Effects of Dietary Nucleotides on Lipid Metabolism and Learning Ability of Rats

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To investigate the effects of dietary nucleotides on lipid metabolism and learning ability, male Sprague-Dawley rats were fed with a nucleotides-supplemented diet or a nucleotides-free diet for 5 weeks. The content of nucleotides in the diet was 1.0% and their composition resembled that in human milk. The content of phosphatidylcholine (PC) and the ratio of PC to phosphatidylethanolamine (PE) in the cerebral cortex of rats fed the nucleotides-supplemented diet were significantly higher than that of rats fed the nucleotides-free diet. However, there was no difference in the content of PC and the ratio of PC to PE in the liver between the two groups. The levels of docosahexaenoic acid (C22:6n-3) and arachidonic acid (C20:4n-6) in the cerebral PC fraction were higher in rats fed the nucleotides-supplemented diet. The learning ability of rats fed the nucleotides-supplemented diet, which was evaluated by the water-filled multiple T-maze test and passive avoidance test, was superior to that of rats fed the nucleotides-free diet. The results presented here suggest that dietary nucleotides may influence lipid metabolism of the cerebral cortex and contribute to the rise in learning ability of rats.

Human milk contains nucleotides as a non-protein nitrogen (NPN) constituent.1) The role of nucleotides has been studied mainly with regard to their effects on lipid metabolism,2)–4) gastrointestinal development,5)–7) and immune function.8)–11) These studies suggested that human milk nucleotides may be important in the growth and development of infants. On the other hand, several studies demonstrated that nucleotides-supplemented milk increases the levels of polyunsaturated fatty acids in plasma and the erythrocytes membrane of term and preterm infants.2)–3) Nucleotides are structural components of many intermediates and precursors in the synthesis pathway of lipids, carbohydrates, and proteins. Sasvári-Székely et al.12) demonstrated that exogenous cytidine and deoxyctydine are used for the synthesis of phospholipids by human tonsillar lymphocytes. Agut et al.13) reported that oral administration of cytidine 5'-diphosphate (CDP)-choline, one of intermediates in the synthesis of phospholipids, increases the content of brain phospholipids. Although these studies suggest that nucleotides may be significant in lipid metabolism, the effects of nucleotides on the development and function of brain have not been evaluated.

Then, we investigated the effects of dietary nucleotides, mixed in the same proportion as those in human milk,14) on the lipid metabolism of the cerebral cortex and liver. In addition, we evaluated the effects of dietary nucleotides on the learning ability of rats using the water-filled multiple T-maze and one-trial passive avoidance test.

Materials and Methods

Chemicals. Five kinds of nucleotide monophosphates [CMP, UMP(2'-Na), IMP(2'Na), GMP(2'Na), and AMP] were purchased from Yamasa Co., Ltd. (Chiba, Japan). Phosphatidylcholine (PC) and phosphatidylethanolamine (PE) were purchased from Sigma Chemicals (St. Louis, MO). All other reagents were purchased from Wako Pure Chemicals (Tokyo, Japan). All solvents were of analytical grade.

Animals and diets. Male Sprague-Dawley rats weighing 100-110 g (Japan Clea, Tokyo, Japan) were housed separately and fed with a commercial non-purified diet (CE-2; Japan Clea) for 3 days so that they could adjust to the new environment. The rats were randomly divided into two groups. The rats in the control group (n = 8) were fed a nucleotides-free diet, and those in the nucleotides group (n = 8) were fed a nucleotides-supplemented diet containing 1.0% of a nucleotides mixture. The composition of each diet is presented in Table I. The nucleotides mixture contained 65% CMP, 7% UMP(2'Na), 8% IMP(2'Na), 8% GMP(2'Na), and 12% AMP to simulate the nucleotides composition in human milk. The room temperature was kept at 23 ± 2°C with a 12 h light:dark cycle. All rats were weighed daily during the experimental period. After the learning test

Table I. Composition of the Experimental Diets

<table>
<thead>
<tr>
<th>Ingredient*</th>
<th>Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>g/kg diet</td>
</tr>
<tr>
<td>Casein</td>
<td>250</td>
</tr>
<tr>
<td>Cornstarch</td>
<td>535</td>
</tr>
<tr>
<td>Sucrose</td>
<td>30</td>
</tr>
<tr>
<td>Cellulose</td>
<td>80</td>
</tr>
<tr>
<td>Soybean oil</td>
<td>60</td>
</tr>
<tr>
<td>Minerals mixture</td>
<td>35</td>
</tr>
<tr>
<td>Vitamins mixture</td>
<td>10</td>
</tr>
<tr>
<td>Nucleotides mixture</td>
<td>10</td>
</tr>
</tbody>
</table>

* All ingredients except for soybean oil and nucleotides were purchased from Oriental Yeast Co., Ltd. (Tokyo, Japan). Soybean oil was purchased from Ueda Oils and Fats Mfg. Co., Ltd. (Hyogo, Japan).

