Regulation of Blood Glucose

Altered Dynamics in Certain Diabetes-like States

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Homeostasis of blood glucose is essential to life. For this reason, the safeguards built into the mechanism that acts to keep blood glucose above a certain critical level are both numerous and complex. The necessity for maintaining homeostasis of blood glucose rests upon one basic fact: namely, that the brain ordinarily can use only glucose as a source of energy.[1-2] Ability of glucose to penetrate into brain cells depends almost entirely upon maintenance of an adequate glucose gradient across the cell membrane; in contrast to many other cells of the body, permeability of brain cells to glucose does not require the presence of insulin.[3]

Since the liver, the muscle mass, and the adipose tissue are capable of extracting appreciable amounts of glucose from circulating blood, it is clearly important for the body to have mechanisms whereby the flow of glucose to these tissues can be promptly reduced whenever the supply of carbohydrate is threatened. At the same time, the tissues concerned must have an alternate source of fuel that is rapidly available. Viewed in this perspective, it can be seen that the body sometimes must make itself temporarily "diabetic" in order to preserve the integrity of its central nervous system.

When a superfluity of glucose is present in blood two important adjustments normally take place to increase the rate at which the disposal of blood glucose can be accomplished. They are an increased uptake of glucose by the liver[4] and an increased release of insulin by the pancreas.[5] Release of extra insulin permits an increased rate of entry of glucose into both muscle and adipose tissue. Whether liver cells are similarly sensitive to insulin is still a matter of argument.[6-8] However, it seems that the mere raising of the blood sugar promotes glucose uptake by liver, muscle and adipose tissue, presumably by a mass action effect or, as Himsworth[9] has expressed it, because of a greater "head of pressure."[10]

The blood sugar level in subjects in the basal state is determined by the rate at which glucose is released by the liver into the circulation and by the rate of removal of glucose (1) by brain, (2) by liver, (3) by extrahepatic nonencephalic tissues (largely skeletal muscle, heart and adipose tissue), and (4) in hyperglycemic states, by the kidney.

Information is available about these rates. Approximate values and ranges are summarized in table 1. The individual values have been selected from the literature on carbohydrate physiology and are presented as approximations only and not as precise final figures. Nevertheless, it seems possible from these data to arrive at certain useful generalizations about glucose balance.

In figure 1, three glucose curves are shown. The first (A) is a hypothetical curve describing what might happen in a patient with diabetes of moderate severity following discontinuance of treatment with short-acting insulin. In such an individual the fasting blood sugar might be as low as 80 mg. per cent. However, lack of insulin would preclude significant extrahepatic utilization of glucose at this concentration and only the brain would continue to remove glucose at its usual rate of approximately 5 gm. per hour. At the same time, lack of insulin might depress liver glucokinase activity sufficiently to stimulate increased glucose output by the liver to a rate of the order of 15 gm. per hour. During the first hour, 10 gm. of glucose would enter the glucose space (estimated as 17 L. in a 70 kg. male[21]) and increase its glucose concentration by 60 mg. per cent.

TABLE 1

Glucose balance (gm. per hour in a 70 kg. male)

	Output	Uptake
Liver	15 (0-17)[11-14] (28, in diabetic acidosis)[15]	0 (at 150 mg. per cent concentration of blood glucose)[4,10]
Brain		5 (2.6 - 5.1)[16,17]
Extrahepatic area (excluding brain)		<4[18,19] (<4 - 30)[20]

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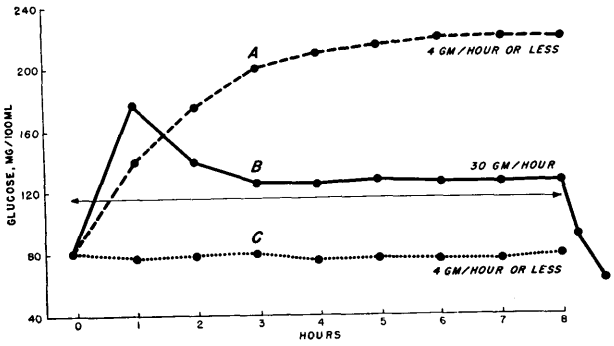

FIG. 1. Relationship of blood glucose concentration and peripheral glucose assimilation rate under varying metabolic circumstances.
A. Glucose curve of hypothetical subject with moderate diabetes following withdrawal of short-acting insulin (basal state).
B. Mean of glucose curves of six normal subjects during eight-hour glucose infusion at 0.5 gm./kg./hr. (Felber, et al.[20]).
C. Glucose curve of a normal subject during prolongation of overnight fast.

