Voluntary wheel running exercise and dietary lactose concomitantly reduce proportion of secondary bile acids in rat feces

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1Division of Applied Bioscience, Research Faculty of Agriculture and 2Meiji Dairies Research Chair, Creative Research Institution Sousei (CRIS), Hokkaido University, Sapporo, Hokkaido, Japan

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Hagio M, Matsumoto M, Yajima T, Hara H, Ishizuka S. Voluntary wheel running exercise and dietary lactose concomitantly reduce proportion of secondary bile acids in rat feces. J Appl Physiol 109: 663–668, 2010. First published July 8, 2010; doi:10.1152/japplphysiol.00777.2009.—According to epidemiologic studies, a negative correlation exists between exercise amount and subsequent cancer development risk in the large intestine. The proportion of secondary bile acids (SBA) in the large intestine is related to subsequent risk for colorectal carcinogenesis. The aim of this study was to investigate the effects of voluntary wheel running exercise and dietary intervention on bile acid (BA) metabolism in the large intestine. Wistar/ST rats (6 wk old) were divided into two groups, exercise and sedentary, after acclimation. Four days after the animals were assigned to a group, rats in each group were fed diets supplemented with different carbohydrate sources including dextrin, sucrose, and lactose. The wheel running period was 4 wk in the exercise group, whereas rats in the sedentary group remained in individual cages during this period. BA composition in collected feces was analyzed with ultraperformance liquid chromatography-electrospray ionization mass spectrometry. We found that wheel running exercise decreased plasma concentrations of cholesterol, triglyceride, and free fatty acids. These decreases were accompanied by a reduction in the proportion of SBA to primary BA (PBA) in feces; however, daily excretion of BA was comparable regardless of wheel running exercise. In addition, ingestion of lactose decreased the SBA-to-PBA ratio and suppressed production of hyodeoxycholic acid in feces. In conclusion, voluntary wheel running exercise, in combination with dietary intervention, could independently reduce the SBA-to-PBA ratio within the large intestine without changing BA excretion. These changes may contribute to the prevention of colorectal carcinogenesis.

ultraperformance liquid chromatography-electrospray ionization mass spectrometry

INACTIVITY and a sedentary lifestyle may cause obesity. Furthermore, obesity can lead to dyslipidemia and glucose dysregulation (25). Diet and exercise might reverse weight gain and obesity (6, 39). A number of epidemiologic studies have shown that exercise leads to a decreased risk of various cancers (13). The most definitive evidence suggests that exercise reduces the incidence of colon cancer (24, 42). Dietary intervention is another factor that influences colorectal carcinogenesis. Epidemiologically, it is known that increased intake of selected bioactive food components including some carbohydrates, n–3 fatty acids, various phytochemicals, minerals, and vitamins may modulate colorectal cancer risk (21).

Bile acids (BAs), especially secondary BA (SBA), have been regarded as a promotive factor for colorectal carcinogenesis (7, 12, 15, 23); however, the precise role of exercise in BA metabolism has not been determined. Barley-based products rich in β-glucan with resistant starch reduce the proportion of SBAs in rats (9). Nondigestible carbohydrate is considered to modulate population and activity of intestinal bacteria (3). Some types of bacteria in the large intestine are responsible for BA conversion from primary BAs (PBAs) into SBAs (29). In particular, the production of SBA depends on microbiiota in the luminal contents of the large intestine (27). Reduction in the proportion of SBA via dietary factors might contribute to the prevention of colon cancer.

Previously, we established (16) a reliable analytical method for measuring BA composition in biological samples using ultraperformance liquid chromatography-electrospray ionization mass spectrometry (UPLC-MS). This method enables us to elucidate the precise BA metabolism. In this study, we investigated whether exercise and dietary intervention influence BA metabolism in rat large intestine by using UPLC-MS analysis.