1) AIN-76 minerals mixture.15)
2) AIN-76 vitamins mixture13) contained 20% of choline bitartrate.
3) Composition of the nucleotides mixture: 65% CMP, 7% UMP(2'Na), 8% IMP(2'Na), 8% GMP(2'Na), 12% AMP. The purity of each of nucleotides was more than 98%.

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Abbreviations: PC, phosphatidylcholine; PE, phosphatidylethanolamine; T-maze, water-filled multiple T-maze.

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in the water-filled multiple T-maze, all rats of both groups were starved overnight, and killed with an overdose of ether anesthesia. Organs were rapidly removed, weighed, and stored at -70°C until used for lipid analysis.

Furthermore, another learning test was done in the passive avoidance. The rats in the control group \( n = 10 \) were fed a nucleotides-free diet, and those in the nucleotides group \( n = 10 \) were fed a nucleotides-supplemented diet. The experimental conditions were same as those for the water-filled multiple T-maze.

**Analysis of PC and PE.** Total lipid in the cerebral cortex and liver was extracted by the method of Folch et al.\(^{18} \) Lipid extracts dissolved in 100% chloroform were spotted on a silica-gel 60 HPTLC plate (Merck, Darmstadt, Germany) together with standard PC and PE solutions. The plate was developed in chloroform-methanol-methyl acetate-isopropanol-0.25% KCl solution (25:10:25:25:9, v/v) as described by Vitiello and Zanetta,\(^{19} \) and stained with molybdenum blue as described by Gustavsson.\(^{18} \) The spots corresponding to PC and PE were scanned at 700 nm with a dual wavelength flying spot scanning densitometer (CS-9000, Shimadzu, Tokyo, Japan) within 15 min after staining.

**Analysis of fatty acids composition of PC and PE.** The fatty acids composition of PC and PE in the cerebral cortex was analyzed by capillary gas chromatography. PC and PE were separated on a silica-gel 60 TLC plate including a fluorescent indicator (Merck) in chloroform-methanol-acetic acid-distilled water (25:15:4:2, v/v) as described by Skipski et al.\(^{19} \) The spots corresponding to PC and PE were scraped from the plate. The scraped pieces of silica gels were mixed with 6.0 ml of sulfuric acid-benzene-methanol (1:29:96, v/v) solution, and heated at 90°C for 150 min for the methylation of fatty acids. The methyl ester of fatty acids was extracted twice with 5.0 ml of petroleum ether, and concentrated under nitrogen-purge. The methyl ester dissolved in hexane was analyzed by gas chromatography on a Hewlett-Packard 5890 gas chromatograph with a fused silica DB-WAX capillary column (0.25 mm i.d. × 30 m, J&W chromatography). The initial temperature was set at 140°C, raised to 230°C after 15 min at a rate of 2°C/min, and maintained at 230°C for 15 min. The other analytical conditions were as follows: injection and detector temperature, 250°C; detector, FID; carrier gas, helium; flow rate, 1.0 ml/min; split ratio, 70:1.

**Learning ability in the T-maze test.** The water-filled multiple T-maze test was done by the method of Biel et al.\(^{20} \) The apparatus (120 cm long, 120 cm wide, 50 cm depth) was designed with both the T-maze and a straightaway course (shown in Fig. 1). Warm water (23 ± 1°C) was poured into the maze, and the safety platform was set at the goal position of the T-maze and a straightaway course. After rats were trained to swim 3 trials a day for 2 days in the straightaway course, the swimming test was done with 5 trials a day for 3 days (total 15 trials) in the T-maze. The time they took to swim from the start to the goal and the number of errors when they entered the blind alley of the T-maze were measured.

