RAPID COMMUNICATION

Effect of Ethanol on the Peripheral Metabolism of Thyroxine

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Synopsis

To determine the effect of ethanol on peripheral metabolism of T₄, deiodinative clearance of T₄ and serum concentration of T₃, T₂ and rT₃ were measured in rats isotopically equilibrated with T₄. Ethanol 8 g/Kg body weight/day was given for 3 days to fasted rats and the results were compared with those normally fed or totally fasted animals. In fasted rats, deiodinative clearance of T₄ and serum T₄ and T₃ concentration, and T₃/T₄ ratio, were decreased significantly, while serum rT₃ concentration and serum rT₃/T₄ ratio was increased significantly when compared to those in normal rats.

When ethanol was administered to fasted rats, deiodinative clearance of T₄, serum T₄ and T₃ concentration and serum T₃/T₄ returned to normal level while serum rT₃ concentration and rT₃/T₄ ratio remained at higher levels than in normally fed animals. These results could not be interpreted on the basis of shift of 5 monodeiodinase to 5' form or vise versa, and imply that the two deionative process may be independent each other.

It was well recognized that the peripheral metabolism of thyroxine (T₄) is under the influence of nutritional state. For example, it was reported that the deiodinative clearance of T₄ is reduced by fasting in rats (Ingbar and Galton, 1975). In man, fasting decreases serum concentration of 3, 5, 3'-triiodothyronine (T₃) and increases that of 3, 3', 5'-triiodothyronine (rT₃) (Portnay et al., 1974; Vagenakis et al., 1975; Merimee and Fineberg, 1976). Furthermore, it was suggested that carbohydrate intake is more important for the maintenance of normal deiodination system of T₄ than the caloric effect (Spaulding et al., 1976). In the latter study, protein and fat was used instead of carbohydrate to give the same caloric effect as carbohydrate.

Materials and Methods

Deionative clearance and total clearance of T₄ were measured by the method described by Ingbar and Galton (1975). Male Wistar rats of 160-180 g body weight received daily injection of 2 μg/100 g body weight of T₄ mixed with ¹³¹I-T₄ for 13 days. They were fed with normal diet and 1% potassium perchlorate solution ad libitum for 10 days. During the 11th to 13th day of T₄ injection, some rats were placed on fasting with forced administration of water (1% potassium perchlorate solution) or ethanol (8 g/Kg body weight/day, dissolved with 1% potassium perchlorate solution), which was given 4 times a day.

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by feeding tube.

Collection of 24 hr urine in a metabolic cage and blood samplings were performed from the 13th to 14th day.

Deiodinative and total clearance of T4 was calculated by the formula shown below:

Deiodinative clearance = \frac{125I \text{ in 24 hr urine}}{125I \text{ in TCA precipitate of 1 ml serum}}

Total clearance = \frac{125I \text{ of injected dose of T4}}{125I \text{ in TCA precipitate of 1 ml serum}}

Serum concentration of T1, T3, and rT3 was measured by commercially available kits obtained from Eiken Immunochemical Laboratories and Dainabott Radioisotope Laboratories, Tokyo.

Results

The results are summarized in Table 1. In fasted rats with forced drinking of water, total T4 clearance, deiodinative clearance of T4, serum concentration of T4 and T3, and serum T3/T4 ratio were significantly decreased whereas serum concentration of rT3 and rT3/T4 ratio were significantly increased when compared to the values obtained in normally fed controls. When ethanol was administered to the fasted animals, deiodinative clearance and total clearance of T4, serum concentration of T4 and T3, and serum T3/T4 ratio were the same as the values in normally fed controls, while serum concentration of rT3 and rT3/T4 ratio were significantly higher than those in normally fed animals. Serum concentration of T3 and T3/T4 ratio in ethanol-treated animals were significantly higher than those in water-treated animals. During this experimental period, urinary volume in each group of animals was not changed significantly. The body weight was increased in normal group and was decreased in fasted group, either treated by water or ethanol.

Discussion

The present experiments clearly demonstrated that the peripheral metabolism of T4 was extensively altered by the nutritional state. For example, total and deiodinative clearance of T4 were reduced by fasting. This result is in accord with the report by Ingbar and Galton (1975). In their ex-

Table 1. The effect of fasting and ethanol treatment on peripheral metabolism of T4.