There is considerable evidence that, over a wide range of blood glucose levels, glucose uptake is a linear function of the arterial glucose concentration.[22,23] This situation appears to obtain in the diabetic as well as in the normal animal although, in the diabetic subject the "head of pressure" has to be greater than in the normal subject to ensure the same degree of utilization.[9] Within certain limits, the liver uptake or output of glucose also can be considered to be a linear function of the arterial glucose level.[4] Accordingly, as the blood sugar level rises an increased rate of glucose assimilation can be anticipated and the hepatic glucose output would be expected to decrease. Thus, the rising glucose curve would be hyperbolic in shape, flattening out as the utilization rate comes into balance with the decreasing rate of glucose output by the liver. At this new equilibrium, the blood sugar would tend to remain constant. At this level of hyperglycemia, the rate of peripheral glucose assimilation might well be similar to that of a nondiabetic control subject in the basal state.

The second curve (B) is one based on the experiments by Felber et al.[20] involving infusion of glucose into normal subjects for eight hours at a rate of 0.5 gm./kg. body weight per hour. This curve is constructed from the means of data from six experiments and shows that after the third hour of infusion the extrahepatic tissues are able to remove approximately 30 gm. per hour at a blood glucose concentration of less than 130 mg. per cent.

Curve C is the glucose curve obtained in a normal subject whose overnight fast has been extended by eight hours. Evidence from a number of sources indicates that in the basal state only a small fraction of the fuel of the extrahepatic tissues is derived from glucose.[24] Andres and co-workers[19] reported experiments in which the respiratory quotient of forearm muscle in the post-absorptive state was 0.80. They found that even when the forearm was extracting only 0.5 μM. of glucose per 100 mg. tissue per minute, 60 per cent of this amount was accounted for by lactate production from the same site. In these studies, the remaining glucose could account for only 7 per cent of the local oxygen uptake.

Andres and associates[19] calculated that the total glucose uptake for heart and skeletal muscle in subjects in the basal state is approximately 3.6 gm. per hour. Presumably the extrahepatic, extra-encephalic tissues of a normal subject in the basal state do not remove much more than 3 or 4 gm. per hour and may remove less as the period of fasting continues.

From the data in table 1 and figure 1, it can be seen that the capacity of the liver to increase its output of glucose cannot normally exceed the ability of the extrahepatic tissues to remove the released sugar, provided (1) that the normal mechanisms of carbohydrate disposal are intact, and (2) that these mechanisms are given time to adjust to the new glucose load.

On the other hand, when the capacity of the extrahepatic tissues (other than the brain) to accommodate to an increased glucose load is diminished, the liver may fail to decrease its rate of glucose output enough to permit the blood sugar to remain within a normal range. Situations in which a normal fasting blood glucose may be observed in the presence of a grossly impaired disposal mechanism include states of glycogen depletion, such as occur in starvation, and in the glycogen storage diseases.

In diabetes mellitus, hepatic glucokinase activity drops sharply, presumably due to insulin lack, while glucose-6-phosphatase activity increases.[10] Under such circumstances, the liver continues to release glucose even though the concentration of glucose in blood may exceed by far the 150 mg. per cent level that ordinarily is associated with glucose equilibrium across the liver. Apparently the same deficiency of insulin that reduces the ability of the extrahepatic tissues to accommodate to an increased glucose load also may cause the liver to inflict such a load. This makes sense, teleologically, if the propositions are accepted that (1) small quantities of carbohydrate are indispensable to the proper functioning of the Krebs cycle and to maintain muscle gly-

cogen* and (2) that hyperglycemia can partly overcome the block in peripheral glucose assimilation imposed by insulin deficiency.

