR EDITOR:

A book, *Familiar Medical Quotations,* which we hope will be a great collection of wit and wisdom from and about physicians of the ages is being assembled. The writings and utterances of physicians, teachers and investigators from the dawn of medical history to the present are being sifted for the nuggets of genius and brilliant good humor which characterize the humanity of a profession. The collection will also include quotes from lay writers—including the Scriptures—dealing with disease, doctors and medical life.

We are particularly anxious to obtain the quotations of individuals who, unlike Shakespeare and Osler, have hidden their occasional gems so that only a few are aware of them.

We welcome all such favorite quotes that your readers would like to see included in this volume. Contributions may be addressed to me c/o *Familiar Medical Quotations,* 34 Beacon St., Boston, Mass. 02106.

Sincerely yours,

MAURICE B. STRAUSS, M.D.
Editor

BOOK REVIEWS

ACETON BIS ZUCKER (Aceton to Sugar), NACHSCHLAGEBUCH FUR ZUCKERKRANKE (A Reference Book for Diabetics). *By G. Katsch, G. Mohnike and H. J. John. 4th edition, 232 pages with 33 illustrations, VEB Georg Thieme, Leipzig, 1964.*

This is an excellent compendium written for the layman, but undoubtedly also of value to the practicing physician, the nurse, the dietitian and the social worker, who have to instruct diabetic patients about the nature of the disease, its complications and its management. In alphabetical order, from A to Z, the various topics are presented authoritatively. The discussions are brief, but concise, where general background information is concerned. They are limited to definitions or translations in the case of medical terms, but are detailed wherever they deal with the management of the disease. Thus, adequate space is given to diet planning and food values, to the measuring of insulin and technic of insulin injections, to urinalysis, to care of the feet, general hygiene, etc. A number of excellent illustrations and tables enhance the value of the book. The diabetic patient who is interested in getting acquainted intelligently and intimately with his disease will find a wealth of information and answers to all the questions which arise in living with diabetes.

DIABETES AS A WAY OF LIFE. *By T. S. Danowski, M.D. $4.50, 186 pp., Coward-McCann, New York, 1964.*

This is the second edition of a manual for diabetic persons, first published in 1957. The book's outstanding qualities are