Gender-specific changes in thyroid hormone-glucuronidating enzymes in rat liver during short-term fasting and long-term food restriction

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Glucuronidation is a major pathway of thyroid hormone metabolism in rats, involving at least three different hepatic UDP-glucuronosyltransferases (UGTs): bilirubin UGT, phenol UGT and androstone UGT. We have studied the effects of short-term (3 days) fasting and long-term (3 weeks) food restriction to one-third of normal intake (FR33) on hepatic UGT activities for thyroxine (T4), triiodothyronine (T3), bilirubin and androstone in male and female Wistar rats with either a functional (high activity, HA) or a defective (low activity, LA) androstone UGT gene. Because food deprivation is known to induce centrally mediated hypothyroidism in rats, results were compared with those obtained in methimazole (MMI)-induced hypothyroid rats. Both fasting and FR33 produced largely parallel increases in T4 and bilirubin UGT activities. These effects were greater in males than in females, and were reproduced in MMI-treated rats. In male and female HA rats, fasting induced insignificant increases in T3 UGT activity and had no effect on androstone UGT activity. In male HA rats, FR33 was associated with an increase in T3 UGT activity, while androstone UGT activity showed little change. However, in female HA rats both T4 and androstone UGT activities were markedly decreased by FR33. Triiodothyronine UGT activity in LA rats was strongly decreased compared with HA rats, but was not further decreased by FR33 in female LA rats, supporting the importance of androstone UGT for T3 glucuronidation. These results demonstrate different sex-dependent effects of food deprivation on hepatic T4 and T3 glucuronidation that are associated with changes in the expression of bilirubin UGT and androstone UGT, respectively. For the increased T4 and bilirubin UGT activities at least, these effects appear to be mediated by the hypothyroid state of the (semi)starved animals.

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The three principal pathways of thyroid hormone metabolism are deiodination, sulfation and glucuronidation (1–3). Of these, deiodination is most important in terms of regulation of hormone bioactivity. The predominant secretory product of the thyroid follicular cells, T4, is regarded as a prohormone with little intrinsic bioactivity. Thyroxine is activated by outer ring deiodination (ORD) to T3, whereas it is inactivated by inner ring deiodination (IRD) to rT3. An important route for inactivation of T3 is by IRD to 3,3',5'-triiodothyronine, a metabolite that is also produced by ORD of rT3. Three membrane-bound deiodinases have been implicated in the peripheral metabolism of thyroid hormone (1,2). The type I iodothyronine deiodinase (ID-I) in the liver and kidneys has both ORD and IRD activity, and plays an important role in the production of plasma T3. The other deiodinas catalyze only ORD (type II) or only IRD (type III), and show further marked differences in enzyme characteristics, tissue distribution and regulation (1,2). Glucuronidation and sulfation are so-called phase II detoxification reactions, the purpose of which is to increase the water solubility, and thus, the biliary and urinary excretion of a variety of endogenous and exogenous substrates (4,5). Normally, however, excretion of iodothyronine sulfates in bile and urine is negligible, because they are rapidly deiodinated by ID-I (3). The UDP-glucuronosyltransferases (UGTs) represent a family of closely related isoenzymes with broad and overlapping substrate specificities that all utilize UDP-glucuronic acid (UDPGA) as the co-factor (4). In rats, at least three UGT isoenzymes are involved with the glucuronidation of thyroid hormone, showing highest activity in the endoplasmic reticulum of liver (3,6–12). Two of these, bilirubin UGT and phenol UGT, show substrate preference for rT3 and T4, while androstone UGT is the predominant enzyme for glucuronidation of T3 (3,12). Iodothyronine glucuronides are efficiently excreted in the bile, but this is not an irreversible pathway of thyroid hormone disposal. The biliary-excreted conjugates are hydrolyzed by bacterial β-glucuronidases in the intestine, and part of the thus
liberated iodothyronines is reabsorbed, constituting a significant enterohepatic cycle (13–15).

Although sulfation and glucuronidation represent major pathways of thyroid hormone metabolism, much less is known about their possible regulation compared with the deiodination pathway. In this study, we investigated the effects of short-term (3 days) starvation and long-term (3 weeks) food restriction to one-third of normal intake (FR33) on hepatic ID-I activity and UGT activities for T4, T3, bilirubin and androsterone in rats. The effects of FR33 were determined in rats with high activity (HA) for androsterone UGT as well as in rats that lack this isoenzyme because of a gene defect, resulting in the low activity (LA) phenotype (16). Because food deprivation is known to decrease thyroid function (17), results were compared with those observed in animals made hypothyroid with methimazole (MMI).