MATERIALS AND METHODS

Animals and experimental protocol. The study was approved by the Hokkaido University Animal Committee. All animals were maintained in accordance with Hokkaido University guidelines for the care and use of laboratory animals. Male 6-wk-old Wistar/ST rats (Japan SLC, Shizuoka, Japan) were used in this study. The rats were kept in an air-conditioned room at 22 ± 2°C and 55 ± 5% humidity. The light period was from 0800 to 2000. Twenty-four male rats were housed individually in wire-bottomed stainless cages (17-cm longitudinal length, 25-cm width, and 17-cm height) and allowed free access to a diet and water. The rats were acclimatized for 3 days under sedentary conditions. During the acclimation period, rats were fed a dextrin-supplemented diet (dextrin diet). Its composition was as follows: 649.5 g carbohydrate/kg diet, 200 g casein (NZMP acid casein; Fonterra, Auckland, New Zealand)/kg diet, 50 g soybean oil (J-Oil Mills, Tokyo, Japan)/kg diet, 50 g cellulose (JustFiber; Morimura Bros., Tokyo, Japan)/kg diet, 35 g mineral mixture/kg diet (37), 10 g vitamin mixture/kg diet (37), 3 g L-cystine (Wako Pure Chemical Industries, Osaka, Japan)/kg diet, and 2.5 g choline chloride (Wako Pure Chemical Industries)/kg diet. Carbohydrate sources were 549.5 g dextrin (TK-16; Matsutani Chemical Industry, Hyogo, Japan) with 100 g sucrose (Nippon Beet Sugar Mfg., Ohihiro, Japan)/kg diet. After the acclimation period, rats were divided (by weight) into either the sedentary or the voluntary wheel running group. Rats in the sedentary group remained in wire-bottomed stainless cages, whereas rats in the exercise group were transferred to cages equipped with a running wheel (Clea Japan, Tokyo, Japan; 31.8-cm diameter, 10-cm width). Rats in the exercise group were allowed to run voluntarily (28). The number of wheel revolutions during each 24-h period was recorded, irrespective of the direction of wheel rotation. After accli-
mating to these conditions for 4 days, the rats in the sedentary and exercise groups were further divided into three dietary groups based on weight and the daily number of wheel revolutions. We modified only the carbohydrate sources in the test diets compared with those in the acclimation period. The carbohydrate sources in the test diets were 549.5 g dextrin with 100 g sucrose/kg diet in the dextrin diet, 649.5 g sucrose/kg diet in the sucrose diet, and 549.5 g sucrose with 10% lactose (Wako Pure Chemical Industries) kg diet in the lactose diet. At the end of the 4-wk-test period, rats were killed after 3-h food deprivation under resting conditions. The abdominal cavity was opened under pentobarbital sodium anesthesia (Nembutal, 35 mg/kg body wt; Abbott Laboratories, Abbott Park, IL), and arterial blood was collected from the aorta abdominalis. Plasma obtained immediately after collection by centrifugation at 1,000 × g was stored at −80°C until analysis.

**RESULTS**

**Plasma lipids including total BA.** Total BA (TBA), total cholesterol (TC), HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), phospholipids (PL), triglycerides (TG), and free fatty acids (FFA) were measured with colorimetric assays (BML, Tokyo, Japan). Concentrations of TC, HDL-C, and LDL-C were expressed as equivalent amounts of free cholesterol [molecular weight (mol wt) = 386.65]. Similarly, PL, TG, and FFA were calculated as equivalent amounts of lecithin [mol wt = 734.05], triolein [mol wt = 885.45], and oleic acid [mol wt = 282.47], respectively.

**Statistics.** Differences in values between the diet and exercise groups were determined with a two-way ANOVA. Differences in the values among the three dietary treatments in the sedentary or exercise group were determined with a Tukey–Kramer test. Differences in values between the sedentary and exercise groups fed the same diet were determined with a Student’s t-test with Bonferroni correction. A probability < 0.05 was considered statistically significant. JMP 5.0 (SAS Institute, Cary, NC) was used for all statistical analyses.