**Learning ability in the one-trial passive avoidance test.** The one-trial passive avoidance test was done using a step-through passive avoidance apparatus (Ohara & Co., Ltd.), as described by Nakahara et al.\(^{21} \) On the acquisition trial, each rat was placed in the light chamber. After a habituation period of 60 s, the guillotine door separating the light and dark chambers was opened, and the latency time to enter the dark chamber was recorded. After the rat entered the dark chamber, the guillotine door was rapidly closed and an electric foot shock (200 V, 0.8 mA, 50 Hz AC) was delivered to the floor grids for 6 s. After 5 s, the rat was removed from the dark chamber and returned to its home cage. Rats that spent over 60 s on the acquisition trial were excluded from the further trial. After 24 h, the latency time of the retention trial was measured in the same way as the acquisition trial, but a foot shock was not delivered. The latency time was recorded to a maximum of 600 s.

**Statistical analysis.** All results are expressed as the mean ± SD. Student's t-test was used to compare differences in results after analyzed by ANOVA. Values of \( p < 0.05 \) were considered significantly different.

**Results**

**Body weight gain, and body and organ weights**

The body weight gain, and body and organ weights are given in Table II. There were no significant differences in body weight gain or body weights between the nucleotides and control groups. No significant differences in brain, liver, or small intestine weights were observed either. These findings indicate that nucleotides supplementation did not influence the growth of rats.

**Content of PC and PE in the cerebral cortex and liver**

The content of PC and PE, and the ratio of PC to PE in the cerebral cortex and liver of rats are shown in Fig. 2. The cerebral PC content in the nucleotides group was significantly higher than that in the control group, but there was no difference in PE content between the two groups. The ratio of PC to PE was 1.37 ± 0.11 for the control group and 1.49 ± 0.07 for the nucleotides group (\( p < 0.05 \)). On the other hand, there was no significant difference in the PC content and the ratio of PC to PE of the liver between the two groups.

**Fatty acids composition of PC and PE**

As shown in Table III, arachidonic acid (C20:4n-6) and docosahexaenoic acid (C22:6n-3) in the cerebral PC fraction of the nucleotides group were significantly higher than those in the control group. In rats fed the nucleotides-supplemented diet, the levels of C20:4n-6 and C22:6n-3 were 23% and 38% higher, respectively. Unlike C20:4n-6, C22:5n-3, and C22:6n-3, there was no difference in the level of other fatty acids. The total levels of n-6 and n-3 fatty acids were also significantly higher in the nucleotides group. The ratio of n-6 to n-3 fatty acids of the PC fraction was 2.52 ± 0.17 for the nucleotides group and 2.89 ± 0.28 for the

**Table II.** Body Weight Gain, and Body and Organ Weights of Rats Fed the Experimental Diets for 5 Weeks\(^{a} \)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Nucleotide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight gain (g/day)</td>
<td>7.1 ± 0.8</td>
<td>7.5 ± 0.4</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>129.5 ± 2.8</td>
<td>132.5 ± 4.5</td>
</tr>
<tr>
<td>Final</td>
<td>333.6 ± 23.7</td>
<td>346.4 ± 14.5</td>
</tr>
<tr>
<td>Organ weight (g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>2.1 ± 0.1</td>
<td>2.1 ± 0.1</td>
</tr>
<tr>
<td>Liver</td>
<td>8.6 ± 0.8</td>
<td>8.9 ± 0.5</td>
</tr>
<tr>
<td>Small intestine</td>
<td>6.3 ± 0.7</td>
<td>6.8 ± 0.8</td>
</tr>
</tbody>
</table>

\(^{a}\) Values are the mean ± SD, \( n = 8 \).

\(^{b}\) The control diet did not contain the nucleotides mixture. The nucleotide diet contained 1.0% of the nucleotides mixture.
control group. The ratio of unsaturated to saturated fatty acids in the PC fraction was 0.67 for the nucleotides group and 0.61 for the control group. The changes in value mainly depended on the increase in the levels of C20:4n-6 and C22:6n-3. Fatty acids composition, the ratio of n-6 to n-3 fatty acids and the ratio of unsaturated to saturated fatty acids of the PE fraction in the two groups were not significantly different. On the other hand, there was no change in fatty acids composition of the liver (data not shown).

Swimming time along the straightaway course

There was no significant difference between the nucleotides group and the control group with regard to the time the rats took to swim along the straightaway course. The swimming time in the first trial was 23.48 ± 26.29 s for the nucleotides group and 30.02 ± 30.57 s for the control group. In the final trial, the swimming time was 5.39 ± 3.51 s for the nucleotides group and 4.98 ± 1.30 s for the control group.

