BLOOD SUGAR REGULATION AND THE ORIGIN OF THE HYPERGLYCEMIAS.

III. THEORY.

By EINAR LANGFELDT.

(From the University Physiological Institute, Christiania, Norway.)

(Received for publication, February 2, 1921.)

On the basis of the experimental results and of the previous exposition of the other facts concerned, an attempt is made to explain the blood sugar regulation and the mechanism of the origin of the hyperglycemias.

Normal Blood Sugar Regulation.

As previously mentioned, Paper I, it is usually supposed that sugar formation in the liver is regulated by circumstances outside the liver. The requirement of the organs for sugar is the discharging moment and in a nervous or chemical way the liver then is influenced to form glucose from glycogen.

In opposition to this opinion we may, according to our investigations, explain the maintenance of the constant blood sugar concentration in a simpler way. It is not necessary to suppose any cause at a distance, and the requirement of the organs for sugar may be disregarded.

We do not know of nor have we proved the existence of any glycogenolytic agency in the liver other than the diastase. As the action of this diastase depends on precise hydrogen ion concentrations, we may suppose that the glycogenolysis is regulated by the hydrogen ion concentration of the liver tissue. The hydrogen ion concentration of the blood is pH 7.33 at 37°C.; that of the tissues is probably a little less alkaline, on account of the continuous formation of carbonic acid, but still on the alkaline side of the neutral point.
According to this opinion sugar formation should be constant, not inconstant as would be the case if the regulation took place according to the requirement. Under normal conditions the liver always discharges the same quantity of glucose.

One may also conclude from the experiments that the blood sugar concentration probably would be higher if the optimum of the chloride diastase lay closer to the hydrogen ion concentration of the liver tissue. We may therefore consider the location of this optimum suitably away from the hydrogen ion concentration of the tissue as an arrangement of security. Here we have an example of an enzyme, which acts not under conditions most favorable to the enzymatic action, but on the contrary in a manner limited by the milieu wherein it is situated.

The maintenance of the blood sugar concentration is considered to take place in the following manner:

Glycogenolysis is governed by the hydrogen ion concentration in the liver cells (a, Fig. 1). With a constant blood flow and constant temperature glucose is discharged at a constant rate from the liver to the blood. A part of this glucose is burned (b), another part is stored in the muscles and cells as glycogen (c), and the remainder returns to the liver, where it again forms glycogen (d). Here glycogen formation depends upon the presence of the pancreas hormone (e), and the material for this formation is chiefly the carbohydrates and the proteins of the food (f).

This theory also explains why the blood sugar concentration is constant when the liver is exhausted of glycogen, and in starvation. In this case the organism is supported from its own stores, from the glycogen of the cells, from protein, and from fat. These substances are broken down in starvation, carried to the liver as dissociated products, and the process is then the same as in the case of the food supply (g).

The conclusion is reached that glycogen formation and glycogenolysis are consecutive processes. The diastase acts continuously and glycogen formation takes place rapidly.

*Origin of the Hyperglycemicas.*

It is evident from Fig. 1, which demonstrates the above hypothesis of blood sugar regulation, and from Fig. 2, in which the experimental results are presented, that hyperglycemia may arise in three ways:
Glycogenolysis is governed by the pH of the liver cells.

Formation of glycogen in muscle and other cells in the presence of the pancreas hormone.

Glycogen formation conditioned on presence of the pancreas hormone.

In starvation:
- Glucose from proteins
- Amino-acids
- Glycerol from fat
- Fatty acids and ketones (?)
Fig. 2. Action of liver diastase after 19 hours under different influences.
1. By a change of the hydrogen ion concentration of the liver tissue so that the pH is identical with or close to the optimum of one of the curves.

2. Or by a displacement of the curve of action of the liver diastase in such a way that the optimum corresponds or is close to the pH of the tissue.

3. Or by a lack in the formation of glycogen on account of the insufficient functioning of the pancreas, which would cause a superfluity of glucose in the blood.

Under normal conditions practically only the phosphate and chloride diastases are of importance, and of these the chloride diastase is more important on account of the greater affinity of the Cl ion for diastase. The optimum of the chloride diastase lies at pH 6.8. This hydrogen ion concentration represents neutral reaction at 37°C. Therefore, to obtain maximum glycogenolysis, the milieu of the diastase in the liver must be neutral.