### RESULTS

Various parameters depicting rat growth and tissue weights are shown in Table 1. After the 4-wk test period, wheel running exercise significantly reduced body weight gain and total food intake by two-way ANOVA analysis; however, dietary intervention did not influence these parameters. In the dextrin diet

<p>| Table 1. Growth, food intake, amount of exercise during 4 wk, and tissue weights at end of test period |
|------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Rat growth, g | Body weight gain, g | Total food intake, g | Amount of exercise, km | Tissue weights, g/100 g body wt |</p>
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<th>Sedentary</th>
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<th>D × E</th>
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<tbody>
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<td>Dextrin</td>
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<td>177.6 ± 7.1</td>
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<td>160.9 ± 15.6</td>
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<td>153.4 ± 23</td>
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<td>524.4 ± 14.6</td>
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<td>504.4 ± 15.3</td>
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<td>78.4 ± 14.6</td>
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<td>36.5 ± 12.2</td>
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</table>

**Values are expressed as means ± SE. D, diet; E, exercise; NS, not significant. ** Significant difference compared with sedentary rats fed the same diet (P < 0.05), n = 4. Values with different superscript letters within the same row in sedentary group are significantly different (P < 0.05, n = 4).
group, wheel running exercise decreased body weight gain. A similar trend was observed in the other dietary groups. Total running distance was not significantly different among diets. A two-way ANOVA revealed that wheel running exercise significantly increased cecal tissue weight and cecal content weight. Specifically, cecal tissue weight was significantly changed by exercise and diet. In the sedentary groups, cecal tissue weights of rats fed the lactose diet were increased compared with rats fed other diets. Wheel running exercise promoted cecal tissue weight in sucrose-fed rats. The weight of gastrocnemius muscle significantly increased by wheel running exercise regardless of diet by two-way ANOVA analysis. In contrast, exercise reduced all adipose tissue weights. We analyzed concentrations of various parameters associated with lipid metabolism in arterial blood plasma (Table 2). Wheel running exercise decreased concentrations of TC, HDL-C, LDL-C, PL, and TG, as revealed by two-way ANOVA.

**Table 2. Concentration of plasma lipids**

<table>
<thead>
<tr>
<th></th>
<th>Dextrin</th>
<th>Sucrose</th>
<th>Lactose</th>
<th>Dextrin</th>
<th>Sucrose</th>
<th>Lactose</th>
<th>Two-Way ANOVA P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBA, μmol/l</td>
<td>4.70 ± 1.20</td>
<td>4.70 ± 2.34</td>
<td>4.33 ± 2.34</td>
<td>6.10 ± 3.67</td>
<td>3.03 ± 0.53</td>
<td>3.15 ± 0.73</td>
<td>NS NS NS</td>
</tr>
<tr>
<td>TC, mmol/l</td>
<td>2.64 ± 0.10</td>
<td>2.74 ± 0.25</td>
<td>2.65 ± 0.19</td>
<td>1.86 ± 0.07b</td>
<td>2.00 ± 0.17</td>
<td>2.03 ± 0.09</td>
<td>NS &lt;0.01 NS</td>
</tr>
<tr>
<td>HDL-C, mmol/l</td>
<td>0.94 ± 0.02</td>
<td>0.98 ± 0.06</td>
<td>0.94 ± 0.05</td>
<td>0.79 ± 0.02a</td>
<td>0.82 ± 0.05</td>
<td>0.81 ± 0.04</td>
<td>NS &lt;0.01 NS</td>
</tr>
<tr>
<td>LDL-C, mmol/l</td>
<td>0.23 ± 0.01</td>
<td>0.23 ± 0.02</td>
<td>0.24 ± 0.02</td>
<td>0.16 ± 0.01a</td>
<td>0.17 ± 0.01</td>
<td>0.19 ± 0.01</td>
<td>NS &lt;0.01 NS</td>
</tr>
<tr>
<td>PL, mmol/l</td>
<td>2.25 ± 0.03</td>
<td>2.39 ± 0.19</td>
<td>2.23 ± 0.14</td>
<td>1.70 ± 0.06b</td>
<td>1.89 ± 0.14</td>
<td>1.81 ± 0.10</td>
<td>NS &lt;0.01 NS</td>
</tr>
<tr>
<td>TG, mmol/l</td>
<td>0.66 ± 0.18</td>
<td>0.82 ± 0.27</td>
<td>0.47 ± 0.10</td>
<td>0.27 ± 0.05</td>
<td>0.47 ± 0.17</td>
<td>0.36 ± 0.09</td>
<td>NS 0.04 NS</td>
</tr>
<tr>
<td>FFA, μmol/l</td>
<td>36.0 ± 3.41</td>
<td>30.9 ± 2.57</td>
<td>31.6 ± 4.94</td>
<td>21.4 ± 2.53a</td>
<td>27.7 ± 3.90</td>
<td>24.7 ± 3.00</td>
<td>NS &lt;0.01 NS</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SE. *Significant difference compared with sedentary rats fed the same diet (P < 0.05, n = 4). TBA, total BA; TC, total cholesterol; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; PL, phospholipids; TG, triglycerides; FFA, free fatty acids.