Materials and methods

Materials

[3',5'-125I]Thyroxine and [3'-125I]T3 were obtained from Amersham (Amersham, UK); T4, T3, propyl-thiouracil (PTU), MMI, HEPES, dithiothreitol (DTT), bilirubin and BSA were from Sigma (St Louis, MO); [1H]androsterone was from NEN (Boston, MA); androsterone was from Steraloids (Wilton, NH); Brij 56 was from Serva (Heidelberg, Germany); UDPGA came from Boehringer Mannheim (Almere, The Netherlands); BCA protein assay reagent came from Pierce (Oud Beijerland, The Netherlands); Sephadex LH-20 came from Pharmacia (Woerden, The Netherlands).

[125I]Triiodothyronine could be used without further purification, but [125I]T4 was purified on Sephadex LH-20 immediately before each assay (12).

Animals

Experiments were done with male and female Wistar rats obtained from Harlan Sprague-Dawley (Zeist, The Netherlands), locally bred albino Wistar R-Amsterdam (Wistar R) rats or locally bred hooded Wistar (R × U) F1 rats. They were housed in a controlled animal room with a 14-h light/10-h dark photocycle, and were provided with commercial rat chow containing 22% protein, 4.8% fat, 66.8% carbohydrates, 0.35 mg/kg iodine and 0.29 mg/kg selenium (RMH-TH. Hope Farms, Woerden, The Netherlands) and tap water ad libitum. At the start of the experiments, rats were 10 weeks old (mean body weights: male rats 216 g; female rats 163 g). Daily food intake of control rats was 24 g in males and 15 g in females. Acute effects of starvation were studied in rats completely deprived of food for 3 days. The long-term effects of food restriction were studied in rats that were provided with only one-third of normal food intake (FR33) for 3 weeks, i.e. 8 g for males and 5 g for females. Control animals continued to have free access to food, and all animals were supplied with drinking water ad libitum. The health state of the animals was checked upon daily. Other groups of rats were made hypothyroid by treatment for 2 weeks with drinking water containing 0.1% (wt/vol) MMI. Euthyroid controls received drinking water without additions. Rats were decapitated under ether anesthesia. Trunk blood was collected and serum was isolated and stored at −20°C until analysis of hormone levels. Livers were isolated, immediately frozen in liquid nitrogen and stored at −80°C until further processing. All procedures were approved by the Animal Welfare Committee (DEC) of the Erasmus University.

Liver enzyme assays

Liver tissue was homogenized in 0.25 mol/l sucrose, 10 mmol/l HEPES and 1 mmol/l DTT, and microsomes were prepared as described previously. Microsomes were suspended in 0.1 mol/l phosphate (pH 7.2), 2 mmol/l EDTA and 1 mmol/l DTT, at a protein concentration of 10–20 mg/ml, and stored in aliquots at −80°C until enzyme analysis. Protein was measured with the BCA reagent according to the protocol of the supplier, using BSA as the standard (12).

Iodothyronine UGT activities. These were assayed usually by incubation of 1 µmol/l T4 or T3 and 100 000 cpms [125I]labeled substrate for 60 min at 37°C with 1 mg microsomal protein/ml and 5 mmol/l UDPGA in 0.2 ml of 75 mmol/l TRIS·HCl (pH 7.8) and 7.5 mmol/l MgCl2 (12). The reactions were stopped by addition of 0.2 ml of ice-cold methanol, and after centrifugation 200 µl of the supernatants was mixed with 0.8 ml of 0.1 mol/l HCl and analyzed for glucuronide formation by chromatography on Sephadex LH-20 micolumns (12).

Activities of UGT for bilirubin and androsterone. These were measured as described previously (12). Assay mixtures for bilirubin UGT activity contained 0.1 mol/l bilirubin, 0.125% BSA, 5 mmol/l UDPGA, 1 mg microsomal protein/ml, 0.025% Brij 56, 0.1 mol/l TRIS·HCl (pH 7.8) and 3.75 mmol/l MgCl2, and were incubated for 15 min at 37°C. Androsterone UGT assay mixtures contained 0.1 mmol/l androsterone, ~50 000 dpm [1H]-androsterone, 5 mmol/l UDPGA, 0.5 mg microsomal protein/ml, 0.005% Brij 56, 0.1 mol/l TRIS·HCl (pH 7.4) and 3.75 mmol/l MgCl2, and were incubated for 15 min at 37°C.

