THE EFFECT OF SODIUM CHLORIDE ON THE GLUCOSE TOLERANCE OF THE DIABETIC RAT

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During a study to determine the effect of certain inorganic substances on the glucose tolerance of the adult albino rat, it was observed that some animals of the strain employed (Connecticut Agricultural Experiment Station) showed a low tolerance to the intraperitoneally administered sugar. The glucose tolerance curves obtained on these rats were typically “diabetic” in nature. At this time a similar observation (1) was reported; 60 per cent of the Yale strain of rats 90 days of age or older showed a poor tolerance to glucose, whereas rats of the Wistar strain had a normal tolerance. Some animals, however, had a nearly normal tolerance to glucose at one test period whereas at another period they showed a low tolerance. The incidence of the low glucose tolerance was less in younger animals, all rats 50 days of age or less having normal tolerance curves. Some dysfunction of the anterior pituitary has been suggested (4) as a possible cause of the diabetic tendency in the Yale strain of rats.

In preliminary studies, the blood sugar values obtained on our rats with a low glucose tolerance showed an unusual trend. There was the expected sharp rise to a high value 30 minutes after the injection of glucose followed by a decrease after the 60 and 90 minute intervals. Then there was usually a secondary rise which

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Effect of NaCl on Glucose Tolerance

frequently exceeded the first and which was sustained during the remainder of a 5 hour period of observation. During the secondary hyperglycemia, the animals frequently became cyanotic and exhibited tetanic contractions of various muscles. The seizures lasted for as long as 2 or 3 hours. These symptoms suggested that a disturbed electrolyte balance, possibly a lowered sodium to potassium ratio, might be involved. Considerable evidence supporting such an explanation is available. It has been shown (3), for example, that the intraperitoneal injection of solutions of glucose causes a migration of sodium and chloride ions into the injected fluid, thus producing a decrease in serum sodium and chloride. Other evidence showing a relationship between electrolyte balance and the metabolism of carbohydrate will be discussed later.

The present investigation was designed to study further the possible relation of sodium chloride to the utilization of glucose by rats showing either a hereditary diabetic tendency or a mild diabetes resulting from partial pancreatectomy.

EXPERIMENTAL

Adult male albino rats of the Connecticut Agricultural Experiment Station strain fed a stock colony ration were used. Pancreatectomized rats were prepared by the usual surgical procedure which produces a mildly diabetic animal not requiring insulin.

A standardized glucose tolerance test was performed on the rats after they had been fasted for 16 to 18 hours. Blood samples were taken from a tail vein 30, 60, 90, 120, 180, and 300 minutes, respectively, after the intraperitoneal administration of 0.35 gm. of anhydrous glucose (as an 8.75 per cent solution) per 100 gm. of body weight. Blood sugar was determined by the Somogyi modification of the Shaffer-Hartmann method (6) on a zinc sulfate-sodium hydroxide filtrate. Extreme care was taken to prevent any loss of sugar by glycolysis.

The tolerance to glucose alone was determined three times on every control and experimental animal. An interval of at least 10 days was allowed to elapse between tests. The entire procedure was then repeated on each animal but this time a glucose solution containing sodium chloride was injected. The glucose solution was made to contain 1.58 per cent sodium chloride, which
is isotonic with 8.75 per cent glucose. This concentration of sodium chloride was used in order to prevent any migration of sodium or chloride ions from the plasma into the injected fluid.

Results

It is evident from the averaged data given in Table I that all of the intact animals did not respond normally to intraperitoneally injected glucose. Approximately 30 per cent of the rats showed a

Table I

| Blood Sugar Values of Intact and Pancreatectomized Rats Administered Glucose by Intraperitoneal Injection |
|---|---|---|---|---|---|---|
| 350 mg. of c.p. glucose per 100 gm. of body weight were administered as an 8.75 per cent solution. The blood sugar values are given in mg. per cent. |

The figures for each group represent average, maximum, and minimum values, respectively.

low tolerance to glucose, as determined by the arbitrary criterion (1) of a blood sugar content of less than 180 mg. per cent at the end of a 5 hour period as the upper limit for a normal tolerance. The poor tolerance of these animals to glucose resembles that of the partially pancreatectomized animals, except for the fact that the latter did not show an early decrease and a subsequent rise in blood sugar values which characterize the usual response of intact rats with a low glucose tolerance. It should be added, however, that the response of some of the rats having a low
tolerance was not invariably the same. As has also been observed by Cole and Harned (1), alternations between normal and poor tolerances were found in a few animals. These rats were arbitrarily classified in the low tolerance group.

The fact that the volume of the injected solution and its hypertonicity were not responsible per se for the hyperglycemia and tetanic seizures in the rats having a low glucose tolerance was demonstrated by the intraperitoneal administration of volumes of isotonic solutions of sodium chloride (1.58 per cent) or of urea.

**Table II**

**Blood Sugar Values of Intact and Pancreatectomized Rats Administered Glucose with Sodium Chloride by Intraperitoneal Injection**

The solution injected contained 8.75 per cent glucose and 1.58 per cent sodium chloride. The blood sugar values are given in mg. per cent.