**Table 3. Concentration and proportion of bile acid in wet feces**

<table>
<thead>
<tr>
<th></th>
<th>Dextrin</th>
<th>Sucrose</th>
<th>Lactose</th>
<th>Dextrin</th>
<th>Sucrose</th>
<th>Lactose</th>
<th>Two-Way ANOVA P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA</td>
<td>0.08 ± 0.01a</td>
<td>0.10 ± 0.02a</td>
<td>&lt;0.05b</td>
<td>0.21 ± 0.01a</td>
<td>0.19 ± 0.04b</td>
<td>0.06 ± 0.05b</td>
<td>&lt;0.01 &lt;0.01 NS</td>
</tr>
<tr>
<td>oMCA</td>
<td>&lt;0.05b</td>
<td>&lt;0.05b</td>
<td>0.06 ± 0.01a</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>0.12 ± 0.05</td>
<td>&lt;0.01 NS NS</td>
</tr>
<tr>
<td>βMCA</td>
<td>0.08 ± 0.02b</td>
<td>0.18 ± 0.04b</td>
<td>0.35 ± 0.07b</td>
<td>0.24 ± 0.03</td>
<td>0.27 ± 0.08</td>
<td>0.86 ± 0.26</td>
<td>&lt;0.01 0.02 NS</td>
</tr>
<tr>
<td>oMCA</td>
<td>0.18 ± 0.03b</td>
<td>0.43 ± 0.09b</td>
<td>0.87 ± 0.16b</td>
<td>0.64 ± 0.18</td>
<td>0.63 ± 0.10</td>
<td>1.03 ± 0.19</td>
<td>&lt;0.01 0.02 NS</td>
</tr>
<tr>
<td>HDCA</td>
<td>1.11 ± 0.09a</td>
<td>0.97 ± 0.24a</td>
<td>&lt;0.05b</td>
<td>1.95 ± 0.36a</td>
<td>1.12 ± 0.36ab</td>
<td>0.24 ± 0.23b</td>
<td>&lt;0.01 NS NS</td>
</tr>
<tr>
<td>DCA</td>
<td>0.19 ± 0.02b</td>
<td>0.21 ± 0.03a</td>
<td>0.06 ± 0.01b</td>
<td>0.54 ± 0.17a</td>
<td>0.18 ± 0.05ab</td>
<td>0.11 ± 0.04b</td>
<td>&lt;0.01 NS NS</td>
</tr>
<tr>
<td>LCA A</td>
<td>0.20 ± 0.02b</td>
<td>0.18 ± 0.04a</td>
<td>0.05 ± 0.01b</td>
<td>0.40 ± 0.08a</td>
<td>0.25 ± 0.07ab</td>
<td>0.08 ± 0.05b</td>
<td>&lt;0.01 0.02 NS</td>
</tr>
<tr>
<td>TBA</td>
<td>1.87 ± 0.08</td>
<td>2.12 ± 0.38</td>
<td>1.42 ± 0.21</td>
<td>4.05 ± 0.54a</td>
<td>2.68 ± 0.62</td>
<td>2.52 ± 0.43</td>
<td>NS &lt;0.01 NS</td>
</tr>
<tr>
<td>Proportion</td>
<td>9.76 ± 1.06a</td>
<td>6.07 ± 0.88a</td>
<td>2.58 ± 0.48a</td>
<td>7.45 ± 0.96a</td>
<td>4.65 ± 0.62a</td>
<td>1.70 ± 0.52b</td>
<td>&lt;0.01 0.03 NS</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SE. *Significant difference compared with sedentary rats fed the same diet (P < 0.05, n = 4). CA, cholic acid; oMCA, βMCA, α, β-, and ω-muricholic acid; HDCA, hyodeoxycholic acid; DCA, deoxycholic acid; LCA, lathocholic acid; PBA, primary BA; SBA, secondary BA. Values with different superscript letters in the same row within sedentary or running group are significantly different (P < 0.05, n = 4). Concentrations of ursodeoxycholic acid (UDCA) and chenodeoxycholic acid (CDCA) were <0.05 µmol/g wet feces.
increased weight of gastrocnemius muscle regardless of diet and decreased adipose tissue weights measured, indicating that the running exercise was enough to grow gastrocnemius muscle as well as energy expenditure in rats. In the literature (10), many studies have found that exercise decreases blood levels of LDL-C, TG, and FFA in humans and rodents. Thus we analyzed plasma lipids to evaluate the physiological efficiency of running exercise. In this study, we found that voluntary wheel running exercise dramatically decreased LDL-C, TG, and FFA in plasma (Table 2). We confirmed that the voluntary wheel running exercise was enough to improve cholesterol metabolism; thus it is possible that this activity influences the metabolism of other lipids, including BAs.

