THE MECHANISM OF REGULATION OF THE BLOOD SUGAR BY THE LIVER

SAMUEL SOSKIN, HIRAM E. ESSEX, J. F. HERRICK AND FRANK C. MANN

From The Metabolic Laboratory, Department of Physiology, Michael Reese Hospital, Chicago, and the Division of Experimental Medicine, The Mayo Foundation, Rochester, Minnesota

Received for publication August 10, 1938

That the liver is essential for the maintenance of the level of blood sugar was demonstrated adequately by the early studies on the dehepatized animal. Because of the complexity of the problem, there has been much speculation concerning the mechanism responsible for the normal constancy of the blood sugar level and for the dextrose tolerance curve after the administration of sugar. From the studies of Soskin and his co-workers (1, 2, 3, 4, 5) on the dextrose tolerance curve under various experimental conditions, it would appear that whenever the blood sugar tends to rise above the normal level, the liver responds by diminishing its output of sugar to the blood. The stimulus which elicits this hepatic inhibitory response is the blood sugar itself, and the threshold of stimulation of the hepatic mechanism in a particular animal coincides with the level of blood sugar which that animal habitually maintains. It is suggested that this mechanism is chiefly responsible for the characteristic dextrose tolerance curve when sugar is administered to the normal animal. The influx of exogenous sugar into the blood stream raises the level of the blood sugar above the threshold of stimulation of the homeostatic mechanism. The liver promptly curtails the supply of sugar which it has been pouring into the blood. The exogenous sugar thus temporarily replaces the supply from the liver. Utilization and storage rapidly return the blood sugar toward its normal level, whereupon the liver resumes its secretion of sugar.

This conception was based on indirect evidence. The facilities of the Institute of Experimental Medicine of The Mayo Clinic made it possible to obtain direct proof of the operation of this homeostatic mechanism of the liver.

METHODS. From one to four months prior to our experiments, a two-stage ligation of the posterior vena cava, just below the liver, was performed on the dogs to be used. This rerouting of the blood from the caudal

1 Read before the meeting of the American Physiological Society, Memphis, Tennessee, April 21–24, 1937.
end of the body, back to the heart through a newly developed collateral system, enabled us to use the blood flow in the thoracic portion of the inferior vena cava as a measure of the total blood flow through the liver. This method was adopted in preference to measurement of the blood flow through the portal vein and hepatic artery, after preliminary experiments had shown that the latter vessel presented anatomic and physiologic difficulties to our measurement of blood flow. The total blood flowing through the liver was divided into its venous and arterial components, by measuring the rate of inflow through the portal vein and by subtracting this value from the rate of total outflow in the thoracic portion of the posterior vena cava. By this method the blood flow in the hepatic artery

![Diagram](http://example.com/diagram.png)

Fig. 1. Diagrammatic representation of procedure. The actual experiments were performed with chest and abdomen closed. The retractor on the heart was used by the artist, but not by the authors. a, Hypodermic needle for withdrawing samples of arterial blood; b, glass syringes; c, thermostromuhr units; d, long, flexible needle for use with London cannula, and e, modified London cannula.

was obtained. The drainage from the diaphragmatic veins was ignored in these experiments. We considered the possibility that a coincident change in the volume of the liver due to storage of blood might render this estimation of blood flow in the hepatic artery inaccurate. But this was excluded as a significant error by the length of our experiments, and by the magnitude of blood flow through the liver as compared to the volume of blood that the liver is capable of storing.

The procedure employed for this study is illustrated in figure 1. Under sodium amytal anesthesia and with the necessary surgical precautions a thermostromuhr unit (6, 7) was placed on the thoracic portion of the inferior vena cava just above the diaphragm, after which the chest was closed securely so that the animal could breathe normally. Another unit was
placed on the portal vein as close to the liver as possible. A modified London cannula (8) was sewed to the portal vein just caudad to the thermostromuhr unit. The abdomen was closed, and the right external jugular vein and the left carotid artery were exposed in the neck. It was not necessary to disturb the animal for our procedures during the remainder of the experiment.

The cannula employed differed from the original London cannula in the longer and semicircular plate for attachment to the blood vessel. We found this form more suitable than the original for acute experiments, in which the vein and cannula are not fixed by fibrous tissue. A somewhat similar modification has been described independently by Tsai (9).