Type I iodothyronine deiodinase (ID-I) activity. This was determined essentially as described previously by incubation of 1 µmol/l rT3 and ~100 000 cpms [125I]rT3 for 30 min at 37°C with 10 µg microsomal protein/ml in 200 µl of 0.1 mol/l phosphate (pH 7.2), 2 mmol/l EDTA and 5 mmol/l DTT (12). Reactions were stopped by addition of 100 µl of 5% (wt/vol) BSA, and radiodide
formation was analyzed by the TCA precipitation method (12).

Miscellaneous

Serum T₄ and T₃ levels were determined by standardRIA procedures. Serum TSH was determined by RIA with the materials and protocols of the NIDDK, using TSH RP-2 as standard. The statistical significance of differences between control male and female rats, and between control and experimental animals, was evaluated by analysis of variance and Student's t-test: p < 0.05 was considered significant.

Results

Table 1 presents the serum hormone levels and hepatic ID-I activities in 3-day fasted and normally fed male and female Wistar rats. Serum T₄, T₃ and TSH levels tended to be higher in male than in female controls. Irrespective of sex, both serum T₄ and T₃ were strongly decreased by starvation. Serum TSH was decreased significantly by starvation in male but not in female animals. Hepatic ID-I activity was markedly higher in male than in female fed controls. Fasting produced a significant decrease in ID-I activity in both sexes, although the effect was more pronounced in males than in females.

Only three of the 24 Wistar rats used in this experiment were found to have the LA phenotype, with androsterone UGT activities <10% of those in the other (HA) rats. Bilirubin and T₄ UGT activities were not different between HA and LA rats, but T₃ UGT activity in LA rats was <50% of that in HA rats. Figure 1 shows the effects of 3-day fasting on hepatic T₄ and bilirubin UGT activities, using data from all rats, and on T₃ and androsterone UGT activities in HA rats. The T₄ UGT activity was lower in male than in female fed controls. Fasting resulted in a significant increase in T₄ UGT activity in both sexes, the effect being greater in males than in females. The T₃ UGT activity was lower in male than in female fed controls. In both sexes, fasting was associated with a minor, insignificant increase in T₃ UGT activity. Bilirubin UGT activity was lower in male than in female control rats. Fasting induced a significant increase in bilirubin UGT activity in males but not in females. Fasting was without effect on androsterone UGT activity in either sex.

Table 2 presents the serum hormone levels and hepatic ID-I activities in male and female rats of the Wistar R × U strain fed ad libitum or for 3 weeks with only one-third of normal food intake (FR33). Serum T₄, T₃ and TSH were all higher in male than in female controls. In both sexes, FR33 produced a significant fall in serum T₄, T₃ and TSH. Again, hepatic ID-I activity was much higher in male than in female ad libitum controls, and FR33 produced a similar, marked decrease in both sexes.

All 20 Wistar R × U rats used in this experiment were found to have the HA phenotype for androsterone UGT activity. Figure 2 shows the effects of prolonged food restriction on hepatic UGT activities in these rats. The T₄ UGT activity was similar in male and female controls, and FR33 resulted in a marked increase in both sexes. The T₃ UGT activity was similar in male and female controls, and FR33 induced a 34% decrease in females but had no effect in males. Bilirubin UGT activity was significantly lower in males than in females, and FR33 produced a significant increase in both sexes, although the effect was greater in males than in females. Androsterone UGT activity showed a 12% decrease in FR33 males and a 56% decrease in FR33 females compared with ad libitum controls.

Similar effects of FR33 on serum hormone levels and liver enzyme activities were observed in Wistar rats. Three of the 24 rats used were found to have the LA phenotype: the T₄ and androsterone UGT activities in the HA control and FR33 rats are shown in Fig. 3. Food restriction had no effect on T₃ UGT activity in male rats but produced a 47% decrease in female rats. Similarly, FR33 did not affect androsterone UGT activity in male rats but resulted in a 63% decrease in female rats.

