Phosphorylase Kinase of the Liver: Deficiency in a Girl with Increased Hepatic Glycogen

Abstract. Studies of a child with glycogenosis revealed an increased concentration of glycogen and low phosphorylase activity in her liver. Using mixtures of homogenates of the patient's liver and of normal liver, we found the low phosphorylase activity to be caused by a deficiency of phosphorylase kinase and not of hepatic phosphorylase. The fact that phosphorylase activity was restored to normal values by the addition of phosphorylase b kinase from rabbit muscle substantiates this conclusion.

Since Hers (1) reported studies of two patients with low activities of hepatic phosphorylase and elevated concentrations of glycogen in the liver, a decrease in the activity of phosphorylase has come to be equated with a deficiency in hepatic phosphorylase (Type VI glycogenosis) (2). Such an interpretation does not take into account the complexity of the phosphorylase system (Fig. 1) which comprises at least three other enzymes (3).
Deficiencies other than that of phosphorylase can be postulated which, nevertheless, would result in a low phosphorylase activity.

A 4-year-old girl with marked hepatomegaly since birth was studied. The edge of her liver was 13 cm below the costal margin in the midclavicular line. Physical examination revealed no other abnormality. During the period of 1 year, the patient’s liver was biopsied six times with a Menghini needle (4). Between 7.7 and 12.1 percent of the six biopsy specimens was glycogen (in normal liver up to 6.5 percent of wet tissue weight is glycogen), and the activity of phosphorylase varied between 0 and 6.0 \( \mu \text{mol} \) of phosphate per gram per minute. In liver tissue of 48 normal individuals, phosphorylase activity ranged from 19.5 to 46.9 \( \mu \text{mol} \) of phosphate per gram per minute with an average of 27.4 (5). Histologically, the patient’s muscle tissue was normal, as were the glycogen content of the muscle and its phosphorylase activity as judged by biochemical analysis. Similarly, the activities of dextrin-1,6-glucosidase (amylo-1,6-glucosidase) and lysosomal acid \( \alpha_1 \)-glucan glucohydrolase (\( \alpha_1 \)-glucosidase) in muscle and in liver, and the activity of glucose-6-phosphatase in liver were normal (6).

The liver tissue was homogenized with a glass hand-homogenizer. Immediately after biopsy and before the beginning of the first period of incubation, the initial phosphorylase activity was determined in a portion of the homogenate which had been prepared in ice-cold tris(hydroxymethyl)aminomethane (Tris) and sodium \( \beta \)-glycerophosphate buffer. After the first period of incubation of 15 to 20 minutes, the following were added to all tubes: adenosine triphosphate (ATP), adenosine-3',5'-phosphate (3',5'-AMP), magnesium chloride, and sodium fluoride, the latter to inhibit phosphorylase phosphatase. The details of concentration are listed in Fig. 2, in which the time of these additions is marked 0. In this report the additions will be referred to as zero-time additions.

A homogenate of normal human liver was incubated at 37°C. The phosphorylase activity at the beginning of the incubation and immediately after the biopsy was 25.5 \( \mu \text{mol} \) of phosphate per gram per minute or 13.6 \( \mu \text{mol} \) of phosphate per millimole of nitrogen in liver tissue per minute. During the first incubation period of 15 to 20 minutes, the phosphorylase was readily deactivated. The deactivation could be reversed by the zero-time additions. The phosphorylase activity increased within 10 to 20 minutes to a value of 22.4 \( \mu \text{mol} \) of phosphate per millimole of nitrogen per minute.

This normal pattern of response differed from the results obtained in two separate attempts at activation of the patient’s liver homogenate in vitro under the same conditions. The two experiments provided comparable sets of data, one of which is illustrated in Fig. 2. Phosphorylase activity in the patient’s liver immediately after biopsy was 5.2 \( \mu \text{mol} \) of phosphate per gram per minute or 3.9 \( \mu \text{mol} \) of phosphate per millimole of nitrogen per minute. This activity was lost during the 15 minutes of the first period of incubation. After the zero-time additions, activation of phosphorylase was obtained at 10 percent of the rate which occurred in the control homogenate.

In the same experiment, at time 0, dehydrated homogenate from the patient was combined with deactivated homogenate from the control. After the zero-time additions, the combined homogenate was similarly incubated. Phosphorylase activity increased rapidly to a value of 21 \( \mu \text{mol} \) of phosphate per millimole of nitrogen per minute. This amount of activation is similar to that of the control homogenate and of the combined homogenate.

A reduction of phosphorylase kinase activity in the patient’s liver by 90 percent or more would account for these results.

GEORGE HUG
WILLIAM K. SCHUBERT
GAIL CHUCK
Children’s Hospital Clinical
Research Center and Department of Pediatrics, University of Cincinnati
College of Medicine, Cincinnati, Ohio

References and Notes
8. Supported by NIH grants AM 08528 and FR 00123.
9. June 1966

Fig. 1. Hepatic phosphorylase system.

Fig. 2. Reactivation of liver phosphorylase in vitro. The homogenates contained 80 mg of tissue per milliliter in 4 \( \times 10^{-3} \) M Tris—sodium \( \beta \)-glycerophosphate buffer, pH 7.8, for the first incubation period of 15 minutes at 37°C. At time 0, additions were made to give these final concentrations: \( 10^{-4} \) M ATP; \( 10^{-6} \) M 3',5'-AMP; 5 \( \times 10^{-3} \) M NaF; 5 \( \times 10^{-2} \) M MgCl2; 2 \( \times 10^{-3} \) M Tris—sodium \( \beta \)-glycerophosphate buffer, pH 7.8; 20 mg of liver tissue per milliliter except for the tube "patient plus control" which contained 40 mg of liver tissue per milliliter. Control, ○; patient’s liver, Δ; patient’s liver plus control, ●; patient’s liver plus phosphorylase b kinase from rabbit muscle, X.
Phosphorylase Kinase of the Liver: Deficiency in a Girl with Increased Hepatic Glycogen
George Hug, William K. Schubert and Gail Chuck (September 23, 1966)
Science 153 (3743), 1534-1535. [doi: 10.1126/science.153.3743.1534]

Editor's Summary

This copy is for your personal, non-commercial use only.

**Article Tools**
Visit the online version of this article to access the personalization and article tools:
http://science.sciencemag.org/content/153/3743/1534

**Permissions**
Obtain information about reproducing this article:
http://www.sciencemag.org/about/permissions.dtl