Changes in Creatine and Urea Formation in Rats Fasted and Fed Low Protein Diets

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Changes in the time course of the urinary excretion of creatinine, creatine and urea, and the activities of kidney transamidinase and liver urea-cycle enzymes were investigated in rats fasted and fed on a 10% casein diet and 10% casein diets supplemented with 10% glycine and/or 1.4% arginine.

The urinary total-creatinine of the fasted rats increased extremely during fasting for 7 days, while that of the animals given the 10% casein diet supplemented with glycine and arginine rose exceedingly on the 3rd day and thereafter no significant change was observed. Most of the increase of total-creatinine could be accounted for by the increase of creatine. The activity of kidney transamidinase in the fasted rats decreased in the 3rd day and thereafter kept nearly constant. The transamidinase activity of rats fed on the 10% casein diet after giving a protein-free diet for 5 days increased in the 3rd day. An inverse relation was observed between the urinary creatine and the transamidinase activity. The urinary urea increased in the rats fasted or fed on the 10% casein diets with the supplement of glycine and/or arginine. In fasting, the activities of liver urea-cycle enzymes, except arginase, had a tendency of increasing with the lapse of time. The arginase activity remained more or less constant. The reason of the extreme increase of urinary creatine during starvation was discussed.

Creatine biosynthesis commences with the transfer of the guanidino moiety of arginine to glycine in the kidney, and the process is catalyzed by transamidinase. Guanidoacetic acid formed in the reaction is then methylated in the liver to form creatine. This system is one of the few known instances of a negative feedback regulation in mammals.

Walker\(^1\) reported that the addition of 1% creatine to a 25% casein diet resulted in the decrease of the activity of kidney transamidinase in rats and that the enzyme activity was gradually declined with the lapse of time. He also showed that the addition of guanidoacetic acid to a 25% casein diet instead of creatine gave the same results perhaps because guanidoacetic acid was converted into creatine. It was also observed that fasting resulted in the similar phenomena, although the level of enzyme activity in fasting was somewhat higher than in the case of adding creatine or guanidoacetic acid.

Pilsum \(et\ al^2\) investigated the changes in the activity of kidney transamidinase in rats fed on a protein-free diet. The enzyme activity decreased considerably within a week after rats were transferred to a protein-free diet as compared with rats fed on a complete diet, and then almost constant level was kept.

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Tomida showed that the urinary creatinine was gradually decreased when rats were given a low protein diet for a long period. Takeuchi et al. observed that the urinary total-creatinine of rats given a 10% casein diet supplemented with glycine and arginine was higher than that of animals fed on the 10% casein diet, but the activity of kidney transamidinase in rats given the supplemented diet decreased considerably in comparison with that in animals fed on the 10% casein diet.

On the other hand, several workers demonstrated that the activities of urea-cycle enzymes in the liver and the amount of urinary urea were altered with the dietary conditions; feeding a high protein diet or the starvation resulted in the increases of enzymes activities; a low protein diet or protein-free diet caused the decreases in their activities; and the activity levels of urea-cycle enzymes were relative to the amount of urinary urea.

However, few studies have reported the relationships between the activity of kidney transamidinase and the excretion of creatine and creatinine. The changes in the formation of creatine and urea, too, have rarely been simultaneously investigated.

In the present experiments, changes in the time course of the activities of kidney transamidinase and urea-cycle enzymes, and the urinary excretion of creatine, creatinine and urea were investigated in rats fasted or fed on 10% casein diet supplemented with glycine and/or arginine.

**MATERIALS AND METHODS**

*Animals and diets.* The animals used in each experiment were male rats of the Donryu strain. The animals were fed on a stock diet (25% casein) for several days before given the experimental diets. Each group in the experiments consisted of 3 to 4 animals.

**Experiment I.** The rats having nearly 170 g of body weight were fed on a protein-free diet for the first 5 days and then divided into five groups; one group was dealt with at once and the other groups were fasted for 1, 3, 5 and 7 days, respectively.

**Experiment II.** The rats weighing about 70 g were fed on a protein-free diet for the first 5 days and then divided into six groups. One group was dealt with immediately and the other groups were fed on a 10% casein diet for 1, 3, 5, 7 and 14 days, respectively.

**Experiment III.** The rats of approximately 55 g of body weight were divided five groups. One group was dealt with at once and the other groups were fasted for 1, 3, 5 and 7 days, respectively.

