EFFECTS OF XYLITOL ON CARBOHYDRATE METABOLISM IN RAT LIVER TREATED WITH CARBON TETRACHLORIDE OR ALLOXAN

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Xylitol is a polyalcohol which is a regular intermediary product of the carbohydrate metabolism.¹ Although there have been many reports on the effects of xylitol on the carbohydrate metabolism in animals and human beings,^{2,3} there have been few published data on the metabolic changes induced by the administration of xylitol in acute and subacute liver injury. Accordingly, studies were undertaken to investigate the effects of xylitol on the carbohydrate metabolism in the livers of rats treated with carbon tetrachloride (CCl₄) or alloxan. The findings presented here have suggested that xylitol is a good source of energy of the rats treated with CCl₄ or alloxan.

MATERIALS AND METHODS

The experiments were carried out by using male rats of wistar strain weighing 150 g. All animals were fed a standard laboratory diet and were deprived of food for 24 hours before they were killed. They were killed by decapitation at intervals. Alloxanized rats were produced by administering alloxan intraperitoneally 50 mg per kilogram of body weight. CCl₄ treated rats were produced by injecting subcutaneously 0.2 ml of 50 per cent CCl₄ (in olive oil) per 100 g of body weight. CCl₄ injection was continued twice a week up to fourteen days. The *in vitro* study using labelled sugars was carried out according

to the procedure described previously.⁴ The liver tissue to be studied was weighed and homogenized in 4 volumes of 0.15M KCL in 0.05M nicotinamide with a glass homogenizer. The incubation medium were as follows; 0.5 μ c (0.05 ml) of glucose-u-C¹⁴ or xylitol-u-C¹⁴; 0.65 ml of 0.1M KCL; 0.3 ml of 0.2M potassium phosphate buffer (PH 7.4); and 0.5 ml of homogenate. The incubations were made in modified Warburg's flasks with a center well and the reactions were carried out for 60 minutes at 37°C in a shaking incubator. At the end of the incubation 1 ml of Hyamine-10X was injected into the center well of each flask to trap the produced CO₂. The reaction was stopped by injecting 0.2 ml of 10N H₂SO₄ into the main part of the flask. The flasks were then shaken in the incubator for an additional 30 minutes to collect the CO₂. Hyamine-10X was transferred to counting bottles and the radioactivity was measured in a liquid scintillation spectrometer. (Nuclear Chicago Model 6725) For the liver glycogen study, another group of CCl₄-treated rats was fasted for 24 hours before oral administration of 2.0 ml of 50 per cent glucose solution followed, after approximately 15 minutes, by intraperitoneal administration of 10 μ c of xylitol-u-C¹⁴ or glucose-u-C¹⁴ per 100 g of body weight. The CCl₄ was injected 24 hours prior to the administration of labelled sugar. The animals were killed by decapitation 3 hours after the administration of labelled sugar. The livers were extirpated and plunged into 30 per cent potassium hydroxide. Glycogen was isolated by the method of Good, Kramer and Somogyi.⁵ The radioactivity in the isolated glycogen was measured in a liquid scintillation spectrometer. The specific activity of the C¹⁴ used was 3.0 mc per mM for glucose-u-C¹⁴ and 3.2 mc per mM for xylitol-u-C¹⁴.

RESULTS

As shown in Table 1, which shows the values for the per cent of the administered doses of xylitol-u-C¹⁴ recovered in CO₂ per 500 mg of the liver, CO₂ production from xylitol-u-C¹⁴ was more marked than that from glucose-u-C¹⁴ in controls. On the contrary, there were markedly reduced CO₂ production both from xylitol-u-C¹⁴ and glucose-u-C¹⁴ in CCl₄-treated rat liver. This tendency lasted for the first ten days which period the CCl₄ injection was kept on twice a week. The CO₂ production from xylitol-u-C¹⁴ was almost returned to the control level 21 days after the first CCl₄ injection, whereas there was still reduced CO₂ production in glucose-u-C¹⁴ group.

Table 2 demonstrates that the CO₂ production from xylitol-u-C¹⁴ was hardly decreased in alloxanized rat liver, whereas CO₂ production from glucose-u-C¹⁴ was markedly reduced. ($P < 0.003$)

Table 1

*Recovery of C¹⁴ in CO₂ produced from Xylitol-u-C¹⁴
and Glucose-u-C¹⁴ by Rat Liver Homogenate
(CCl₄ treated male rats, wistar strain)*

	Sample No.	CO ₂ production by liver incubated with		Significance level
		Glucose-u-C ¹⁴	Xylitol-u-C ¹⁴	
Control	7	5.96±0.74	6.88±0.95	0.003<P<0.05
Time after first CCl ₄ injection				
22 hr	6	0.66±0.07	0.71±0.27	P>0.05
10 days	8	0.55±0.46	0.59±0.17	P>0.05
21 days	3	2.85±0.46	5.42±1.62	0.003<P<0.05
35 days	6	4.08±1.02	5.86±1.84	0.003<P<0.05

The data are expressed as % of administered C¹⁴ recovered in CO₂ per 500mg of liver.

