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. Although there have been many reports on the effects of xylitol on the carbohydrate metabolism in animals and human beings, 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. 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; 0.5μc (0.05 ml) of glucose-u-C\textsubscript{14} or xylitol-u-C\textsubscript{14}; 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 CO\textsubscript{2}. The reaction was stopped by injecting 0.2 ml of 1ON H\textsubscript{2}SO\textsubscript{4} into the main part of the flask. The flasks were then shaken in the incubator for an additional 30 minutes to collect the CO\textsubscript{2}. 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 CCl\textsubscript{4}-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 10μc of xylitol-u-C\textsubscript{14} or glucose-u-C\textsubscript{14} per 100 g of body weight. The CCl\textsubscript{4} 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. The radioactivity in the isolated glycogen was measured in a liquid scintillation spectrometer. The specific activity of the C\textsubscript{14} used was 3.0 mc per mM for glucose-u-C\textsubscript{14} and 3.2 mc per mM for xylitol-u-C\textsubscript{14}.

RESULTS

As shown in Table 1, which shows the values for the per cent of the administered doses of xylitol-u-C\textsubscript{14} recovered in CO\textsubscript{2} per 500 mg of the liver, CO\textsubscript{2} production from xylitol-u-C\textsubscript{14} was more marked than that from glucose-u-C\textsubscript{14} in controls. On the contrary, there were markedly reduced CO\textsubscript{2} production both from xylitol-u-C\textsubscript{14} and glucose-u-C\textsubscript{14} in CCl\textsubscript{4}-treated rat liver. This tendency lasted for the first ten days which period the CCl\textsubscript{4} injection was kept on twice a week. The CO\textsubscript{2} production from xylitol-u-C\textsubscript{14} was almost returned to the control level 21 days after the first CCl\textsubscript{4} injection, whereas there was still reduced CO\textsubscript{2} production in glucose-u-C\textsubscript{14} group.

Table 2 demonstrates that the CO\textsubscript{2} production from xylitol-u-C\textsubscript{14} was hardly decreased in alloxanized rat liver, whereas CO\textsubscript{2} production from glucose-u-C\textsubscript{14} was markedly reduced. (P<0.003)
Table 1

Recovery of C\textsuperscript{14} in CO\textsubscript{2} produced from Xylitol-u-C\textsuperscript{14} and Glucose-u-C\textsuperscript{14} by Rat Liver Homogenate (CCl\textsubscript{4} treated male rats, wistar strain)

<table>
<thead>
<tr>
<th>Sample No.</th>
<th>CO\textsubscript{2} production by liver incubated with</th>
<th>Significance level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Glucose-u-C\textsuperscript{14}</td>
<td>Xylitol-u-C\textsuperscript{14}</td>
</tr>
<tr>
<td>Control</td>
<td>5.96±0.74</td>
<td>6.88±0.96</td>
</tr>
<tr>
<td>Time after first CCl\textsubscript{4} injection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22 hr</td>
<td>0.66±0.07</td>
<td>0.71±0.27</td>
</tr>
<tr>
<td>10 days</td>
<td>0.55±0.46</td>
<td>0.59±0.17</td>
</tr>
<tr>
<td>21 days</td>
<td>2.85±0.46</td>
<td>5.42±1.62</td>
</tr>
<tr>
<td>35 days</td>
<td>4.08±1.02</td>
<td>5.86±1.84</td>
</tr>
</tbody>
</table>

The data are expressed as % of administered C\textsuperscript{14} recovered in CO\textsubscript{2} per 500mg of liver.
(mean ± standard deviation)
The CCl\textsubscript{4} injection was continued twice a week up to 14 days.

Table 2

Recovery of C\textsuperscript{14} in CO\textsubscript{2} produced from Xylitol-u-C\textsuperscript{14} and Glucose-u-C\textsuperscript{14} by Rat Liver Homogenate (alloxan diabetic rats)

<table>
<thead>
<tr>
<th>Sample No.</th>
<th>CO\textsubscript{2} production by liver incubated with</th>
<th>Significance level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Glucose-u-C\textsuperscript{14}</td>
<td>Xylitol-u-C\textsuperscript{14}</td>
</tr>
<tr>
<td>Control</td>
<td>5.96±0.74*</td>
<td>6.88±0.95</td>
</tr>
<tr>
<td>Alloxan diabetes</td>
<td>1.70±0.95**</td>
<td>6.77±3.28</td>
</tr>
</tbody>
</table>

Significance of Difference in *vs. **is P<0.003.
The data are expressed as % of administered C\textsuperscript{14} recovered in CO\textsubscript{2} per 500mg of liver.
(mean ± standard deviation)

As shown in figure 1, which demonstrates the data on the recovery of C\textsuperscript{14} in the glycogen of control and CCl\textsubscript{4}-treated rat liver after the intraperitoneal administration of glucose-u-C\textsuperscript{14} or xylitol-u-C\textsuperscript{14}, xylitol is an efficient precursor of liver glycogen as well as glucose. Although there was a decreased glycogen
DISCUSSIONS

Xylitol is a polyalcohol which has recently been recognized as a normal intermediary product in the glucuronate-xylulose cycle. There have been many reports in recent years on the effects of xylitol on the carbohydrate metabolism in human beings and animals. We have reported 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. 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-C\textsubscript{14}, McCormick and Touster have reported that the guinea pig converts xylitol-1-C\textsubscript{14} to respiratory C\textsubscript{14}O\textsubscript{2} 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 \textit{et al} have shown that after intravenous administration of xylitol-C\textsubscript{14} 50 per cent is oxidized to C\textsubscript{14}O\textsubscript{2} 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 CO\textsubscript{2} in the livers treated with CCl\textsubscript{4} as is glucose. Furthermore, the data in Table 1 show that the CO\textsubscript{2} production from xylitol-u-C\textsubscript{14} almost returned to the control level 35 days after the first CCl\textsubscript{4} administration, whereas CO\textsubscript{2} production

![Fig. 1. Incorporation of xylitol-u-C\textsubscript{14} and glucose-u-C\textsubscript{14} in rat liver glycogen.](image)
EFFECTS OF XYLITOL ON CARBOHYDRATE METABOLISM

from glucose-u-C\textsuperscript{14} is still below the control level. The results suggest that xylitol is more efficiently oxidized to CO\textsubscript{2} than glucose in the livers treated with CCl\textsubscript{4}.

Fig. 1 shows the results on the conversion of xylitol-u-C\textsuperscript{14} and glucose-u-C\textsuperscript{14} to liver glycogen. It is evident that xylitol is an efficient glycogen precursor as reported by McCormick and Touster.\textsuperscript{9} Furthermore, xylitol is more efficiently oxidized to CO\textsubscript{2} in the livers of alloxanized rats than glucose (P<0.003). Recent studies\textsuperscript{11} on glucose-C\textsuperscript{14} in the livers of mice treated with virus or CCl\textsubscript{4} have shown the increased C\textsuperscript{14}O\textsubscript{2} production from glucose-1-C\textsuperscript{14}. These data suggest that the metabolism of glucose through the pentose phosphate cycle increases in the livers of mice treated with virus or CCl\textsubscript{4}. Moreover, there have been demonstrated\textsuperscript{12} 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 reported\textsuperscript{13} 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 CCl\textsubscript{4} 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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