<table>
<thead>
<tr>
<th>Group No.</th>
<th>No. of rats</th>
<th>Fasting</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120</th>
<th>180</th>
<th>300</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Intact rats, normal tolerance</td>
<td>7</td>
<td>81</td>
<td>217</td>
<td>214</td>
<td>162</td>
<td>150</td>
<td>128</td>
<td>99</td>
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<td></td>
<td>95</td>
<td>206</td>
<td>224</td>
<td>192</td>
<td>173</td>
<td>156</td>
<td>137</td>
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<tr>
<td></td>
<td></td>
<td>73</td>
<td>241</td>
<td>204</td>
<td>145</td>
<td>136</td>
<td>116</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>2. Intact rats, low tolerance</td>
<td>6</td>
<td>74</td>
<td>276</td>
<td>248</td>
<td>220</td>
<td>194</td>
<td>154</td>
</tr>
<tr>
<td></td>
<td></td>
<td>95</td>
<td>318</td>
<td>292</td>
<td>256</td>
<td>228</td>
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<td>64</td>
<td>204</td>
<td>216</td>
<td>168</td>
<td>176</td>
<td>120</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>3. Partially pancreatectomized rats</td>
<td>5</td>
<td>90</td>
<td>319</td>
<td>240</td>
<td>176</td>
<td>155</td>
<td>121</td>
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<td></td>
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<td>429</td>
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<td></td>
<td>66</td>
<td>260</td>
<td>180</td>
<td>105</td>
<td>105</td>
<td>76</td>
<td>76</td>
</tr>
</tbody>
</table>

The figures for each group represent average, maximum, and minimum values, respectively.

(2.91 per cent) equal to that of the glucose solution used. No significant alteration in the blood sugar level occurred within 5 hours.

The results obtained on the animals given glucose with sodium chloride are given in Table II. The tolerances to glucose of the normal intact animals were but slightly lowered by the administration of sodium chloride. However, the intact rats with a low glucose tolerance and the pancreatectomized rats now showed a normal tolerance to glucose. Moreover, none of the animals which received the solution of sodium chloride and glucose mani-
fested the symptoms of muscular tetany seen in the same animals given glucose alone. An excessive water intake was observed in these animals, an observation previously recorded by Darrow and Yannet (3) for animals injected with a hypertonic solution of sodium chloride.

Another small group of animals, the data for which are not included in Table II, was injected with a solution of glucose containing 0.9 per cent sodium chloride. Again there was observed a normal tolerance to glucose.

DISCUSSION

The observation that sodium chloride improves the tolerance of the diabetic rat to intraperitoneally administered glucose is supported by the results of other types of experiments. For example, McQuarrie and coworkers (5) have found that in some human diabetics the ingestion of sodium chloride improves the utilization of carbohydrate. The improvement is manifested by a protein-sparing action, decreased glycosuria, lowered fasting blood sugar, increased respiratory quotient, and decreased ketosis. Furthermore, sodium chloride administration to rats increases the deposition of glycogen in the liver (2).

It also appears possible that the prevention of an altered electrolyte balance by the administered sodium chloride may explain its favorable effect on the glucose tolerance. The intraperitoneal injection of solutions of glucose alone is known to cause a migration of sodium and chloride ions into the injected fluid and to cause a decrease in the concentration of these ions in the serum (3). A decreased sodium to potassium ratio in the plasma could therefore occur. This alteration itself might conceivably produce a hyperglycemia and impair the utilization of the injected glucose, since it has been shown (7) that the injection of subtoxic amounts of potassium salts into rats produces a marked rise in blood sugar and a decrease in liver, muscle, and cardiac glycogen. Furthermore, the administration of potassium chloride causes an increased hyperglycemia in some diabetic patients (5). Thus, sodium and potassium ions appear to have antagonistic effects on carbohydrate metabolism.

In the present experiments, the favorable effect of sodium chloride might be explained therefore in either of two ways. It
appears possible that the secondary rise observed in the blood sugar values of the intact rats having a low glucose tolerance when they are injected with glucose alone might be a result of a decrease in the sodium to potassium ratio in the body fluids and tissues. The administration of sodium as the chloride could obviously prevent such a lowering of the ratio. On the other hand, the presence of sodium chloride in the solution of glucose may have exerted a direct favorable effect on the utilization of glucose, perhaps by way of an augmented rate of glycogenesis.

The possibility that the addition of sodium chloride to the injected glucose may have produced an increased diuresis and an increased renal excretion of glucose should also be considered. Preliminary qualitative experiments have indicated that this factor is of little importance in improving the glucose tolerance. Others (5) have even observed a decreased glycosuria in some human diabetics after the administration of sodium chloride. However, further quantitative studies on this question are now in progress.

An explanation of the reason why some intact rats show a normal tolerance to glucose without added sodium chloride whereas other intact rats and partially pancreatectomized animals show a normal tolerance only when sodium chloride is also injected is not possible at the present time. Obviously, further experimental work is needed to elucidate these questions.

SUMMARY

A study of the effect of sodium chloride on the glucose tolerance of intact rats with a low tolerance and of partially pancreatectomized diabetic rats has been made.

In contrast to the typically diabetic tolerance shown to glucose alone, the tolerances of both types of diabetic rats were normal when glucose was administered with sodium chloride.

The possible importance of the sodium chloride in increasing glycogenesis or in preventing a hyperglycemia due to a decreased sodium to potassium ratio or in increasing the renal excretion of glucose is discussed.

BIBLIOGRAPHY

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