(mean ± standard deviation)

The CCl₄ injection was continued twice a week up to 14 days.

Table 2

*Recovery of C¹⁴ in CO₂ produced from Xylitol-u-C¹⁴ and
Glucose-u-C¹⁴ by Rat Liver Homogenate
(alloxan diabetic rats)*

	Sample No.	CO ₂ production by liver incubated with		Significance level
		Glucose-u-C ¹⁴	Xylitol-u-C ¹⁴	
Control	7	5.96±0.74*	6.88±0.95	0.003<P<0.05
Alloxan diabetes	10	1.70±0.95**	6.77±3.28	P<0.003

Significance of Difference in *vs. **is P<0.003.

The data are expressed as % of administered C¹⁴ recovered in CO₂ per 500mg of liver.
(mean ± standard deviation)

As shown in figure 1, which demonstrates the data on the recovery of C¹⁴ in the glycogen of control and CCl₄-treated rat liver after the intraperitoneal administration of glucose-u-C¹⁴ or xylitol-u-C¹⁴, xylitol is an efficient precursor of liver glycogen as well as glucose. Although there was a decreased glycogen

Fig. 1. Incorporation of xylitol-u-C¹⁴ and glucose-u-C¹⁴ in rat liver glycogen.

formation from xylitol in the CCl₄-treated group, the degree of decrease was less than that of glucose.

DISCUSSIONS

Xylitol is a polyalcohol which has recently been recognized as a normal intermediary product in the glucuronate-xylulose cycle.¹ There have been many reports in recent years on the effects of xylitol on the carbohydrate metabolism in human beings and animals.^{2,3,6} We have reported⁷ that blood xylitol and lactate increase after xylitol administration whereas blood sugar remains unchanged in healthy persons and in patients with diabetes mellitus or liver disease. The rapid decrease of blood xylitol level after the infusion and the small urinary loss of xylitol have also been demonstrated.^{7,8} These results suggest that xylitol administered to human beings can be utilized in various states such as diabetes mellitus or liver disease. In animal experiments with the use of xylitol-C¹⁴, McCormick and Touster⁹ have reported that the guinea pig converts xylitol-1-C¹⁴ to respiratory C¹⁴O₂ to an appreciable extent (10%), a portion of the polyol apparently being excreted in the urine (25%). They have also confirmed that xylitol is an efficient precursor of liver glycogen in the rat and in the guinea pig. Schmidt *et al*¹⁰ have shown that after intravenous administration of xylitol-C¹⁴ 50 per cent is oxidized to C¹⁴O₂ and the activity excreted in the urine is somewhat higher than after oral administration. The present investigation has demonstrated that in the acute stage of liver injury xylitol is as inefficiently oxidized to CO₂ in the livers treated with CCl₄ as is glucose. Furthermore, the data in Table 1 show that the CO₂ production from xylitol-u-C¹⁴ almost returned to the control level 35 days after the first CCl₄ administration, whereas CO₂ production

from glucose-u-C¹⁴ is still below the control level. The results suggest that xylitol is more efficiently oxidized to CO₂ than glucose in the livers treated with CCl₄.

Fig. 1 shows the results on the conversion of xylitol-u-C¹⁴ and glucose-u-C¹⁴ to liver glycogen. It is evident that xylitol is an efficient glycogen precursor as reported by McCormick and Touster.⁹ Furthermore, xylitol is more efficiently oxidized to CO₂ in the livers of alloxanized rats than glucose ($P < 0.003$). Recent studies¹¹ on glucose-C¹⁴ in the livers of mice treated with virus or CCl₄ have shown the increased C¹⁴O₂ production from glucose-1-C¹⁴. These data suggest that the metabolism of glucose through the pentose phosphate cycle increases in the livers of mice treated with virus or CCl₄. Moreover, there have been demonstrated¹² that the participation of the direct oxidative pathway increases relatively in the livers of alloxanized rats in spite of the decreased level of glucose-6-phosphate dehydrogenase. We have reported¹³ that the direct oxidative pathway continues to be increased relatively in the rat livers chronically treated with carbon tetrachloride. On the basis of these findings, it may be said that xylitol, which is an intermediate in the uronic acid pathway entering the pentose-phosphate cycle through D-xylulose-5-phosphate, is an excellent source of energy in the livers of rats treated with CCl₄ or alloxan. It is obvious that the present data are largely preliminary and much further work is need to clarify their significance.

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