The action on the blood sugar concentration of acids given per os or by transfusion of the liver, the influence of the gastric juice in depancreatized dogs, and the postmortem glycogenolysis are thus explained.

The second way in which hyperglycemia may arise is by displacement of the optimum of the liver diastase to or close to the hydrogen ion concentration of the liver tissue.

Such a displacement takes place under the influence of adrenalin or, in a higher degree, by simultaneous influence of adrenalin and thyroiodine. It may be that the diastase forms a complex compound with these substances, as it does with phosphates, chlorides, and many other substances, and that the affinity between diastase and adrenalin-thyroiodine extract is greater than between diastase and chloride ion. The new complex compound has its optimum at pH 7.73. The glycogenolysis is very intensive, and even at pH 7.33 it is just as heavy as the Cl diastase at pH 6.8.

That the adrenalin alone, when much diluted, is inactive, but very active when thyroiodine is added, is consistent with the action of subcutaneously injected adrenalin on the blood sugar. When thyroidectomy is performed previous to the adrenalin injection, the adrenalin is either inactive or much larger doses are required (1). This is completely explained by these experiments.
Thyroidine, when added alone, is without effect; only with adrenalin has it any influence on the glycogenolysis. By this experiment the variable and inconstant results, which are obtained in investigations regarding the effect on the blood sugar concentration by feeding thyroidine, are explained. The effect depends mainly on the secretion of adrenalin under the influence of the sympathetic nervous system, which does not react in the same manner in every case of hyperthyroidism.

That the extracts of hypophysis are without effect on glycogenolysis is also in agreement with the biological experiments on the action of these substances on the blood sugar. It has not been possible to produce experimentally hyperglycemia or glycosuria by injection of extracts of hypophysis. Nevertheless spontaneous glycosuria or genuine diabetes is observed not infrequently in the case of acromegalia. This glycosuria may be due to a temporary disturbance of function in any of the other endocrine organs. A qualitative alteration of the function of the anterior lobe of hypophysis is also possible. However, the normal hypophysis has no direct influence on glycogenolysis.

The third way in which a hyperglycemia may arise is by a lack in the formation of glycogen, such as very probably takes place in pancreatic diabetes, to which diabetes mellitus is due. The experimental pancreatic diabetes belongs partially also to the first group, as there is not only a lack in the glycogen formation, but there also undoubtedly takes place an increased glycogenolysis in the liver on account of the absence of the neutralizing pancreatic juice.

All the experimental hyperglycemics belonging to the first and second group and owing to increased glycogenolysis are of a transitory nature. The former theories on this problem are based mainly on experiments regarding transitory hyperglycemics and glycosurias. Thus the theory of nerve control is based on piqure and on numerous clinical observations on the influence of the nervous system and nervous disturbances on the glycosuria in diabetes. Characteristic of these experiments and observations was the transitory nature of the glycosuria or of the increase of an already existing glycosuria. The same is the case in the adrenalin-thyroidine experiments of Eppinger, Falta, and Rudinger (1), which resulted in the "Wechselwirkung" theory of
diabetes. All these glycosurias are transitory glycosurias, which disappear when the glycogen is exhausted. None is chronic and it is therefore not logical to draw from these, conclusions about chronic diabetes.

In opposition to hyperglycemia caused by increased glycogenolysis and limited in duration by the stores of glycogen, hyperglycemia due to insufficient formation of glycogen are chronic. Here the blood is always supplied in some way with sugar, and thus there is no limit for the duration of the hyperglycemia.

Where the glycosurias which occur in some infectious diseases and in some intoxications shall be placed in this classification must be determined in future investigations.

BIBLIOGRAPHY.

BLOOD SUGAR REGULATION AND THE ORIGIN OF THE HYPERGLYCEMIAS: III. THEORY
Einar Langfeldt


Access the most updated version of this article at http://www.jbc.org/content/46/2/403.citation

Alerts:
- When this article is cited
- When a correction for this article is posted

Click here to choose from all of JBC's e-mail alerts

This article cites 0 references, 0 of which can be accessed free at http://www.jbc.org/content/46/2/403.citation.full.html#ref-list-1