Counteractive Effects of Propionate or 1,2-Propanediol Against Hypoglycemia and Ketonemia of Tributyrin-Treated Cows

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ABSTRACT
We administered tributyrin (500 ml), tributyrin (500 ml) plus magnesium propionate (400 g), tributyrin (500 ml) plus sodium propionate (400 g), or tributyrin (500 ml) plus 1,2-propanediol (400 ml) as a single dose into rumens of lactating cows and then measured in blood the plasma concentrations of glucose, acetacetate, 3-hydroxybutyrate, free fatty acids, and insulin as a function of time. Tributyrin administration caused hypoglycemia and hyperketonemia similar to the ketotic condition in less than 3 h and greatly stimulated insulin secretion. There was a negative correlation of -0.88 between glucose and ketone concentrations in blood plasma. Administration of either magnesium propionate, sodium propionate, or 1,2-propanediol could counteract the hypoglycemia and hyperketonemia induced by tributyrin administration without significantly changing the insulin response. Of the two propionate compounds, magnesium propionate was more effective than sodium propionate for alleviating hypoglycemia and hyperketonemia.

INTRODUCTION
Intravenous administration of butyrate (less than 2.5 mmol/kg body weight) to insulin-treated lambs, rabbits, sheep (5, 17), and lactating goats and cows (1) can cause rapid increase of blood glucose concentrations, whereas intraruminal administration of butyrate (more than 10 mmol/kg body weight) to goats (12, 22), sheep (10), and lactating cows (24) can induce hypoglycemia and hyperketonemia.

Butyrate can be metabolized by rumen epithelium and liver with the production of ketones (2, 15), and only trace amounts of butyrate appear in the peripheral circulation under usual feeding conditions (2). Although the possibility that butyrate may be gluconeogenic in lactating cows has been suggested (13), no net synthesis of carbohydrate from butyrate has been proved for the ruminant animal (3, 7, 14).

In (11) we administered 1,2-propanediol or magnesium propionate into rumens of spontaneously ketotic cows and measured changes of blood metabolite concentrations from 0 to 4 h posttreatment. Because of no reliable method to produce spontaneously ketotic cows experimentally, we produced hypoglycemic and hyperketonemic conditions of lactating cows by intraruminal administration of tributyrin (glyceryl tributyrate). We used tributyrin instead of sodium butyrate, because large quantities of sodium butyrate might produce harmful physiological effects probably from the uptake of large amounts of sodium as suggested in (19). Then we measured counteractive effects of three gluconeogenic substances for alleviating hypoglycemia and hyperketonemia.

MATERIALS AND METHODS
Holstein cows producing about 20 kg of milk daily were used. Before morning feedings we administered the following test solutions into rumens of cows via rubber tube (external diameter 11 mm) inserted through the nose. Five hundred milliliters of tributyrin was mixed with 1.5 liters of water. Magnesium propionate and sodium propionate were made to 25% aqueous solutions of pH 6.5 by added HCl, and

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1600 ml of these solutions was mixed with 500 ml of tributyrin. Four hundred milliliters of 1,2-propanediol was mixed with 500 ml of tributyrin and 1.5 liters of water. Test solutions were administered in less than 7 min. Beginning 30 min after administration of test solutions, cows were fed morning feeds and received routine milking procedure. For tributyrin, tributyrin plus magnesium propionate, tributyrin plus sodium propionate, and tributyrin plus 1,2-propanediol administration, 6, 7, 6, and 4 cows were used, respectively. Jugular blood samples were taken into heparinized tubes immediately before administration (0 h) and .5, 1.5, 3, 6, and 7.5 h postadministration. Glucose, acetoacetate, 3-hydroxybutyrate, free fatty acids, and insulin in blood plasma were analyzed as in (11). Analyses of variance of two-way classifications (cow and treatment) and one-way classification (treatment) were used to determine differences before and after treatment and those between treatments, respectively (23).

RESULTS

Changes of glucose, ketone (acetoacetate plus 3-hydroxybutyrate), and insulin concentrations of blood plasma of cows after intraruminal administration of tributyrin or tributyrin plus magnesium propionate are in Figure 1. Appetite and milk yield of cows were not affected adversely. Tributyrin administration caused a decrease of glucose concentration and increases of ketone and insulin concentrations. The most severe hypoglycemia and hyperketonemia were at 3 h. For cows treated with tributyrin there was a negative correlation of -.88 between plasma glucose and ketone concentrations. Magnesium propionate administration counteracted hypoglycemic and hyperketonemic effects of tributyrin administration. Between the two groups in Figure 1, both glucose concentrations at .5 to 6 h and ketone concentrations at .5 to 7.5 h showed significant differences (P<.05 or .01), but insulin concentrations showed no significant difference.