Table 3 presents the serum hormone levels and hepatic ID-I activities in male and female rats of the Wistar R strain fed ad libitum or for 3 weeks with the FR33 diet. Serum T₄ and TSH but not T₃ were higher in male than in female controls. In both sexes, FR33 produced significant decreases in serum T₄, T₃ and TSH, although the changes in serum T₄ and T₃ were less and those in serum TSH more pronounced in

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Table 1. Effects of 3-day fasting on serum T₄, T₃ and TSH levels and hepatic type I iodothyronine deiodinase (ID-I) activity in Wistar rats.*

<table>
<thead>
<tr>
<th>Group</th>
<th>T₄  (nmol/l)</th>
<th>T₃  (nmol/l)</th>
<th>TSH (ng/ml)</th>
<th>ID-I (pmol·min⁻¹·mg⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, control</td>
<td>66 ± 9</td>
<td>1.49 ± 0.19</td>
<td>1.07 ± 0.26</td>
<td>582 ± 77</td>
</tr>
<tr>
<td>Male, fasted</td>
<td>25 ± 9b</td>
<td>0.57 ± 0.16b</td>
<td>0.61 ± 0.19b</td>
<td>322 ± 37b</td>
</tr>
<tr>
<td>Female, control</td>
<td>45 ± 10b</td>
<td>1.39 ± 0.27</td>
<td>0.69 ± 0.19b</td>
<td>311 ± 41b</td>
</tr>
<tr>
<td>Female, fasted</td>
<td>30 ± 7c</td>
<td>0.76 ± 0.17c</td>
<td>0.64 ± 0.26</td>
<td>231 ± 92c</td>
</tr>
</tbody>
</table>

* Results are presented as mean ± SD of six rats in each group.

b Significantly different from male controls (p < 0.025 or less).

c Significantly different from female controls (p < 0.05 or less).
males than in females. Hepatic ID-I activity was markedly higher in male than in female Wistar R rats, and FR33 induced a significant decrease in both sexes, very similar to the results obtained in Wistar R × U rats (Table 2).

Only four of the 32 Wistar R rats used in this experiment were found to have the HA phenotype. Bilirubin and T4 UGT activities were not different between these HA and the 28 LA rats, but T3 UGT activity in the HA rats was ~3 times higher than that in the LA animals. Figure 4 shows the effects of FR33 on the T4 and bilirubin UGT activities, using data from all rats, and on the T3 and androsterone UGT activities in the LA rats. The T4 UGT activity was lower in male than in female controls, and FR33 produced a highly significant increase in both sexes. In the LA rats, T3 UGT activity was markedly lower in male than in female controls. Food restriction resulted in a significant

Table 2. Effects of 3-week food restriction on serum T4, T3 and TSH levels and hepatic type I iodothyronine deiodinase (ID-I) activity in Wistar R × U rats.

<table>
<thead>
<tr>
<th>Group</th>
<th>T4 (nmol/l)</th>
<th>T3 (nmol/l)</th>
<th>TSH (ng/ml)</th>
<th>ID-I (pmol·min⁻¹·mg⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, control</td>
<td>74 ± 7</td>
<td>1.34 ± 0.13</td>
<td>1.33 ± 0.34</td>
<td>733 ± 112</td>
</tr>
<tr>
<td>Male, FR33</td>
<td>48 ± 3b</td>
<td>0.96 ± 0.10b</td>
<td>0.12 ± 0.08b</td>
<td>346 ± 66b</td>
</tr>
<tr>
<td>Female, control</td>
<td>44 ± 6b</td>
<td>1.09 ± 0.11b</td>
<td>0.17 ± 0.11b</td>
<td>266 ± 32b</td>
</tr>
<tr>
<td>Female, FR33</td>
<td>25 ± 7c</td>
<td>0.70 ± 0.21c</td>
<td>0.02 ± 0.03c</td>
<td>114 ± 23c</td>
</tr>
</tbody>
</table>

* Rats were fed ad libitum or for 3 weeks with one-third of normal food intake (FR33). Results are presented as means ± sd of five rats in each group.

b Significantly different from male controls (p < 0.025 or less).

c Significantly different from female controls (p < 0.025 or less).
Fig. 2. Effects of 3-week food restriction (FR33) on hepatic UDP-glucuronyltransferase (UGT) activities for $T_4$, $T_3$, bilirubin (Bili) and androsterone (Andro) in male and female Wistar R × U (high activity) rats. Hatched bars: control rats; black bars: food-restricted rats. Results are the means ± so of five rats per group; *p < 0.001 vs normally fed males and **p < 0.025 or less vs normally fed controls.