<table>
<thead>
<tr>
<th></th>
<th>normal diet</th>
<th>water-treated</th>
<th>ethanol-treated</th>
<th>statistical significance (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>A vs B</td>
</tr>
<tr>
<td>Deiodinative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>clearance of T4</td>
<td>20.4 ± 2.9(4)*</td>
<td>13.7 ± 2.4(4)</td>
<td>24.2 ± 5.9(7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(ml/100 g/day)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total clearance</td>
<td>66.0 ± 9.9(4)</td>
<td>45.9 ± 8.9(4)</td>
<td>56.7 ± 15.1(7)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>of T4 (ml/100 g/day)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume of 24 hr</td>
<td>11.2 ± 3.6(4)</td>
<td>12.8 ± 2.3(4)</td>
<td>11.9 ± 2.5(7)</td>
<td>N.S.</td>
</tr>
<tr>
<td>urine (ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight**</td>
<td>180 ± 7(4)</td>
<td>190 ± 14(4)</td>
<td>209 ± 21(7)</td>
<td>N.S.</td>
</tr>
<tr>
<td>(g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Changes in</td>
<td>22.5 ± 9.6(4)</td>
<td>-38.8 ± 3.5(4)</td>
<td>-43.6 ± 5.6(7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>body weight (g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4 (ng/100 ml)</td>
<td>4.1 ± 0.2(3)</td>
<td>3.5 ± 0.4(6)</td>
<td>4.4 ± 1.6(8)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>T3 (ng/100 ml)</td>
<td>67.7 ± 7.5(3)</td>
<td>35.5 ± 14.1(6)</td>
<td>60.3 ± 16.5(8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>T3/T4</td>
<td>16.7 ± 1.9(3)</td>
<td>10.2 ± 3.7(6)</td>
<td>13.8 ± 2.8(8)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>rT3 (ng/100 ml)</td>
<td>40.3 ± 4.6(3)</td>
<td>113.8 ± 31.1(6)</td>
<td>135.1 ± 48.8(8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>rT3/T4</td>
<td>10.0 ± 1.6(3)</td>
<td>39.9 ± 11.8(6)</td>
<td>28.9 ± 10.7(8)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

* Mean ± SD, obtained in parenthesized number of animals
** Body weight at the start of fasting or ethanol administration.
periments, the reduction in total and deiodinative clearance of $T_4$ was resulted from two factors, namely, the elevation of serum $T_4$ concentration and reduction in the radioactivity derived in the urine. When the experiment was reproduced according to their set-up, hemoconcentration due to the fasting was always observed (not shown). It is obvious that the elevation of $T_4$ in their experiments was resulted from the hemoconcentration. In the present experiments, forced drinking of water was carried out to avoid hemoconcentration and to make the urinary volume comparable to the normally fed controls. Thus, the reduction in total and deiodinative clearance of $T_4$ observed in the present experiments was solely resulted from the reduction in deiodination of $T_4$, because both $^{125}$I-$T_4$ and serum $T_4$ concentration directly measured by radioimmunoassay were decreased significantly in fasted animals. The results were essentially the same when total or deiodinative clearance of $T_4$ as postulated by Nisula et al. (1977). The reason of the reduction in $T_4$ concentration in the fasted group was obvious in the present experiment, the effect of forced drinking of water has to be taken into account. To minimize the latter effect, serum $T_3/T_4$ ratio was calculated and compared among the groups studied. As is obvious from Table 1, serum $T_3/T_4$ ratio was significantly decreased in the fasted group and this reduction was almost completely countered when ethanol was administered. The changes of serum $T_3/T_4$ ratio in conjunction with the changes of deiodinative clearance of $T_4$ clearly indicate the conversion of $T_4$ to $T_3$ decreased by fasting and recovered by ethanol administration.

At the same token, the changes in serum $rT_3/T_4$ would indicate either the significant elevation of conversion of $T_4$ to $rT_3$ or depression of $rT_3$ degradation induced by fasting. Ethanol failed to counteract the effect of fasting in this aspect. The reports on the effect of ethanol on $T_4$ metabolism have been scarce and fragmental. Israel et al. described that acute ethanol administration causes an accelerated accumulation of radioactive $T_4$ in the liver (Israel et al., 1973). The effective dose in an acute experiment was reported to be more than 4 g/Kg body weight for a single ingestion and the dose less than 2 g/Kg, which was employed in the present experiment, was ineffective. Thus, the re-
covery of deiodinative clearance of T₄ due
to an acceleration of T₄ accumulation in
liver is not likely to be the cause of the
ethanol. The recovery of deiodinative
clearance of T₄ may well be due to
the resumption of T₄-deiodination to T₃.
Spaulding and his associates reported that
800 Cal of carbohydrate when given to
fasted subjects completely recovered the
serum T₃ and rT₃ concentration altered by
fasting. When the same calories were given
by fat or protein, serum T₃ concentration
was remaining at the levels of fasting and
serum rT₃ concentration was reduced to
the normal levels. This discordance of the
changes in T₃ and rT₃ was qualitatively
similar to the effect of ethanol shown in
the present experiment expect that ethanol
brought T₃ levels to normal but rT₃ to the
levels of fasting. The changes in T₃ and
rT₃ resulted from administration of fat,
protein or ethanol could not be explained
on the basis of reciprocal shifting of 5
monodeiodinase to 5′ from or vise versa.
To delineate the effect of ethanol on pe-
ripheral metabolism of T₄, close correlation
of the effect of T₄ and that of ethanol
has to be taken into consideration. It was
demonstrated that the hypermetabolism
state produced in liver by chronic ethanol
administration was markedly reduced in
surgically thyroidectomized rats (Israel et
al., 1975b) and that propylthiouracil abol-
ishes the hypermetabolic state induced by
ethanol (Israel et al., 1975a). Thus, it is
possible that the effect of ethanol on liver
may be mediated through the changes in
T₄ metabolism. The extent of the effect
of ethanol on central nervous system, cardio-
vascular system or on redox state in liver
in situ to influence the present findings
has remained to be elucidated.

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