Concentrations of five blood constituents at pre- and postadministration times in the four treatment groups are in Table 1. From pre- to postadministration time, in each group glucose concentration decreased (P<.05 or .01), and ketone and insulin concentrations increased (P<.05 or .01), and free fatty acid concentra-

Figure 1. Concentrations of glucose, ketones, and insulin in blood plasma after intraruminal administration of tributyrin or tributyrin plus magnesium propionate. Open circles show results from 6 cows administered tributyrin and black circles show results from 7 cows administered tributyrin plus magnesium propionate (mean ± SE).
TABLE 1. Concentrations of blood plasma constituents of lactating cows before treatment and after administration of tributyrin (TB) with or without magnesium propionate (Mg-Pr), sodium propionate (Na-Pr), or 1,2-propanediol (PD).a

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Before or after treatment</th>
<th>Glucose</th>
<th>3-Hydroxybutyrate</th>
<th>Free fatty acids</th>
<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>X</td>
<td>SD</td>
<td>X</td>
<td>SD</td>
</tr>
<tr>
<td>TB (6)</td>
<td>Before</td>
<td>3.60</td>
<td>.38</td>
<td>.08</td>
<td>.03</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>1.91***a</td>
<td>.43</td>
<td>.80***a</td>
<td>.16</td>
</tr>
<tr>
<td>TB + Mg-Pr (7)</td>
<td>Before</td>
<td>3.39</td>
<td>.32</td>
<td>.08</td>
<td>.01</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>2.82*b</td>
<td>.29</td>
<td>.18**b</td>
<td>.03</td>
</tr>
<tr>
<td>TB + Na-Pr (6)</td>
<td>Before</td>
<td>3.44</td>
<td>.35</td>
<td>.09</td>
<td>.03</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>2.39**c</td>
<td>.17</td>
<td>.25**c</td>
<td>.02</td>
</tr>
<tr>
<td>TB + PD (4)</td>
<td>Before</td>
<td>3.37</td>
<td>.24</td>
<td>.06</td>
<td>.01</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>2.59*bc</td>
<td>.40</td>
<td>.35**d</td>
<td>.09</td>
</tr>
</tbody>
</table>

aData are shown as mean and SD. In parentheses are numbers of cows. Means after treatment were taken 3 h after administration except for insulin TB + Mg-Pr, TB + Na-Pr, and TB + PD taken .5, 1.5, and .5 h after administration, respectively. Means after treatment denoted by * and ** were significantly different from those before treatment at 5 and 1%, respectively. Means after treatment denoted by different letters were significantly different at 5%.
sodium propionate to alleviate hypoglycemia and hyperketonemia of lactating cows.

**DISCUSSION**

In blood plasma of the lactating cow, glucose concentration is sensitive to uptake of volatile fatty acids from the rumen and to their subsequent metabolism. Homeostatic mechanisms normally maintain glucose concentration in blood within narrow limits, and a partial breakdown of homeostatic mechanisms can change glucose concentration to some extent (20). This phenomenon is related to the large requirement for glucose as a precursor for synthesis of milk lactose (18). Butyrate is not a gluconeogenic substrate (3, 7, 14), but in the ruminant animal butyrate can stimulate gluconeogenesis (8, 9) or glycogenolysis (16) and contribute to increase glucose concentration in blood. Propionate and 1,2-propanediol are gluconeogenic substrates used for the treatment of ketosis (4, 6, 11, 21).

In our present work, tributyrin administered provided about 8.5 mmol butyrate/kg body weight, which is much less than butyrate used previously for intraruminal administration (10, 12, 22, 24). Tributyrin administration can cause hypoglycemia and hyperketonemia similar to those of spontaneously ketotic cows (11). But unlike in ketosis, free fatty acid concentration remains low and insulin secretion is stimulated greatly. Administration of gluconeogenic substances can counteract hypoglycemic and hyperketonemic effects of tributyrin without changing the insulin secretion rate significantly, which suggests that shortage of gluconeogenic substrates may cause hypoglycemia, whereas supply of them can contribute to prevent ketogenesis.

For the two propionate salts, magnesium propionate is more effective than sodium propionate for alleviating hypoglycemia and hyperketonemia. The reason for this remains to be solved. The experimental method of this work may be useful to examine gluconeogenic and antiketogenic effects of various substances in vivo for the lactating cow.

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