Fig. 3. Effects of 3-week food restriction (FR33) on hepatic UDP-glucuronyltransferase (UGT) activities for $T_3$ and androsterone (Andro) in male and female Wistar (high activity) rats. Hatched bars: control rats; black bars: food-restricted rats. Results are the means ± so of 4–6 rats per group; **p < 0.005 or less vs normally fed controls.
Table 3. Effects of 3-week food restriction on serum T₄, T₃ and TSH levels and hepatic type 1 iodothyronine deiodinase (ID-I) activity in Wistar R rats.a

<table>
<thead>
<tr>
<th>Group</th>
<th>T₄ (nmol/l)</th>
<th>T₃ (nmol/l)</th>
<th>TSH (ng/ml)</th>
<th>ID-I (pmol·min⁻¹·mg⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, control</td>
<td>46 ± 7</td>
<td>1.30 ± 0.08</td>
<td>0.76 ± 0.45</td>
<td>382 ± 58</td>
</tr>
<tr>
<td>Male, FR33</td>
<td>30 ± 5b</td>
<td>1.05 ± 0.13b</td>
<td>0.11 ± 0.06b</td>
<td>178 ± 47b</td>
</tr>
<tr>
<td>Female, control</td>
<td>31 ± 6b</td>
<td>1.24 ± 0.08</td>
<td>0.35 ± 0.15b</td>
<td>160 ± 23b</td>
</tr>
<tr>
<td>Female, FR33</td>
<td>11 ± 4c</td>
<td>0.69 ± 0.17c</td>
<td>0.18 ± 0.15c</td>
<td>87 ± 35c</td>
</tr>
</tbody>
</table>

a Rats were fed ad libitum or for 3 weeks with one-third of normal food intake (FR33). Results are presented as means ± SD of eight rats in each group.
b Significantly different from male controls (p < 0.05 or less).
c Significantly different from female controls (p < 0.05 or less).

Increase in T₃ UGT activity in males but not in females. Bilirubin UGT activity was lower in male than in female control Wistar R rats, and FR33 induced a significant increase in males but not in females. Obviously, androsterone UGT activity is extremely low in the control LA rats and shows little change in FR33 animals.

Treatment of male and female Wistar R rats with MMI resulted in strong decreases in serum T₄ and T₃ levels and hepatic ID-I activities and large increases in serum TSH levels (not shown), attesting to their hypothyroid status. All 20 Wistar rats used in this experiment were found to have the LA phenotype. Figure 5 shows the hepatic T₄ and bilirubin UGT

![Graph](image-url)
activities in the control and hypothyroid rats. Both $T_4$ and bilirubin UGT activities were higher in female than in male controls, and both enzyme activities were increased by MMI-induced hypothyroidism irrespective of sex.

Discussion

Previous studies in our laboratory have suggested that glucuronidation of thyroid hormone in rat liver involves at least three different UGT isoenzymes (7–12). This was based on the following observations:

(i) induction of phenol UGT activity by treatment of rats with 3-methylcholanthrene (MC)-type inducers, including MC itself, polychlorophenyls, dioxin and hexachlorobenzene, increased the glucuronidation of $T_4$ and rT$_3$ but had little effect on the glucuronidation of T$_3$ (7, 9, 12);

(ii) induction of bilirubin UGT activity by treatment of rats with clofibrate or ciprofibrate also increased the glucuronidation of $T_4$ and rT$_3$ but again had little effect on T$_3$ glucuronidation (8, 12);

(iii) UGT activities for $T_4$ and rT$_3$ were strongly diminished, while T$_3$ UGT activity was apparently normal in Gunn rats, which have a defect in the UGT1 gene locus coding for multiple bilirubin and phenol UGTs (10);

(iv) relative to Wistar HA and Sprague-Dawley rats, T$_3$ UGT activity is strongly decreased while $T_4$ and rT$_3$ UGT activities show little change in Wistar LA, Fischer and WAG rats, which have a defect in the gene coding for androsterone UGT (7–10, 12).

Furthermore, studies using V79 cells transfected with cDNA of UGT1-encoded isoenzymes showed significant glucuronidation of iodothyronines by the bilirubin UGT HP3 and the phenol UGT HP4 with, in both cases, substrate preference for rT$_3$ > $T_4$ > T$_3$ (11). Thus, for the interpretation of the present results it is assumed that the following UGTs are involved with the glucuronidation of $T_4$ and T$_3$ in rat liver: bilirubin UGT (the homolog of HP3), which prefers $T_4$ over T$_3$; phenol UGT (the homolog of HP4), which also prefers $T_4$ over T$_3$; and androsterone UGT, which prefers T$_3$ over T$_4$ and is lacking in Wistar LA rats (3, 12).