At appropriate intervals during the experiments, three samples of blood for estimation of blood sugar (10) were drawn simultaneously by the following methods: Portal blood was obtained by inserting a long, flexible needle into the portal vein through the London cannula mentioned previously. Samples of blood were obtained from the thoracic portion of the inferior vena cava just above the thermostromuhr unit by inserting a French type of urethral catheter into the right external jugular vein and through the innominate vein, superior vena cava and right auricle into the thoracic portion of the inferior vena cava. When the dog is lying on his back with the head extended, the direction of these vessels is such that the catheter usually meets no obstruction, and is not diverted in any other direction. However, care must be taken to prevent air from rushing into the right auricle of the heart. To avoid the formation of intravascular blood clots the catheter was not allowed to remain in place, but was inserted and withdrawn each time a sample of blood was required. Arterial blood was drawn by inserting a fine, hypodermic needle through the wall of the exposed but unobstructed left common carotid artery.

Results. The quantity of sugar entering and that leaving the liver at any given time were calculated in milligrams per minute by correlating the rate of blood flow through the liver with the simultaneously determined values for blood sugar in the inflowing and outflowing blood respectively. The difference between the rates at which sugar was entering and leaving the liver indicated the direction and magnitude of the movement of sugar. These observations were repeated at intervals of fifteen minutes for as long as five hours.

The amount of sugar entering the liver in the portal vein and that entering in the hepatic artery were determined separately from the blood flow and level of blood sugar in the respective vessels. This was important, not only because the level of the blood sugar in the two blood vessels often differed considerably, but especially because we found, in agreement with Schwiegk (11), that the portion of the total blood flow to the liver carried by each vessel varied greatly in different animals, and from time to time in
It is, therefore, not permissible to use the rate of blood flow or the level of blood sugar in either vessel as an index of the total inflow of blood or of the entry of blood sugar into the liver.

It is of interest briefly to compare the rates of blood flow through the liver obtained with the thermostromuhrr under our experimental conditions, with those previously obtained by use of a mechanical flowmeter. Schmid (12) reported that the total blood flow through the liver of the cat averaged about 54 cc. per 100 grams of liver per minute. For the dog, Burton-Opitz (13) found the average flow through the liver to be about 85 cc. per 100 grams of liver per minute. In the experiments of Macleod and Pearce (14) the total blood flow through the livers of dogs ranged from 64 cc. to 144 cc. per 100 grams of liver per minute. Our results resembled those of Macleod and Pearce. During the control periods of our experiments, before sugar was administered, the average total rate of blood flow through the liver varied in different animals from 40 to 160 cc. per 100 grams of liver per minute. After injection into the femoral vein of 1.75 grams of dextrose per kilogram of body weight in a 30 per cent solution in five minutes, the hepatic blood flow usually increased for a few minutes, but by the time the first complete set of determinations was made, fifteen minutes after the termination of the injection, the blood flow had usually returned to its rate before the injection. In different animals, the portal vein or the hepatic artery sometimes carried as much as 90 per cent or as little as 10 per cent of the total amount of blood entering the liver. Although such large differences in proportionate flow were the exception rather than the rule, smaller reciprocal variations frequently occurred during the course of an experiment, while the total outflow of blood from the liver remained constant. The intravenous administration of the solution of dextrose did not alter these proportions in any consistent manner.

The great mass of data involved precludes the tabular presentation of all our results. Table 1 in which are given the results in one experiment is illustrative of all. But even in this table the data are not complete, since the rate of blood flow is given only when samples of blood were taken, and the duplicate determinations of blood sugar which were made to check our analyses are not included. This is by no means the most technically perfect of our experiments, but is presented because it happens to show a number of incidental phenomena which were observed singly or occasionally in the other experiments. Note the variation between the output and intake of sugar by the liver during the control period, the output being predominant. Note the cessation of the net hepatic output of sugar following dextrose administration, and the sustained intake of sugar lasting one hour. The significance of this rate of sugar intake as regards the disposal of the injected dextrose may be judged from the fact that, even fifteen minutes after the termination of the injection when the values of blood
sugar had already fallen from their initial peaks, the liver was still retaining sugar at a rate of more than 0.5 gram per minute. Note that the resumption of sugar output coincided with the return of the portal and hepatic blood sugar levels to their normal control values. These blood sugar levels then show the characteristic temporary swing below the previous control values, during the time taken by the liver to adjust its output accurately to the requirements of the organism. As regards the rates of blood flow, note the large variations at different times during the experiment, in the proportions of the total inflowing blood carried by the portal vein and hepatic artery respectively. Finally, it may be seen that the technical difficulty which caused some anoxemia toward the end of the