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**Table 1. The Composition of Experimental Diets**

<table>
<thead>
<tr>
<th>Diet</th>
<th>Casein %</th>
<th>Glycine %</th>
<th>Arginine-HCl %</th>
<th>NaHCO₃ %</th>
</tr>
</thead>
<tbody>
<tr>
<td>10% Casein</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10% Casein + 10% Glycine</td>
<td>10</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10% Casein + 1.4% Arginine</td>
<td>10</td>
<td>10</td>
<td>1.4</td>
<td>0.56</td>
</tr>
<tr>
<td>10% Casein + 10% Glycine + 1.4% Arginine</td>
<td>10</td>
<td>10</td>
<td>1.4</td>
<td>0.56</td>
</tr>
</tbody>
</table>

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was treated immediately and the other groups were fed on a 10% casein diet and 10% casein diets supplemented with 10% glycine and/or 1.4% arginine for 1, 3, 7 and 14 days, respectively.

The composition of diets was as shown in Table I. During the experimental period all the animals were housed in the individual cages and given food and water ad libitum. The animals were given the diets in the form of thick pellet with water. The body weight and food consumption were recorded daily.

**Analysis.** The treatment of animals, the determination of urinary total-creatinine and the activity assay of kidney transamidinase were as described previously. The determination of urinary creatinine was as that of total-creatinine except for the omission of autoclaving. The amount of urinary creatine was calculated by subtracting the creatinine from the total-creatinine and multiplying the difference by the factor of 1.32. The urinary urea was determined by the method of Archibald as modified by Ratner. The activities of urea-cycle enzymes; carbamylphosphate synthetase, ornithine transcarbamylase, argininosuccinate synthetase and arginase, were assayed as described previously. The activities of kidney transamidinase and urea-cycle enzymes were expressed as units/g kidney or liver, and as total units/kidney or liver. One unit of enzyme activity is defined as the one that forms one μmole of the product per hour under the respective assay conditions.

**RESULTS**

**Experiment I**

Results of Experiment I are shown in Fig. 1 and Table II. The decreases of body and liver weight during fasting for 7 days were 50 g and 1.5 g, respectively, but no change in kidney weight was observed.

The urinary total-creatinine increased exceedingly during the fasting, reaching 190% of the original value on the 7th day. The creatinine in urine decreased on the 1st day and recovered to the starting level on the 3rd day, staying constant thereafter. The urinary creatine on the 7th day rose to 320% of that at the start.

The activity of kidney transamidinase expressed as total units/kidney on the 3rd day fell to 32% of the initial level, and after that it remained constant. The similar result was observed when the activity was expressed as units/g kidney.

The urinary urea on the 1st day and the 7th day increased to 180% and 430% of that at the start, respectively.
The activities of liver urea-cycle enzymes had a tendency of increasing with the lapse of time except arginase, of which activity was almost unchanged. The activities of carbamylphosphate synthetase, ornithine transcarbamylase and argininosuccinate synthetase on the 14th day increased to 190%, 165% and 215% of the original value as units/g liver; and 130%, 12000 and 140% of the starting value as total units/liver, respectively.

Experiment II

Figure 2 and Table III show the results of Experiment II.

The increases of body, liver and kidney weight for 14 days were 32 g, 1.6 g and 0.2 g, respectively.

The urinary total-creatinine decreased to 50% and 60% of initial value on the 3rd day and the 14th day, respectively.

The activity of kidney transamidinase expressed as total units/kidney increased to 190% on the 3rd day and 220% on the 14th day of the starting activity. The similar result was observed when the activity was expressed as units/g kidney.

Experiment III

Results of Experiment III are shown in Table IV

The growth of rats fed on the 10% casein diet supplemented with 10% glycine (CG
TABLE III. BODY, LIVER AND KIDNEY WEIGHTS; URINARY CREATINE; AND KIDNEY TRANSAMIDINASE ACTIVITIES IN RATS FED ON THE 10% CASEIN DIET AFTER 5 DAYS FEEDING ON PROTEIN-FREE DIET.

<table>
<thead>
<tr>
<th>Period of feeding</th>
<th>Body weight gaina</th>
<th>Liver weight</th>
<th>Kidney weight</th>
<th>Urinary total creatinine</th>
<th>Kidney transamidinase activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>days</td>
<td>g</td>
<td>g</td>
<td>g</td>
<td>mg/day</td>
<td>units/g kidney</td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>1</td>
<td>1.2±1.8d</td>
<td>2.28±0.07</td>
<td>0.61±0.02</td>
<td>1.8±0.2</td>
<td>3.7±0.4</td>
</tr>
<tr>
<td>3</td>
<td>7.2±1.7</td>
<td>2.78±0.13</td>
<td>0.67±0.03</td>
<td>2.0±0.1</td>
<td>4.0±1.1</td>
</tr>
<tr>
<td>5</td>
<td>6.6±1.2</td>
<td>2.31±0.06</td>
<td>0.65±0.04</td>
<td>0.9±0.1</td>
<td>7.1±0.8</td>
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<tr>
<td>7</td>
<td>12.0±2.3</td>
<td>2.68±0.13</td>
<td>0.59±0.02</td>
<td>1.1±0.2</td>
<td>6.3±0.4</td>
</tr>
<tr>
<td>14</td>
<td>44.2±1.6</td>
<td>4.26±0.34</td>
<td>0.83±0.06</td>
<td>1.2±0.2</td>
<td>7.0±1.3</td>
</tr>
</tbody>
</table>

b) Units/g kidney; μmoles of product per g of wet kidney per hour.
c) Total units/kidney; μmoles of product per wet kidney per hour.
d) Mean ± standard error.

Fig. 2. Relative Changes in the Urinary Total-Creatinine and the Activities of Kidney Transamidinase in Rats Fed on the 10% Casein Diet.

Same explanations are used as in Fig. 1.

- - Transamidinase
○○ Total creatinine

The growth of the group fed on the 10% casein diet supplemented with arginine alone (CA group) was markedly superior to that of the 10% casein group from the 7th day to the 14th day. Changes in liver and kidney weight among groups and also in each group were not observed during the feeding period.

The urinary total-creatinine on the 14th day increased to 180% in the 10% casein group, 195% in the CG group, 215% in the CA group and 475% in the CGA group as compared with the starting level. The creatinine in urine of 10% casein, CG, CA and CGA group on the 14th day were 240%, 265%, 230% and 300% of the value at the start, respectively.

The levels of urinary urea on the 14th day, group) was considerably inferior to the 10% casein group, but the growth depression by excess glycine was somewhat alleviated in the group fed on the 10% casein diet containing excess glycine supplemented with arginine (CGA group). The growth of the group fed on the 10% casein diet supplemented with arginine alone (CA group) was markedly superior to that of the 10% casein group from the 7th day to the 14th day. Changes in liver and kidney weight among groups and also in each group were not observed during the feeding period.

The urinary total-creatinine on the 14th day increased to 180% in the 10% casein group, 195% in the CG group, 215% in the CA group and 475% in the CGA group as compared with the starting level. The creatinine in urine of 10% casein, CG, CA and CGA group on the 14th day were 240%, 265%, 230% and 300% of the value at the start, respectively. The urinary creatine of 10% casein, CG and CA group unchanged almost and did not differ from one another, whereas that of the CGA group on the 14th day was larger than the amount at the start.

The activities of kidney transamidinase in each group on the 3rd day decreased to about 50% of that at the start and then almost constant level was kept regardless of the way of the expression of activity. No clear difference among the enzyme activities of each group was observed through the experimental period.

The levels of urinary urea on the 14th day,
<table>
<thead>
<tr>
<th>Diet</th>
<th>Period of feeding</th>
<th>Body weight change</th>
<th>Liver weight</th>
<th>Kidney weight</th>
<th>Urinary total creatinine</th>
<th>Urinary creatinine</th>
<th>Urinary creatine</th>
<th>Kidney transaminase activity</th>
<th>Urinary urea</th>
<th>Liver arginase activity</th>
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<tr>
<td></td>
<td>days</td>
<td>g</td>
<td>g</td>
<td>g</td>
<td>mg/day</td>
<td>mg/day</td>
<td>mg/day</td>
<td>units/g kidney</td>
<td>mg/g liver</td>
<td>total units/liver</td>
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<tr>
<td>Start</td>
<td>0</td>
<td>-0.3±0.2</td>
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<td>3.2±0.1</td>
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<td>10% Casein</td>
<td>14</td>
<td>28.2±2.5</td>
<td>3.3±0.09</td>
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<tr>
<td>10% casein + 10% glycerine</td>
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<td>16.8±2.4</td>
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<td>10% casein + 1.4% arginine</td>
<td>14</td>
<td>20.1±2.5</td>
<td>3.1±0.07</td>
<td>1.5±0.06</td>
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<td>66.4±6.6</td>
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</tr>
</tbody>
</table>

**Table IV.** Body, Liver and Kidney Weights, Urinary Creatinine and Creatine, Kidney Transaminase Activities, Urinary Urea, and Liver Arginase Activities in Rats Fed on the 10% Casein Diets and 10% Casein Diets Supplemented with Glycine and/or Arginine.

**Notes:**

- **a)** Body weight change = final body weight - initial body weight.
- **b)** Units/g kidney or liver; µmoles of product per g of wet kidney or liver per hour.
- **c)** Total units/kidney or liver; µmoles of product per wet kidney or liver per hour.
- **d)** Mean ± standard error.
when expressed as mg/day, were 260% in the CA group, 300% in the CG group and 560% in the CGA group as compared with that in the 10% casein group. The urinary urea of CG, CA and CGA group on the 14th day, when expressed as mg/g intake-N, were 150%, 140% and 260% of that in the 10% casein, respectively.

DISCUSSION

The urinary total-creatinine of fasted rats increases exceedingly during fasting, while that of the animals fed on the 10% casein diet supplemented with glycine and arginine (CGA group) increases in the first 3 days and thereafter stays more or less constant. The increase of total-creatinine is almost due to the increase in creatine and the ratio of urinary creatine to total-creatinine is 70 to 80% in the fasted and CGA group. However, the amount of urinary total-creatinine in the CGA group is very small as compared with the amount of supplemented glycine and arginine. This shows that ingested excess glycine does not smoothly run into the creatine metabolism system.14) Bloch et al.14) have also reported that an amount corresponding to only about 2% of the total creatine in body is synthesized per day by animals fed on a creatine-free diet. The extreme increase of urinary creatine in fasting may not be due to that of creatine biosynthesis, but due to the intact release of muscle creatine as a result of the exhaustion of muscle, judging from the fact that the increase of creatine is in correlation with the loss of body weight. If the muscle mass of rat is roughly estimated at 20% of the weight loss (about 50 g) for 7-day fasting, considering that the muscle mass of rat occupies approximately 40% of body weight,15) calculated urinary creatine will be about 30 mg for 7 days as muscle creatine content is about 3 mg per g of muscle,16,17) which is comparable to the urinary creatine obtained for 7-day fasting. The extreme increase of urinary creatine has been also observed in muscular dystrophy,18-23) in which muscle creatine appears to be excreted owing to vitamin E deficiency. Changes in the activities of kidney transamidinase take place within 3 days after fasting or feeding on the test diets. The enzyme activity is low when the urinary creatine is high, and the activity decreases as the ratio of urinary creatine to total-creatinine increases. Fitch et al.24) has also reported the similar result. The above phenomenon may be caused by the inhibitory effect of creatine.25-28)

Starvation increases exceedingly the urinary urea as well as the total-creatinine and gradually the activities of liver urea-cycle enzymes except arginase, which coincides with Schimke's observation.29) The 10% casein diet with glycine and/or arginine also increases the urinary urea, but hardly changes the level of liver arginase activity. Similar observation has been

reported by several workers.\textsuperscript{12,30~32} Though
the urinary urea of the CGA group on the
14th day, when expressed as mg/g intake-N,
is larger than that of the animals fed on the
10\% casein diet containing excess glycine (CG
group), the body weight gain of the former
group is a little higher than that of the latter
group. This may show that the addition of
arginine to the 10\% casein diet supplemented
with glycine accelerates catabolism of excess
glycine by increasing the formation of urea.

In view of the above phenomena, in the
CGA group, arginine may promote the for-
mation of urea from excess glycine rather than
the formation of creatine and may alleviate
to some extent the growth depression by ex-
cess glycine. In fasting, the increases in the
activities of liver urea-cycle enzymes and ur-
nary urea are in proportion to the rise of the
rate of protein breakdown in body, while the
increase of urinary creatine may be independ-
ent of the activity of kidney transamidinase
by the reason as mentioned above.

\textsuperscript{32} J. H. Hutchinson, R. L. Jolley and D. H. Lab-