Glycogenesis and Glycolysis in the Liver from Congenital Galactosemia

By

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Glycogenesis and glycolysis in the liver from a galactosemic patient were investigated. The activity of glycogenesis in galactosemic liver showed a significantly low level as compared with that in control livers, while there was no remarkable difference in the activity of glycolysis between the patient's and control livers. It was suggested that the decrease in glycogenesis in galactosemic liver was due to inhibitory effect of galactose-1-phosphate on phosphoglucomutase process.

Congenital galactosemia is an inborn error of metabolism due to a defect of galactose-1-phosphate uridyl transferase.

It has been generally postulated that this enzyme defect results in an accumulation of galactose-1-phosphate (Gal-1-P) which may cause cellular injury. However, little is known about secondary derangement in cellular metabolism caused by the primary enzyme defect.

The purpose of the present study is to investigate glycogen metabolism, which is closely related to galactose metabolism, in the liver of congenital galactosemia.

METHODS AND MATERIALS

A liver specimen was biopsied from a patient with congenital galactosemia whose diagnosis was confirmed by galactose tolerance test and Schwarz's test¹⁾. As controls, surgical patients without liver involvement were subjected to liver biopsy. Immediately after the removal of liver specimens, the tissue slices were prepared at 0°C. Each slice was put into incubation flasks of the Warburg manometer under the conditions shown in Table I.

The activity of glycolysis in the liver was investigated by manometric determination of lactic acid produced for two hours at 37°C under anaerobic

TABLE I. Experimental Conditions

	Glycolysis	Glycogenesis
In cap	K.R.B.* 2.0 ml Slice	K.R.B. 2.0 ml Slice
Side	Glucose 0.2 ml (10 mg)	Glucose 0.2 ml (10 mg) C ¹⁴ -Glucose 0.1 ml (2 μ c)
Atmosphere	95% N ₂ , 5% CO ₂	95% N ₂ , 5% CO ₂
Time (h.)	2	1
Temperature	37°C	37°C
Determination	Lactic acid	Radioactivity in glycogen fraction

* Krebs-Ringer-bicarbonate solution

condition.

The activity of glycogenesis in the liver was investigated by determining isotopically the conversion rate of C¹⁴-labeled glucose to glycogen. The incubation was carried out for one hour at 37°C under the anaerobic condition. At the end of the incubation, the glycogen fraction was isolated from the reaction mixture by Abder-Akler's method²⁾. The radioactivity in the glycogen fraction was counted by a gas flow counter with the scaler of Radiation Counter Aloka DC-5.

RESULTS

Table II showed the results of *in vitro* activity of glycolysis in the livers from the patient and control subjects. The activity of glycolysis in galactosemic liver was found to be within control level.

Table III showed the results of *in vitro* activity of glycogenesis in the livers from the patient and control subjects. The activity of glycogenesis was of significantly low level in the patient's liver as compared with that in control livers.

TABLE II. Activity of Glycolysis in the Livers from Patient with Congenital Galactosemia

	Patient	Controls
Glycolysis		16.9
		35.2
Q ^{N₂} _{CO₂} μ l CO ₂ /h.	28.9	18.6
		42.0

Note: Figures are given as values per 1 mg of nitrogen in the liver.

TABLE III. Conversion of C¹⁴-Glucose to Glycogen by the Liver from a Patient with Congenital Galactosemia

	Recovered in the glycogen fraction (cpm)	Wet weight of liver slice (mg)	The content of nitrogen in liver slice (mg)	Counts in the glyco- gen fraction per 1 mg of nitrogen in liver slice
Patient	195	80	1.28	152
Controls	331	85	1.25	265
	513	90	1.92	267
	790	88	1.67	473
	581	92	1.51	385

Note: Each flask initially contained 135,000 cpm of labeled glucose.

DISCUSSION

It is reasonable to presume that Gal-1-P accumulates in the tissue of galactosemic patient because of defect of Gal-1-P uridyl transferase. In fact, Schwarz *et al.*³⁾ found the accumulation of large amounts of Gal-1-P in erythrocytes of patients with galactosemia both *in vivo* and *in vitro*. These observations were confirmed by other investigators^{4,5)}. The accumulation of Gal-1-P in the liver of galactosemic patient was demonstrated by Tada⁶⁾.

Such an excessive accumulation of Gal-1-P in the tissue is supposed to be responsible for various manifestations of this particular disorder through the injurious effect of Gal-1-P for cellular metabolism^{6,7)}. It is, however, not fully understood how Gal-1-P affects cellular metabolism. The possible role of Gal-1-P in pathogenesis of the disease has been postulated by the recognition of the *in vitro* inhibition on some enzyme systems by Gal-1-P⁸⁾. According to Najjar and Ginsburg⁸⁾, Gal-1-P has *in vitro* an inhibitory effect on phosphoglucomutase which catalyzes the conversion of glucose-1-phosphate to glucose-6-phosphate. This kind of inhibition could be reasonably expected as an instance of competitive inhibition arising from a very slight structural difference between glucose-1-phosphate and galactose-1-phosphate.

The present results, a decreased activity of glycogenesis in galactosemic liver, might be explained by inhibitory effect on phosphoglucomutase by Gal-1-P accumulated in the liver.

Since phosphoglucomutase process is reversible, it is possible that glycogenolysis may be also interfered by Gal-1-P. Such a disturbance in synthesis and breakdown of glycogen secondarily due to Gal-1-P accumulation may play a role for cellular damage in this particular disorder.

Literature

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