Swimming time and the number of errors in the T-maze

Figure 3 shows swimming time from the start to the goal in the T-maze. Although 15 trials were done, only the results obtained from the first to the eighth trial are shown because there was no difference after the ninth trial. The time to reach the goal for both groups decreased with the increase in the number of trials, but it did not decrease further after the fifth trial. In the first trial, the time was 86.32 ± 47.67 s for the nucleotides group, and 90.35 ± 43.5 s for the control group. There was no significant difference between the two groups. In the third and fourth trial, the swimming time was significantly shorter in the nucleotides group than in the control group. Then, there was no significant difference between the nucleotides and control group after the fifth trial.

As shown in Fig. 4, the number of errors decreased drastically in both groups and remained the same after the fifth trial. In all trials, the number of errors made by the nucleotides group was less than those made by the control group. In the third, fourth, and sixth trial, the number of errors made by the nucleotides group was significantly less than those made by the control group.

**Table III.** Fatty Acids Composition of Phosphatidylcholine (PC) and Phosphatidylethanolamine (PE) in the Cerebral Cortex of Rats Fed the Experimental Diets

<table>
<thead>
<tr>
<th>Fatty acid</th>
<th>Phosphatidylcholine (PC)</th>
<th>Phosphatidylethanolamine (PE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Nucleotide</td>
</tr>
<tr>
<td>16:0</td>
<td>46.03 ± 1.71</td>
<td>43.96 ± 1.71</td>
</tr>
<tr>
<td>18:0</td>
<td>12.87 ± 0.95</td>
<td>13.42 ± 1.18</td>
</tr>
<tr>
<td>18:1 (n-9)</td>
<td>20.18 ± 1.11</td>
<td>20.18 ± 1.26</td>
</tr>
<tr>
<td>18:1 (n-7)</td>
<td>5.55 ± 0.30</td>
<td>5.59 ± 0.30</td>
</tr>
<tr>
<td>18:2 (n-6)</td>
<td>1.03 ± 0.18</td>
<td>1.17 ± 0.49</td>
</tr>
<tr>
<td>20:3 (n-6)</td>
<td>0.16 ± 0.02</td>
<td>0.17 ± 0.02</td>
</tr>
<tr>
<td>20:4 (n-6)</td>
<td>4.29 ± 0.40</td>
<td>5.27 ± 0.54*</td>
</tr>
<tr>
<td>22:4 (n-6)</td>
<td>0.51 ± 0.10</td>
<td>0.65 ± 0.10</td>
</tr>
<tr>
<td>22:5 (n-3)</td>
<td>0.05 ± 0.01</td>
<td>0.06 ± 0.02*</td>
</tr>
<tr>
<td>22:6 (n-3)</td>
<td>2.10 ± 0.30</td>
<td>2.90 ± 0.33*</td>
</tr>
</tbody>
</table>

* Values are the mean ± SD, n = 8. * Significantly different from the control diet, p < 0.05.

a The control diet did not contain the nucleotides mixture. The nucleotides diet contained 1.0% of the nucleotides mixture.
The latency to enter the dark chamber on the acquisition trial was 17.8 ± 23.9 s for the nucleotides group, and 7.9 ± 7.7 s for the control group. There was no significant difference between the two groups. One rat of each group was excluded from the further retention trial because they spent more than 60 s in the latency time on the acquisition trial. On the retention trial, the latency time was longer in the nucleotide group, but not significant (Table IV). The median of the latency time in the nucleotides group was twice that in the control group.

Discussion

György demonstrated that nucleotides supplementation significantly improved the growth rate of weaning rats fed a low-protein diet (10%), but not that of rats fed a high-protein diet (20%). In this study, the growth of rats fed the nucleotides diet containing 25% protein was the same as that of rats fed the control diet, supporting the results reported by György. Dietary nucleotides may be involved in the growth and protein synthesis of growing rats during malnutrition.