It is obvious that the hyperglycemia of diabetes mellitus frequently is far from successful as an adaptive measure. When the blood sugar exceeds the renal threshold, glucose is wasted, sometimes in prodigal fashion. Literally, diabetes mellitus as a clinical phenomenon is a "disease of adaptation."

DIABETES-LIKE STATES

The notion of the diabetes-like state has come to be associated with hyperglycemias not primarily due to insulin lack. Such a picture has distinct limitations both etymologically and biochemically. First, the term "diabetes" has nothing directly to do with hyperglycemia or melituria; it refers only to polyuria. Second, modern methods of assay for insulin-like activity so far have failed to document certain clinically clear-cut cases of diabetes mellitus as being due to insulin deficiency.[25] Thus, we are left with the inaccurate term "diabetes-like" and the uncomfortable awareness that the syndrome known as diabetes mellitus is not one but several different diseases.

On the other hand, there are a number of conditions characterized by abnormal hyperglycemia that are clearly not diabetes mellitus. Four of these have been selected for brief discussion and for comparison with what might be called diabetes mellitus proper. These are (1) "hunger diabetes," (2) "glucagon-diabetes," (3) "epinephrine diabetes," and (4) "steroid diabetes."

"Hunger diabetes" is a term that refers to the transient, impaired glucose tolerance and glucosuria that occur after a period of fasting or of carbohydrate privation. It is characterized by a normal or lower than normal fasting blood sugar, an excessive rise in blood glucose after a glucose load, with a subsequent return to control glucose values that is somewhat delayed.[27] Liver glycogen stores are depleted and there is unconfirmed evidence that much of the first supply of glucose ingested after a prolonged fast is stored in the liver rather than being oxidized.[28]

Several theories have been proposed to explain hunger diabetes; it has been variously attributed to temporary failure of insulin secretion in response to hyperglycemia,[29] decreased liver glucokinase activity,[30] and increased secretion of substances rendering peripheral cells relatively impermeable to glucose.[31]

Although the mechanism of hunger diabetes has not been defined, a recent study has shown that the relative assimilation index (an index of peripheral glucose uptake) decreases by approximately 60 per cent in normal subjects given carbohydrate-poor diets for a three-day period.[32] The same study confirmed the observation[33] that net glucose tolerance does not diminish in subjects maintained for several days on diets of which the sole carbohydrate is fructose.

Thus, it would seem that hunger diabetes principally involves impairment of peripheral glucose utilization. Such impairment seems adequately to explain the abnormal glucose tolerance that occurs in this disorder although some diminution of the ability of the liver to remove glucose cannot be ruled out.

The diabetes-like state induced in man when repeated injections of glucagon are given is very similar to hunger diabetes. Again, the fasting blood sugar is normal or low; and again, impairment of peripheral glucose assimilation is noted.

In figure 2A, the response of the blood glucose of a normal subject given a standard breakfast containing 63 gm. of carbohydrate is shown. There is virtually no rise in venous glucose and no glucosuria; in B of the same figure, the response of the same subject to an identical breakfast is shown after three days of repeated glucagon injections (4 mg. intramuscularly every six hours). This time markedly impaired tolerance and glu-

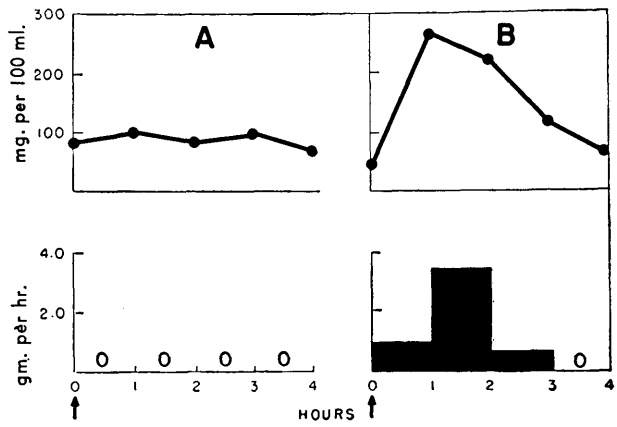

FIG. 2. Changes in blood glucose (mg./100 ml.) and glucosuria (gm./hr.) in a normal subject after breakfast.[34]
A. Before glucagon treatment.
B. During glucagon treatment. Arrows represent ingestion of an identical breakfast containing 63.0 gm. of carbohydrate.