In general, high concentrations of BA in the luminal contents of the large intestine are thought to be undesirable for preventing colorectal cancer (8, 36). Some BAs have been reported to enhance intestinal paracellular permeability in human intestinal Caco-2 cells (35). In general, the decrease of barrier function in gut mucosa is closely related to occurrence of inflammation (30). Furthermore, ulcerative colitis is suggested to increase the risk of developing colorectal carcinoma (18). Thus the increase of permeability in large intestinal mucosa may cause inflammation, and subsequently lead to the pathway for colon cancer. Additionally, epidemiologic evidence indicates a negative correlation between exercise amount and subsequent risk of developing colorectal cancer (5, 24, 34, 42). In experimental studies, a treadmill running exercise reduced the number of 1,2-dimethylhydrazine-induced aberrant crypt foci, a biomarker for colorectal carcinogenesis, in rats (14). In Apc<sup>min</sup> mice, voluntary (20) and treadmill (4) running exercise inhibited intestinal tumorigenesis. However, there is no information on BA metabolism in these studies showing inhibitory effects of exercise on the incidence of colorectal carcinogenesis. In this study, we hypothesized that modulation of BA metabolism by exercise is involved in the subsequent risk for colorectal cancer. To investigate BA composition in the large intestine, we analyzed feces in this study by using the UPLC-MS technique (16). The voluntary wheel running exercise tended to increase almost all types of BA, as well as TBA concentrations, in wet feces (2-way ANOVA; Table 3). Results shown in Table 4 indicate that voluntary wheel running exercise promotes water absorption in the distal region of the large intestine, below the cecum. In addition, neither exercise nor diet modulates TBA concentration in dry weight-basis measurements (Supplemental Table S1). The calculated daily excretion of BA was comparable regardless of running exercise. As a result, wheel running exercise increased BA concentration in wet feces by promoting water absorption, without modulating BA excretion. As shown by these results, despite great decreases in plasma cholesterol levels with running exercise, homeostasis of BA concentration was tightly maintained.

