HYPOGLYCEMIC AND HYPOLIPIDEMIC EFFECT OF CHITOSAN IN NORMAL AND NEONATAL STREPTOZOLOCIN-INDUCED DIABETIC MICE

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The hypoglycemic and hypolipidemic effect of chitosan was investigated in normal and neonatal streptozotocin-induced diabetic (NSZ) mice, one of the animal models of lean type non-insulin-dependent diabetes mellitus (NIDDM) with hypoinsulinaemia. Chitosan (5% food admixture) reduced the blood glucose (P<0.01), cholesterol (P<0.01) and triglyceride (P<0.01) of normal mice after 4 weeks, and also significantly lowered the blood glucose (P<0.05) and cholesterol (P<0.05) of NSZ mice under the same conditions. But these parameters of KK-Ay mice, which exhibit obese type NIDDM with hyperinsulinaemia, were not affected by chitosan administration. It is concluded that chitosan would be useful for the treatment of lean type NIDDM with hypoinsulinaemia.

KEY WORDS chitosan; hypoglycemic effect; hypolipidemic effect; normal mice; neonatal streptozotocin-induced diabetic mice; KK-Ay mice

Chitosan, a polymer of glucosamine, is widely used for anticancer, 1, 2 hypcholesterolomic 3, 4 and hemagglutinatg5 purposes. However, there is no experimental evidence of the antidiabetic action of this agent. The aim of this study was, accordingly, to examine the hypoglycemic and hypolipidemic effect of chitosan in normal and two types of NIDDM mice, obese ones with hyperinsulinaemia (KK-Ay mice) 6 and lean ones with hypoinsulinaemia (neonatal streptozotocin-induced diabetic (NSZ) mice 7).

MATERIALS AND METHODS

Chitosan (Fig. 1) was generously donated by Fujibio Company. Male mice (ddY, 5 weeks old, SLC Japan) were kept in the experimental animal room for 7 days with free access to food and water. NSZ mice were produced by subcutaneous injection with 90 mg/kg body weight of streptozotocin (STZ, Sigma, Tokyo, Japan), freshly dissolved in citrate buffer, pH4.5. Five weeks after injection of STZ, the blood glucose levels of all the mice were determined. KK-Ay mice (Clea Japan) 12 weeks of age were also used. NSZ and KK-Ay mice with blood glucose levels above 250 mg/dl were considered to be diabetic, and were used in this study. The animals were fed a diet containing 5% chitosan for 4 weeks. For
the determination of blood factors, blood samples were withdrawn from the cavernous sinus with a capillary. Blood glucose, cholesterol and triglyceride in these animals were determined using commercial reagents ("Glucose C-Test Wako", "Cholesterol E-Test Wako", and "Triglyceride G-Test Wako"; Wako Pure Chemical Industries, Ltd.). All the data were expressed as means±S. E. and Student's $t$ test was used for the statistical analysis. The values were considered to be significantly different when the $P$ value was less than 0.05.

![Chemical structure of chitosan](image)

Fig. 1. Structure of Chitosan

RESULTS AND DISCUSSION

The present study clearly showed that chitosan produces consistent hypoglycemic and hypolipidemic effects in normal and NSZ mice, one of the animal models of lean type NIDDM with hypoinsulinaemia. We studied a diet containing chitosan 5%, as previously reported.\(^3\) The mean blood glucose, cholesterol and triglyceride levels of normal mice at 4 weeks are shown in Table 1. Chitosan-treated normal mice had significantly decreased blood glucose (control 202±8 mg/dl, chitosan 168±6 mg/dl, $P<0.01$), cholesterol (control 178±4 mg/dl, chitosan 122±4 mg/dl, $P<0.01$) and triglyceride (control 166±8 mg/dl, chitosan 115±5 mg/dl, $P<0.01$). In NSZ mice, significant hypoglycemic (control 345±23 mg/dl, chitosan 268±23 mg/dl, $P<0.05$) and hypocholesterolemic (control 217±8, chitosan 190±9 mg/dl, $P<0.05$) effects were also observed after the administration (Table 1). However, KK-Ay diabetic mice, one of the animal models of obese type NIDDM with hyperinsulinaemia, had unchanged blood levels of glucose, cholesterol and triglyceride. From these findings, chitosan is useful for lean type NIDDM, and it is important that chitosan is selected as a therapeutic agent according to the type of diabetes. Furthermore, chitosan improved lipid metabolism, indicating that is useful for diabetic complications, because diabetic patients have elevated blood cholesterol and triglyceride levels by metabolic derangement. In addition, the body weight of chitosan-treated mice is not significantly different from corresponding controls(Normal: control 36.1±1.4, chitosan 34.9±0.7 g), (NSZ: control 36.1±1.2, chitosan 35.5±0.7 g), (KK-Ay: control 41.5±2.0, chitosan
44.0±2.2 g), suggesting that the hypoglycemic and hypolipidemic effects were not derived from the alteration of nutritional status. These findings indicate that chitosan may be useful for treatment of non-insulin dependent diabetes mellitus (NIDDM).

Table 1. Effect of Chitosan on Blood Glucose, Cholesterol and Triglyceride in Normal, NSZ and KK-Ay Mice

<table>
<thead>
<tr>
<th></th>
<th>Glucose (mg/dl)</th>
<th>Cholesterol (mg/dl)</th>
<th>Triglyceride (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Control 168±6**</td>
<td>178±4 **</td>
<td>166±8 **</td>
</tr>
<tr>
<td></td>
<td>Chitosan</td>
<td>122±4 **</td>
<td>115±5 **</td>
</tr>
<tr>
<td>NSZ</td>
<td>Control 268±23*</td>
<td>217±8 #</td>
<td>198±45</td>
</tr>
<tr>
<td></td>
<td>Chitosan</td>
<td>190±9 *</td>
<td>165±26</td>
</tr>
<tr>
<td>KK-Ay</td>
<td>Control 429±65</td>
<td>160±23</td>
<td>442±66 #</td>
</tr>
<tr>
<td></td>
<td>Chitosan</td>
<td>176±13</td>
<td>429±85</td>
</tr>
</tbody>
</table>

Each value represents the mean±S. E. from 5-7 mice.
*P<0.05, **P<0.01, significantly different from corresponding control.
§P<0.05, #P<0.01, significantly different from normal mice.

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REFERENCES


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