*There is evidence that a certain amount of carbohydrate is required by the tricarboxylic acid cycle for what Peters has called "operative purposes."[24] This seems to be the amount needed to replace the dicarboxylic acids that are lost from the cycle by attrition. Moreover, the muscles require a store of glycogen so that they can continue to function temporarily in situations where energy must be expended under conditions of oxygen deficit.

cosuria occur, even though the fasting blood sugar is slightly lower than in the control test.[34]

It has been proposed that in its early stages at least, the diabetes-like state induced by glucagon is akin to hunger diabetes since fasting blood sugar remains normal or low, liver glycogen is depleted, and the condition can be ameliorated by carbohydrate feeding. Recently it has been reported that a single injection of glucagon administered during the night will be followed by some degree of impairment of the basal glucose tolerance the following morning.[35]

When a diabetes-like state occurs because of a pheochromocytoma it can have all of the characteristics of garden variety diabetes mellitus: fasting hyperglycemia, ketosis and impaired glucose tolerance.[36] This entire picture has been known to disappear following removal of the offending tumor.[37]

Epinephrine is commonly thought of in terms of its hyperglycemic-glycogenolytic effect and it is not widely recognized that epinephrine is a powerful inhibitor of glucose assimilation in the periphery.[38-40]

It has been pointed out that when epinephrine induces glycogenolysis in muscle an increased intracellular concentration of glucose-6-phosphate occurs, which in turn inhibits phosphorylation of glucose.[41,42] In any event, epinephrine "diabetes" also involves a considerable degree of impairment of peripheral glucose assimilation, thereby permitting the hyperglycemia initiated by epinephrine-induced hepatic glycogenolysis to persist.

Last, there is evidence that the glucocorticoids inhibit peripheral glucose assimilation in addition to their other effects.[43-47] Ingle[48] has clearly shown that the intravenous administration of adrenal cortical extract to the eviscerated rat over a period of twenty-four hours decreases its tolerance for glucose given by constant infusion. This effect was observed only in animals treated with insulin.

Although a number of experiments in man and laboratory animals have indicated that the glucocorticoids may interfere with peripheral glucose assimilation, it should be mentioned that DeBodo and Altszuler,[49] in a review published in 1958, concluded that there is no clear-cut evidence of an inhibition of glucose utilization by the adrenocortical steroids.

Certainly, discussion of a possible inhibitory effect on glucose uptake by glucocorticoids should not distract attention from the firmly established action of these hormones upon hepatic glucose production from three-carbon precursors.[50] However, it seems unlikely from what is known about the dynamics of blood glucose regulation that increased hepatic glucose output alone can account for the elevated fasting glucose levels observed so frequently during cortisone treatment and in Cushing's syndrome.

In table 2 an attempt has been made to summarize a few of the gross metabolic characteristics of certain diabetes-like states as they compare with those of classical diabetes mellitus. From this table it can be seen that there are major differences in such parameters as level of fasting blood sugar and liver glycogen content that may help distinguish the disorders from one another; the trait they all share (with the possible exception of steroid diabetes) is impairment of peripheral glucose assimilation.