### TABLE 1

**Data on blood flow, blood sugar, and intake and output of sugar by the liver in one animal***

<table>
<thead>
<tr>
<th>TIME (min-</th>
<th>Portal vein</th>
<th>Hepatic artery</th>
<th>Vena cava</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Blood sugar</td>
<td>Intake of sugar</td>
<td>Blood sugar</td>
</tr>
<tr>
<td>mgm. per 100 cc.</td>
<td>cc. per minute</td>
<td>mgm. per minute</td>
<td>cc. per minute</td>
</tr>
<tr>
<td>0</td>
<td>83.3</td>
<td>254</td>
<td>211.6</td>
</tr>
<tr>
<td>15</td>
<td>88.3</td>
<td>267</td>
<td>222.4</td>
</tr>
<tr>
<td>30</td>
<td>78.2</td>
<td>280</td>
<td>210.4</td>
</tr>
</tbody>
</table>

**33 grams of dextrose in 30 per cent solution given intravenously**

<table>
<thead>
<tr>
<th>TIME (min-</th>
<th>Portal vein</th>
<th>Blood sugar</th>
<th>Intake of sugar</th>
<th>Total intake of sugar by liver</th>
<th>Output of sugar</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>83.3</td>
<td>417.0</td>
<td>358</td>
<td>1492.9</td>
<td>357.2</td>
</tr>
<tr>
<td>15</td>
<td>88.3</td>
<td>441.5</td>
<td>313</td>
<td>1720.5</td>
<td>432.1</td>
</tr>
<tr>
<td>30</td>
<td>78.2</td>
<td>461.5</td>
<td>289</td>
<td>1661.5</td>
<td>420.1</td>
</tr>
</tbody>
</table>

* Weight of dog 18.9 kgm. Weight of liver 655 grams.
experiment, was followed immediately by a relatively tremendous output of sugar from the liver and a consequent steep rise in the blood sugar levels. This accidental observation and others like it, indicate the sensitivity of the liver to abnormal conditions, and confirm the satisfactory physiologic status which prevailed during most of our experiments, in which the output of sugar from the liver was of an entirely different order of magnitude.

The result of administration of a single dose of sugar to another dog is illustrated in figure 2. Like the experiment reported in table 1, a reversal of movement of sugar from a greater output to a greater intake occurred following administration of dextrose. But it should be noted that throughout the second hour after administration of sugar the liver was neither retaining nor exerting sugar. It is clear that, following the disposal of most of the sugar administered in this experiment, hepatic storage of sugar ceased while the liver tarried before resuming its supply of sugar to the blood. During this interval the level of sugar in the arterial blood fell below its original control value, and does not return to normal until after the liver has resumed its output. The inhibition of the hepatic secretion of sugar is, therefore, a real and separate phenomenon from
storage of sugar. This is demonstrated also under different conditions, during the constant injection of smaller amounts of dextrose (fig. 3).

Figures 3 and 4 are representative of a group of experiments in which a comparison of the effect of the administration of different amounts of sugar was simplified by the use of a constant injection instead of a single large dose. The liver responded more or less in proportion to the amount of sugar administered. The constant prolonged injection of 0.5 gram per kilogram of body weight per hour (fig. 3) inhibited the output of sugar, but for some reason, probably related to the physiologic state of the liver as well as to the rate of administration, storage did not occur. Under these circumstances the level of the blood sugar rose somewhat before a new level was established. The prolonged constant injection of 0.75 gram per kilogram of body weight per hour (fig. 4) caused storage as well as inhibition of output. The animal was able, therefore, to establish a balance at a lower level for blood sugar in spite of the greater amount of sugar it had to deal with. In another experiment, the record of which has been omitted to conserve space, the prolonged constant injection of 1.5 grams of dextrose per kilogram of body weight per hour could not be compensated for in spite of both an inhibition of output and a large storage of sugar. In this experiment, although the output promptly ceased and the intake varied from about 100 to 200 mgm. per minute throughout the period of injection, the arterial blood sugar gradually rose from its initial level of 70 mgm. per cent to a final value of 262 mgm. per cent at the end of the injection period.

