Dynamics of Liver Glycogen

The Topochemistry of Glycogen Synthetis, Glycogen Content and Glycogenolysis under the Experimental Conditions of Glycogen Accumulation and Depletion* **

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Summary. Using histochemical techniques the glycogen content and the activities of glycogen synthetase (UDPGGT) and phosphorylase were studied in the livers of 106 golden hamsters under following experimental conditions: a) starvation of 16, 36, 48, 72 and 96 hours; b) alloxan-diabetes of 24, 48 and 72 hours of alloxan diabetes. — Starvation leads to a depletion of liver glycogen during the first 48 hours, which is finally restricted to zone 3 of the liver acinus. After starvation of 72 and 96 hours a new glycogen accumulation is demonstrable in the microvasculatory periphery of the acinus (zone 3 and 2). The process of glycogen depletion is characterized in the beginning by a high phosphorylase activity in all zones of the acinus, later only in the forefield of glycogen content. The weak activity of glycogen synthetase is mainly restricted to zone 3. — All phases of glycogen depletion are to be found in alloxan diabetic animals, too. Out of 45 hamsters 23 showed an extreme depletion of glycogen; typical for this situation is a weak or absent glycogen synthetase activity in zone 3 and a broad field of phosphorylase activity in zones 1 and 2. The short stimulation by insulin leads to a considerable increase of glycogen synthetase activity at the portally oriented border of the glycogen area and to a shift of the moderate phosphorylase activity to zone 1.

Thus the histochemical characteristics of glycogen depletion are: a shift of the reduced glycogen content in direction of the microvasculatory periphery of the liver acinus (zone 3), caused by a high phosphorylase activity in the portal forefield, while glycogen synthetase activity is low in the glycogen area. The histochemical characteristics of glycogen accumulation are: after a short phase of glycogen synthesis in all hepatocytes a moderate phosphorylase activity in zone 1 leads to a mobilization of the portal glycogen deposits and to an increasing accumulation of glycogen in the peripheral part of the acinus. At the portally oriented border of the glycogen area a high synthetase activity leads to a broadening of the glycogen area in direction of the portal branches. At the end of this process the “normal” pattern of the liver acinus occurs: all hepatocytes are filled with glycogen, the glycogen enzymes are restricted to the periportal border of zone 1.

Introduction

The problem of normal and abnormal patterns of glycogen content in the liver parenchyma has been the subject of nearly innumerable studies since Claude Bernard (1859). Nevertheless, until now, it has not been possible to obtain a generally accepted view on the topochemistry of glycogen accumulation and glycogen depletion. This may be surprising since histology of the liver parenchyma seems to be very simple and results of histochemical techniques for the demon-

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stration of glycogen (PAS-reaction, McManus, 1948) are too exact concerning their reproductivity as to interprete the contradictory findings to be mere artifacts.

Summarizing the opinions about glycogen distribution in normal liver parenchyma there are three main aspects: according to Smith (1931), Kater (1933), Chipp and Duff (1942), Novikoff and Essner (1960), glycogen is mainly stored in the periportal area. According to Bock and Hoffmann (1872), Rosenberg (1910), Eger and Klärner (1948), Zeiger (1952) and others, the central part of the liver lobule is the main location of glycogen storage. Corrin and Aterman (1968) describe a “glycogenic wave”: glycogen is stored in empty hepatocytes and released by filled ones at the same time depending on the feeding situation. Following this concept glycogen can be stored in and released from any area of the liver lobule.

In all studies it is pointed out that at certain times and under certain conditions all hepatocytes are able to store and to release glycogen. However, no regularity could be detected. Thus the metabolic conditions of the unequal i.e. regional distribution of glycogen in the parenchyma which has repeatedly been observed remain unclear. There are two important observations which cannot be explained: how can the glycogen content of one area be shifted to another; why do the hepatocytes of one region start to synthesize or release their glycogen content at a certain concentration of blood glucose in the sinusoids whereas the cells of the neighbouring area will not?

There are several reasons to explain the contradictory opinions about the dynamics and localization of liver glycogen:

1. The authors do not agree on the histological substrate. Is the liver lobule around the central vein the functional unit of the liver or is it the liver acinus around the afferent vessels? A number of misunderstandings can be explained by the fact that the functional units of the lobule are not congruent with the zones of the acinus. — In previous studies on the topochemistry of glycogen and glycogen synthetase (Sasse, 1969a, b; Sasse and Köhler, 1969; Sasse and Schenk, 1975) it was pointed out that the functional units of the liver are not situated in equidistant areas around the central vein but correspond to the microvasculatory zones of the acini (Rappaport, 1960), the axis of which are the portal branches and the periphery of which is drained by the “terminal hepatic venule”. The zones of identical supply are of irregular shape because the terminal portal branches mostly run out of the section plane.

2. In many cases it was unknown whether the liver was in the anabolic or in the catabolic state. Therefore it is necessary to study the glycogen content under definite conditions. Generally starving was chosen which can lead to false interpretations if gluconeogenic processes begin. A more drastic depletion of glycogen can be attained by inducing a diabetes by a single injection of alloxan. The resulting loss of glycogen can be so complete that only sporadically distributed glycogen particles can be detected by the electron microscope (Morgan and Jersild, 1970). Contrary to such definite phases of glycogen depletion the application of insulin to alloxan-diabetic animals is followed by a drastic restoring of glycogen; this anabolic effect causes an increase of liver weight (Steiner and Williams, 1959). Thus the period immediately following the injection of insulin might be regarded as a forced anabolic phase.