TABLE 2

Tentative classification of certain diabetes-like states

	Fasting Blood Glucose	Hepatic Glucose Output	Peripheral Glucose Assimilation	Liver Glycogen Content	Ketonemia
DIABETES MELLITUS	↑	↑	↓	↓	↑
"GLUCAGON DIABETES"	N or ↓	↓	↓	↓	↑
"EPINEPHRINE DIABETES"	↑ or N	↑	↓	↓	↑
"HUNGER DIABETES"	↓ or N	↓	↓	↓	↑
"STEROID DIABETES"	N or ↑	↑	N or ↓	↑	N or ↑

It is of course dangerous to generalize about peripheral assimilation of glucose. For example, there is some evidence that epinephrine promotes uptake of glucose by adipose tissue, while it inhibits entry of glucose into muscle.[51,52] The effect of glucocorticoids on peripheral glucose uptake seems quite variable. For the purpose of this discussion, rate of peripheral glucose utilization must be thought of as a "net" value, analogous to the concept of "total peripheral resistance."

It seems helpful to consider the metabolic events that occur in the diabetes-like conditions induced by starvation, glucagon and epinephrine as disorders of glucose conservation. An attempt has been made to show that increased hepatic output of glucose alone is neither a practical nor a feasible way to maintain integrity of the blood glucose level. Even if the liver were able to pour out enough glucose to mimic the effects of a prolonged glucose infusion it would be doing so at enormous cost to the body's stores of protein. In the case of the glucocorticoids, they too seem to be concerned with the need for maintaining glucose homeostasis except that here the emphasis seems to be on increased gluconeogenesis.

SUMMARY

In summary, the relative effectiveness of the liver and the extrahepatic tissues in maintaining glucose homeostasis has been assessed. Analysis of available data leads to the conclusion that peripheral disposal mechanisms normally can accommodate to large glucose loads; hence, it appears that some impairment of peripheral glucose assimilation must be present before a diabetes-like state can occur. This proposition also is consistent with the teleological concept that conservation of glucose, and hence of protein precursors of glucose, is an appropriate metabolic response for the body to make to carbohydrate privation.

SUMMARIO IN INTERLINGUA

Regulation del Glucosa del Sanguine: Alterate Dynamica in Certe Statos Diabetoide

Es evalutate le efficacia relative del hepate e del tissus extrahepatic con respecto al mantenentia del homeostase de glucosa. Le analyse del currentemente disponibile datos resulta in le conclusion que mechanismos peripheric es normalmente capace a adjustar se al demandas de grande cargas de glucosa. Isto significa que le un o le altere vitiation del processo de assimilation peripheric de glucosa debe esser presente ante que un stato diabetoide pote occurrer. Iste these es etiam in congruentia con le concepto teleologic que le conservation de glucosa, e ergo del precursores proteinic de glucosa, es un responsa appropriate del parte del corpore quando illo es private de hydrato de carbon.

ACKNOWLEDGMENT

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Sulfated Polysaccharides and Atherosclerosis

Many lines of investigation are being pursued in man and experimental animals to find a way of preventing, or controlling, the arterial damaging process of atherosclerosis . . . Heparin seems to be effective because it activates a "lipemia-clearing factor" and thus promotes enzymatic lipolysis. A synthetic heparinoid, sulfated alginic acid (SAA), has also been shown to have antilipemic and atherosclerosis-modifying properties in the rabbit. Additionally, it promotes marked lipid phagocytosis in the spleen (N. Gutmann and P. Constantinides, *A.M.A. Arch. Path.* 59:717, 1955). In the present study this synthetic sulfated polysaccharide (SAA) was compared to heparin in respect to its effects on pre-established atherosclerosis in the rabbit (P. Constantinides, P. Saunders, and A. Wood, *A.M.A. Arch. Path. 62*:369, 1956). . . .

SAA also appeared to have a significant effect in retarding the process of coronary atherosclerosis and in reducing the incidence of myocardial necrosis. The effect of SAA differed particularly from that of heparin in that it produced large lipid-laden spleens, while heparin decreased the xanthomatosis of this organ as compared to the control animals. More renal glomerular lipid was also observed in the SAA treated groups, but this appeared to be associated with protection of these animals from renal scarring. Two animals died from massive hemorrhage early in the therapeutic period in each of the treated groups, but reduction in the quantities of administered heparin and SAA eliminated this complication.

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