COMMENT. The secretion of sugar into the blood by the liver of the fasting animal was demonstrated by the brilliant pioneer work of Claude Bernard (15). He also found that glycogen accumulated in the liver after feeding of carbohydrate, although he was inclined to believe that this was not a result of the direct conversion of the ingested sugar into glycogen. Bernard and his contemporaries made extensive use of the method of comparing the sugar contents of the inflowing and outflowing blood of the liver. The inadequate state of knowledge concerning methods of estimating the level of sugar, the phenomenon of glycolysis, and so forth, however, resulted in controversial conceptions of liver function and eventually obscured the significance of Bernard's dictum, that "The normal blood sugar level is the result of a precise equilibrium between the processes of anabolism (sugar formation in the liver) and catabolism (sugar utilization in the tissues)."

More recent comparisons of the sugar contents of the inflowing and outflowing blood of the liver during the absorption of sugar from the gastrointestinal tract (8, 16–20) or during the intravenous administration of sugar (21), have largely confirmed Bernard's original conception. But we cannot accept the calculations by which some of the later workers have
Figs. 3 and 4 (to be grouped together). Comparison of the effects of different amounts of sugar administered by prolonged constant intravenous injection. In these, and in other experiments not shown, the liver intake of sugar is more or less proportionate to the rate of sugar administration. The lowest rate of injection (fig. 3), however, results in a suppression of the output of sugar from the liver, without any storage of sugar. In this case the constant injection of 0.5 gram of dextrose per kilogram of body weight per hour was just sufficient to replace the previous endogenous supply of blood sugar from the liver, and there is little change in the arterial blood sugar level.
attempted to give their results quantitative significance. In view of our present work it is evident that no constant or average hepatic blood flow can be assumed for purposes of calculation. It is also clear that, in the absence of measurements of blood flow, differences in the blood sugar between the inflowing and outflowing blood can indicate little more than the direction of movement of sugar into or out of the liver.

The observations which Soskin and his co-workers made on the inflowing and outflowing blood of the liver, in normal and depancreatized dogs (1) were subject to the same limitations as those of other investigators. Their coincidental studies of the dextrose tolerance curve, however, led them to differentiate between the storage of incoming carbohydrate and the suppression of output of sugar. This, in turn, gave rise to their interpretation of the observed hepatic activity as a homeostatic mechanism for the maintenance of a constant level of blood sugar, as described in our introductory remarks. The quantitative results, obtained in our study by correlating the blood sugar difference with the blood flow, yield direct proof for the interpretations and conclusions of Soskin and his co-workers. The reader is referred to the papers by these investigators for a consideration of the significance and implications of this hepatic mechanism.

SUMMARY AND CONCLUSIONS

The rate of blood flow through the liver and the arterial and venous components of the total hepatic blood flow were observed by means of the thermostromuhr in specially prepared dogs. The output or intake of sugar by the intact liver in situ was calculated in milligrams per minute by correlating the rates of blood flow with the simultaneously determined content of blood sugar of the inflowing and outflowing blood.

The movement of sugar out of, or into, the liver was observed during control periods and after the intravenous administration of sugar. Prolonged constant injections of dextrose as well as single large doses (dextrose tolerance tests) were used. During the control periods the liver was observed to secrete sugar into the blood. The administration of dextrose was invariably followed by cessation of excretion of sugar by the liver and by retention of a portion of the incoming sugar. Inhibition of the output of sugar was observed in the absence of storage of sugar, following the administration of certain smaller doses of sugar and at certain intervals after the administration of large doses. At these times, the level of the animal’s arterial blood sugar temporarily fell below the original control values and remained low until resumption of secretion of sugar by the liver restored it to its previous levels.

Our results yielded direct and quantitative evidence of the homeostatic regulation of the level of blood sugar by the liver, a mechanism for which only indirect evidence was previously available.
REGULATION OF BLOOD SUGAR BY THE LIVER

REFERENCES

(16) Kotschneff, N. Pfüger’s Arch. 216: 661, 1928.