In agreement with previous reports (e.g. Refs. 17 and 18) we found that both short-term fasting and long-term food reduction result in marked decreases in serum $T_4$, T$_3$ and TSH levels. Because food deprivation also causes an increase in serum TBG in rats and, hence, a decrease in the serum free T$_3$ fraction, the serum free T$_3$ concentration shows an even greater decrease than the total serum T$_3$ concentration (19, 20). Therefore, food deprivation is associated in rats with a centrally mediated hypothyroid state, which is manifested by, among other things, a marked decrease in liver ID-I activity (1, 2). Therefore, the findings obtained in food-deprived rats were compared with those effected by MMI-induced hypothyroidism. Also in agreement with previous reports (e.g. Refs. 21 and 22), we found a marked sex dependence of hepatic ID-I activity in all Wistar rats, being much higher in males than in females.

In the present study, hepatic bilirubin UGT activity was consistently higher in female than in male control rats and was independent of the phenotype for androsterone UGT activity. Both short-term fasting and long-term food reduction resulted in an increase in bilirubin UGT activity that was greater in males than in females. In agreement with findings in thyroidectomized rats (23–25), bilirubin UGT activity was increased in MMI-induced hypothyroid rats of both sexes. These results suggest that the increase in hepatic bilirubin UGT activity in response to short-term fasting or long-term food restriction is mediated, at least in part, by the hypothyroid state of the animals.
Within the same Wistar substrain, T4 UGT activity was not different between HA and LA rats, confirming that androsterone UGT is not an important enzyme for T4 glucuronidation (12). In short-term fasted rats, T4 UGT activity seemed to change in parallel with bilirubin UGT activity. However, long-term food restriction appeared to induce a much larger increase in UGT activity for T4 than for bilirubin, which was most obvious in female LA rats (Fig. 4). This suggests that, in addition to bilirubin UGT, another isoenzyme is involved with the glucuronidation of T4 in rat liver, the activity of which is increased by long-term food restriction. It is unknown if this third UGT is identical to the above-mentioned MC-inducible phenol UGT (12).

In keeping with data reported by others (26), androsterone UGT activity was similar in male and female HA control rats. In addition, we found that in neither sex was androsterone UGT activity affected by acute starvation. Perhaps the most intriguing results of the present study were the effects of prolonged food restriction on androsterone and T3 UGT activities. Whereas long-term food restriction had very little effect on androsterone and T3 UGT activities in male HA rats, it strongly decreased both activities in female HA rats (Figs. 2 and 3). Not only was the T3 UGT activity strongly decreased in control LA compared with control HA rats, prolonged food restriction increased T3 UGT activity in male LA rats and had little effect in female LA rats. These results underscore the importance of androsterone UGT for T3 glucuronidation in rats and strongly suggest that the decreased T3 glucuronidation induced by prolonged food restriction in female HA rats is mediated by the decrease in androsterone UGT activity. To what extent each bilirubin UGT and phenol UGT contribute to T3 glucuronidation, and in particular to the increase induced by short-term fasting and long-term food restriction in male HA and LA rats, remains unknown. Also, the mechanism of the female-specific down-regulation of androsterone UGT during prolonged food restriction requires further investigation. Because the effects of hypothyroidism were only investigated in LA rats, our findings do not answer the question: Is the food restriction-induced decrease in androsterone UGT activity in female rats mediated by the hypothyroid state of the animals?

In conclusion, we found that acute starvation and prolonged food restriction induced different sex-dependent changes in T4 and T3 glucuronidation in rat liver. The T4 UGT activity is increased in both paradigms in parallel with bilirubin UGT activity, the effects being greater in males than in females and probably mediated by the hypothyroid state of the animals. In male rats, T3 glucuronidation shows a tendency to increase in both paradigms, whereas in females it is markedly decreased by prolonged food restriction in parallel with androsterone UGT activity. This decreased T3 glucuronidation is not observed in rats lacking androsterone UGT. The consequences of these changes in hepatic T4 and T3 UGT activities, in addition to changes in co-factor (UDPGA) concentration (27), for the nutrition-dependent regulation of thyroid hormone metabolism in vivo remain to be determined.

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