Recently, the importance of nucleotides in lipid metabolism is being intensively researched. Gil et al. reported that dietary nucleotides affect fatty acids composition in plasma of infants; especially, polyunsaturated fatty acids with more than 18 carbons of the n-6 series were significantly increased in infants fed nucleotides-supplemented milk formula. Pita showed that C20:4n-6, C22:6n-3 levels in plasma increased, and the cholesterol to phospholipid molar ratio of the erythrocyte membrane slightly decreased in infants fed a nucleotides-supplemented milk formula, compared to a nucleotides-unsupplemented milk formula. Again, Sasvári-Székely et al. and Agut et al. reported that exogenous cytidine, deoxycytidine, and its metabolites were used for the activation of phospholipid intermediates. In this study, we demonstrated that the PC content in cerebral cortex of the nucleotides group was significantly higher than that in the control group. The ratio of PC to PE was also higher in the nucleotides group (Fig. 2). Moreover, the levels of C20:4n-6 and C22:6n-3 in the cerebral cortex of the nucleotides group were also significantly higher than those of the control group (Table III). These differences were significant in the PC fraction, but not in the PE fraction. Gil et al. and Pita speculated that dietary nucleotides might influence the synthesis of polyunsaturated fatty acids and/or desaturase activity of hepatocytes and enterocytes during the neonatal period, because the activities of Δ5 and Δ6 desaturases were limited in newborn infants. However, our study suggests that the high content of polyunsaturated fatty acids in the PC fraction of the nucleotides group may be responsible for the activation of PC metabolism, because the ratio of PC to PE was higher in the nucleotides group than in the control group. PC is formed via the CDP-choline route and the methylation of PE. Consequently, this study suggests that dietary nucleotides, especially CMP, may influence the activation of the CDP-choline route or the methylation of PE and thus accelerate the PC synthesis.

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We also showed that dietary nucleotides did not affect the PC content and the ratio of PC to PE in the liver. Nucleotides can be formed by de novo synthesis or by a salvage pathway of preformed bases and interconversion to the desired compound. In the liver, de novo synthesis mainly works. On the other hand, intestinal mucosa, red blood cells, and brain cells synthesize nucleotides via a salvage pathway and exogenous supply of nucleotides may be important for optimal function for these cells. Accordingly, our results suggest that cerebral cells may also require an exogenous supply of nucleotides.

Large amounts of phospholipids and polyunsaturated fatty acids were present in the brain. It is well known that these lipids play an important role in the development and function of the brain. Yamamoto et al. reported that the dietary ω-6 linolenate/linoleate balance influenced the n-3/n-6 balance of polyenoic fatty acids in the brain phospholipids and rats fed ω-6 linolenate rich diets showed superior ability regarding brightness-discrimination. Again, Lamphey et al. and Yonekubo et al. reported that diets containing n-3 fatty acids improved the learning ability of rats. Furthermore, it was demonstrated that the administration of phospholipid as a substrate of acetylcholine might improve Alzheimer’s disease. These studies indicated that both polyunsaturated fatty acids and phospholipids in the brain may be important for the learning ability. We demonstrated that rats fed a nucleotides-supplemented diet could swim the same distance in a shorter time and made fewer errors in the T-maze (Figs. 3 and 4). Moreover, we demonstrated that the latency time of the passive avoidance was longer in a nucleotides-supplemented diet group (Table IV). These findings indicate that lipid increases in the brain by dietary nucleotides intake may be important for the learning ability. Nishikawa et al. reported that C22:6n-3 potentiated the N-methyl-D-aspartic acid (NMDA)-induced response, and suggested the possibility that C22:6n-3 might be essential in the genesis of long term potentiation. Our result also suggest that C22:6n-3 may activate the NMDA-receptors.

However, Yamamoto et al. reported that the C22:6n-3 level in the cerebral PC fraction was 1.4% in the n-3 fatty acids deficient group and 4.5% in the n-3 fatty acids supplemented group, and Yonekubo et al. reported that the C22:6n-3 level in the n-3 fatty acids deficient and supplemented group was 1.1% and 4.4%, respectively. The increase in C22:6n-3 level of the cerebral PC fraction was slight in this study. Accordingly, there is little possibility that the C22:6n-3 may affect the learning ability in this study. The PC is considered to be important mediators of transmembrane signaling and intracellular messengers. It is not obvious whether our results presented here are concerned with the signal transduction and second messengers, but we speculate that the PC increases may have effects on signaling of acetylcholine or glutamate, thereby contributing to the rise in the learning...
behavior. Moreover, there is a possibility that dietary nucleotides may affect the production of a hormone, because a hormone is considered to be important for the learning and memory. These points require further investigation.

Thus, we concluded that dietary nucleotides intake may cause the increase in the PC content and C20:4n-6, C22:6n-3 levels of the cerebral cortex, and contribute to the rise in the learning ability of rats. Our results support the idea that nucleotides may be a semiessential nutrient for infants. Further studies may be required to clarify the physiological role of milk nucleotides in the growth and development of infants.

References