Decrease in SBA concentration is associated with prevention of colorectal cancer (8). SBA, including DCA and LCA, are thought to be tumor promoters (12, 23). SBA/PBA proportion may be another key factor involved in colorectal cancer prevention. Furthermore, this parameter does not depend on moisture content. As shown in Table 3, voluntary running exercise decreased the SBA/PBA proportion. One of the reasons why the SBA-to-PBA ratio decreased in the exercise group may be the suppression of some bacterial population associated with conversion of PBA into SBA, because some types of intestinal bacteria are very sensitive against BA (2, 38). Presumably, promotion of water absorption and decrease of the water ratio in large intestinal contents by exercise lead to increased BA concentration in the luminal contents and decrease some population in microbiota associated with BA conversion, resulting in reduction of the SBA-to-PBA ratio. In the literature, exercise reduced transit time in the gastrointestinal tract (22, 33) and inactivity prolonged colonic transit time (26) in humans. Other reports show correlation between colonic transit time and DCA concentration (43, 44). It is possible that conversion from PBA to SBA may be retarded because of a decrease in transit time by exercise.

Diet influences BA composition via cecal fermentation (19). In fact, we observed that diet influences BA composition in feces more prominently than exercise. Sucrose is extensively absorbed in the proximal small intestine. In contrast, lactose is difficult to absorb in the proximal small intestine because of a reduction of lactase activity in adults (32). As a result, a large amount of lactose that reaches the luminal contents of the large intestine may modulate cecal fermentation caused by resident intestinal bacteria. Poorly digestible carbohydrates, such as

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1 Supplemental Material for this article is available online at the Journal website.
lactose, decrease cecal pH by enhancing the production of lactic acid accompanied by modification of the intestinal microbiota responsible for BA transformation in rats (1). However, the lactose diet in this study (100 g lactose/kg diet) did not affect cecal fermentation (Supplemental Table S2). Nonetheless, this level of lactose ingestion successfully modulated BA composition. As supplementation of lactose was 320 g/kg diet in that study (1), the lactose diet in this study was not enough to contribute to the cecal fermentation. However, the result of this study may indicate that BA composition can be modified by diet without modulating organic acid concentrations in cecal contents. In this study, oMCA and HDCA concentrations in feces dramatically changed in the lactose-fed group. This result is probably due to microbiota related to the BA conversion. One of the related bacteria, HDCA-1 (11), is a gram-variable rod bacterium and plays a role in conversion from βMCA into HDCA. Thus one of the reasons why lactose ingestion decreased HDCA concentration and partially increased oMCA concentration may be reduction of the HDCA-1 population in the cecal contents.

Five weeks of voluntary wheel running exercise increased butyrate concentrations via the progression of fermentation in the cecum of rats (28). In addition, this effect was accompanied by an increase in a butyrate-producing bacterium in the large intestine. On the other hand, exercise did not influence production of organic acids in cecal contents in the present study. Diet compositions were nearly comparable; however, the source of the diet constituents and the strain of rat differed between the two studies. Presumably, the influence of exercise on cecal fermentation depends on dietary constituents and/or the rat strain selected. Precise mechanisms regulating the influence of exercise on cecal fermentation need to be elucidated.

In this study, we confirmed that voluntary wheel running exercise and dietary intervention reduced the proportion of SBA/PBA in the feces. Exercise may also be associated with a decreased risk of colorectal cancer via reduction of SBA/PBA proportion in large intestine. The effects of dietary intervention were quite prominent, indicating that dietary factors are critical for BA conversion. Furthermore, these results indicate that the combination of exercise and diet improves BA composition in the luminal contents of the large intestine.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES


