Note

Effects of Sex Hormones on the Metabolism of Tryptophan to Niacin and to Serotonin in Male Rats

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It is known that deaths attributable to pellagra, which is considered to be a disease caused by the disturbance of tryptophan metabolism, have been approximately two-fold higher in women than in men. We investigated the effects of the administration of female and male sex hormones on the contents of tryptophan and such metabolites as serotonin, nicotinamide, N'1-methylnicotinamide, N'1-methyl-2-pyridone-5-carboxamide, and N'1-methyl-4-pyridone-3-carboxamide, and on the conversion ratio of tryptophan to niacin in male rats. Feeding a diet containing estrone or testosterone had no effect on the concentrations of tryptophan and serotonin in the blood and brain, or on the concentration of 5-hydroxyindole-3-acetic acid in the brain. On the contrary, feeding a diet containing estrone caused to a decrease in the urinary excretion of nicotinamide, N'1-methylnicotinamide, N'1-methyl-2-pyridone-5-carboxamide, and N'1-methyl-4-pyridone-3-carboxamide, and of the conversion ratio of tryptophan to niacin when compared with the control rats. Feeding a diet containing testosterone had no effect on any parameter. We postulate from these findings that the cause of higher pellagra deaths in women than in men is attributable to the decrease in the formation of niacin from tryptophan, but not in the formation of serotonin by the female hormone. It seems likely that female sex hormones inhibit the synthesis of niacin from tryptophan, and that women, especially during pregnancy, will be more at risk to pellagra than are men.

Key words: hormone; estrone; serotonin; niacin; tryptophan

It has been reported that pellagra death for women was two-fold higher than that for men. 1) Pellagra is believed to be caused by a deficiency of niacin and/or its precursor Trp. 2-4) However, we think that pellagra is caused by the result of disturbances to the metabolism of Trp to niacin, a vitamin, and/or to serotonin, a neurotransmitter. We have reported that the administration of estrone to female rats resulted in a decreased conversion ratio of Trp to niacin. 5) Accordingly, we considered that the higher pellagra death for women than for men would be attributable to the female hormone, estrone. However, doubts arose about the influence of sex hormones on the metabolism of Trp to serotonin and of estrone on both the metabolism of Trp to serotonin and to niacin when male rats were studied. In the present experiment, the effects of estrone and testosterone on the contents of Trp and such metabolites as serotonin, Nam, MNA, 2-Py and 4-Py, and the conversion ratio of Trp to niacin were investigated for male rats.

 Estrone and testosterone propionate were purchased from Wako Pure Chemical Industries (Osaka, Japan). 2-Py and 4-Py were synthesized by the methods of Colowick 6) and Shibata et al. 7) All other chemicals used were of the highest purity available from commercial sources. Male rats of the Wistar strain (7 weeks old) were obtained from CLEA Japan (Tokyo, Japan) and immediately placed in individual metabolic cages (CT-10; CLEA Japan). To accustom the rats to these conditions, they were initially fed ad libitum for 7 days with an NiA-free, 20% casein diet (control diet; Table I) before being divided into three groups. The rats (now 8 weeks old) were then fed ad libitum for 28 days with the experimental diet (Table I). The animal room temperature was maintained at around 22°C and around 60% humidity, and a 12-h light/12-h dark cycle was maintained. Body weight and food intake were measured daily at around 09:00 a.m., and food and water were renewed daily. Urine samples (09:00 a.m.-09:00 a.m.; 24-h urine) were periodically collected in amber bottles with 1 ml of 1 M HCl and stored at −25°C until needed. The rats were killed by decapitation at around 09:00 a.m. on the last day of the experiment. A 10-μl sample of blood was taken from the carotid artery for measuring the contents of Trp 8) and serotonin. 9) The brain 9) and liver 5) of each animal were removed and immediately treated as described in the literature for measuring Trp, serotonin and 5-HIAA in the brain, and for measuring such enzyme activities as Trp oxygenase, kynureninase, kynurenine 3-hydroxylase, ACMSDase, NAD+ synthetase, Nam methyltransferase, 2-Py-forming MNA oxidase, and 4-Py-forming MNA oxidase that are involved in the metabolism of Trp to niacin in the liver. To calculate the conversion ratio of Trp to niacin, the urinary contents of Nam, and of metabolites MNA, 2-Py and 4-Py were measured. The conversion ratio was calculated as the sum of the urinary excretion of [Nam + MNA + 2-Py + 4-Py (mol/day) × 100] / [Trp intake (mol/day)]. The contents of Nam, 2-Py and 4-Py

Table 1. Composition of the Diets

<table>
<thead>
<tr>
<th></th>
<th>NiA-free, 20% casein (%)</th>
<th>NiA-free, 20% casein + testosterone (%)</th>
<th>NiA-free, 20% casein + estrone (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin-free casein</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>t-Methionine</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Gelatinized cornstarch</td>
<td>45.9</td>
<td>45.82</td>
<td>45.898</td>
</tr>
<tr>
<td>Sucrose</td>
<td>22.9</td>
<td>22.9</td>
<td>22.9</td>
</tr>
<tr>
<td>Corn oil</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Mineral mixture (Oral's ratio)*</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Vitamin mixture (Oral's NiA-free ratio)*</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Testosterone</td>
<td>0</td>
<td>0.08</td>
<td>0</td>
</tr>
<tr>
<td>Estrone</td>
<td>0</td>
<td>0.002</td>
<td>0.002</td>
</tr>
</tbody>
</table>

* Compositions of the mineral and vitamin mixtures are those of Oriental Yeast Kogyo (Tokyo).
Table II. Effects of Estrone and Testosterone on the Metabolism of Trp to Serotonin

<table>
<thead>
<tr>
<th></th>
<th>NiA-free, 20% casein</th>
<th>NiA-free, 20% casein + testosterone</th>
<th>NiA-free, 20% casein + estrone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Trp (nmol/ml of whole blood)</td>
<td>68.3 ± 1.6</td>
<td>69.2 ± 3.1</td>
<td>70.8 ± 2.9</td>
</tr>
<tr>
<td>Blood estrone (nmol/ml of whole blood)</td>
<td>11.2 ± 0.7</td>
<td>11.6 ± 0.4</td>
<td>12.4 ± 0.9</td>
</tr>
<tr>
<td>Brain Trp (nmol/g)</td>
<td>21.3 ± 1.0</td>
<td>20.4 ± 0.7</td>
<td>21.6 ± 0.4</td>
</tr>
<tr>
<td>Brain serotonin (nmol/g of brain)</td>
<td>2.84 ± 0.03</td>
<td>2.71 ± 0.08</td>
<td>3.05 ± 0.16</td>
</tr>
<tr>
<td>Brain 5-HIAA (nmol/g of brain)</td>
<td>1.43 ± 0.05</td>
<td>1.34 ± 0.06</td>
<td>1.33 ± 0.06</td>
</tr>
</tbody>
</table>

Each value is expressed as the mean ± SEM for five rats.

in the urine were simultaneously measured by the HPLC method of Shibata et al., while the content of MNA in the urine was measured by the HPLC method of Shibata. The contents of Trp, serotonin, and 5-HIAA were measured by HPLC methods. Each enzyme activity was measured as described in the literature.

Changes in the daily body weight and food intake of the control, estrone and testosterone groups are shown in Fig. 1. Feeding the diet containing testosterone had no effect on any parameter when compared with those of the control group. However, feeding the diet containing estrone decreased the body weight gain when compared with the results for the control and testosterone groups. The food intake throughout the experimental period by the control, testosterone and estrone groups was 544 ± 12 g (mean ± SEM for five rats), 519 ± 10 g, and 428 ± 16 g, respectively. These results indicate that dietary estrone reduced the appetite of male rats as well as that of female rats.

The effects of testosterone and estrone on the contents of Trp, serotonin, and 5-HIAA are shown in Table II. The contents of Trp in the blood and brain were not affected by feeding the diet containing testosterone or estrone, and the contents of its metabolite, serotonin, in the blood and brain were not affected, either. The content of 5-HIAA in the brain was not changed by feeding any of the sex hormone diets.

The effects of estrone and testosterone on the urinary excretion of Nam, MNA, 2-Py and 4-Py, and on the conversion ratio of the Trp to niacin are shown in Figs. 2 and 3, respectively. Each of the Trp metabolites and the conversion ratio were gradually decreased until around day 12 by feeding the diet containing estrone, the decreased values then remaining constant. Bender and Totoc11 have also reported that the administration of estrone sulfate to female rats led to a significant reduction in the liver content of NAD and then in urinary excretion of MNA. On the contrary, some investigators in U.S.A. have reported that the conversion ratio of Trp to niacin increased in pregnant humans and rats, and that the administration of estrone to female rats induced an increase in MNA excretion. Therefore, the American investigators consider that the conversion of Trp to niacin is higher in the pregnant than in the nonpregnant state. A major difference in the experimental method between the present and the reported works is the composition of the diets, which contained niacin in the reported experiments, but not in the present work.

The urinary excretion of Nam and of its metabolites, including MNA, by the rats fed with the testosterone diet did not decrease when compared with those of the control group (Fig. 2), although Lohan14 has reported that an intramuscular injection of testosterone in sesame oil for 5 consecutive days to female rats induced decreased MNA excretion.

The enzyme activities involved in the metabolism of Trp to niacin in liver were measured. It was found that only the activity of ACMSDase was higher in the group fed with the estrogen diet (2.28 ± 0.17 μmol/h/g of liver) than in the groups fed with the control (0.91 ± 0.08) and testosterone diets (0.76 ± 0.04). This phenomenon is consistent with that obtained for female rats. Higher activity of the enzyme means lower formation of niacin from Trp. It is possible that estrone induced the m-RNA synthesis of ACMSDase, because the formation of niacin gradually decreased (Figs. 2 and 3).

We think that the female sex hormone itself decreased the conversion ratio of Trp to niacin because the methods used here are highly reliable and the administration of estrone resulted in increased ACMSDase activity.

It seems likely that female sex hormones would inhibit the synthesis of niacin from tryptophan, and that, women, especially during pregnancy, would be more at risk of pellagra than are men.
Fig. 2. Effects of Estrone and Testosterone on the Urinary Excretion of Nam (A), MNA (B), 2-Py (C), and 4-Py (D).

○, control; ▲, testosterone; □, estrone. Each point represents the mean ± SEM for five rats; points with different superscript letters on the last day of the experiment are significantly different at p < 0.01, as determined by the Student-Newman-Keuls multiple-comparison test.

Fig. 3. Effects of Estrone and Testosterone on the Conversion Ratio of Trp-to-niacin.

○, control; ▲, testosterone; □, estrone. Each point represents the mean ± SEM for five rats; points with different superscript letters on the last day of the experiment are significantly different at p < 0.01, as determined by the Student-Newman-Keuls multiple-comparison test.

References