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Serum Concentrations of Thyroid Hormones and Extrathyroidal Thyroxine-5′-monodeiodinase Activity during Lactation in the Rat (42458)

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Abstract. Serum thyroxine (T_4) and triiodothyronine (T_3) concentrations and T_4-5′-monodeiodinase activity in liver and kidney homogenates were studied in Sprague–Dawley rats during lactation. Blood and tissue samples were collected from nulliparous and pregnant rats 2 days before delivery and from lactating rats 0, 2, 7, 12, 19, and 26 days after delivery. Litters were removed from half of the mothers immediately after delivery to create a postpartum nonlactating group for study at the same times. Pregnant rats had lower serum T_4 and T_3 concentrations and higher liver T_4-5′-monodeiodinase activity than nulliparous females. Low serum T_4 persisted throughout lactation but further decrease in serum T_3 was observed. Activity of T_4-5′-monodeiodinase in liver and kidney homogenates was significantly reduced during lactation as compared to nonlactating rats. Serum concentration of T_4 and T_3 and T_4-5′-monodeiodinase activity in liver and kidney returned toward control values 5 days after weaning (Postpartum Day 26). Our findings suggest that the relative hypothyroid state observed during lactation in rats is associated with a significant decrease in T_4 to T_3 conversion in the liver and kidneys.

The involvement of thyroid hormones in maintaining normal lactation is well recognized (for reviews, see (1, 2)). However, decreased concentrations of circulating thyroxine (T_4) have been reported in lactating cows (3, 4), mares (5), and rats (6) as compared to nonlactating animals. Also, a number of studies have shown an inverse relationship between milk yield and plasma T_4 concentration in the cow (4, 7, 8) and between nursing intensity and serum T_4 in the lactating rat (9). In lactating rats, Fukuda *et al.* (10) reported decreased concentrations of plasma T_4 and triiodothyronine (T_3) and increased concentrations of plasma thyrotrophin (TSH), suggesting a functional hypothyroid state in lactating animals.

The only source of T_4 in the circulation is thyroidal secretion while T_3, the most metabolically active hormone, is mainly generated in extrathyroidal tissues by enzymatic 5′-monodeiodination of T_4 (11, 12). Previous investigations with rats have shown that T_4-5′-monodeiodination in liver is significantly decreased in hypothyroidism (13–16).

The purpose of this study was to investigate, in lactating rats, the temporal relationship between changes in the concentrations of serum T_4 and T_3 and the enzymatic activity of T_4-5′-monodeiodination in homogenates of liver and kidney. Additionally, pregnant rats were examined because increased conversion of T_4 to T_3 in extrathyroidal tissues of pregnant rats was suggested (10) but no direct measurements of T_4-5′-monodeiodinase activity were reported.

Materials and Methods. *Animals.* Pregnant Sprague–Dawley rats (14–16 days of gestation; 280–340 g) and nulliparous female rats of the same age (210–220 g) were purchased from Dominion Laboratories, Inc. (Dublin, VA).[3] The animals were fed standard pelleted rat chow (Agway Inc., Syracuse, NY) and tap water *ad libitum.* They were maintained in individual cages containing wood shavings in a temperature (24 ± 2°C)-, light (14 hr)-, and humidity (45%)-controlled room.

Experimental design. At the onset of the experiment, six virgin females and six pregnant

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rats, 2 days before expected time of delivery, were killed. After spontaneous delivery, a group of six rats was sacrificed (Postpartum Day 0) and the remaining rats were divided into two groups. In one group, referred to as the lactating group, litter size was adjusted to 10 pups per mother to provide equal suckling intensity. Pups were weaned on Day 21 postpartum. In the second postpartum nonlactating group, litters were removed from mothers immediately after delivery. Subgroups of six females each from lactating and nonlactating groups were killed 2, 7, 12, 19, and 26 days after delivery. Animals were stunned by a blow to the head and killed by exsanguination from neck arteries. Although stress has been shown to reduce TSH release in the rat, the time involved in immediate blood collection was too short to expect a significant decrease in serum T_4 or T_3. Since all animals were subjected to the same protocol, stress-related effects were the same across physiological states. Serum was separated by centrifugation and stored at −20°C until assayed. Immediately after exsanguination, the tissues were dissected and weighed. Livers and kidneys were then frozen on dry ice and stored at −20°C for 2–4 days, a procedure which was shown not to induce any detectable decrease in T_4-5′-monodeiodinase activity (17).

T_4-5′-monodeiodinase determination. Conversion of T_4 to T_3 was determined *in vitro* by a method described previously (18). In brief, tissues were homogenized using a Polytron homogenizer (Brinkmann Instruments Inc., Westbury, NY) in 3 vol (weight/vol) ice-cold buffer (0.1 *M* phosphate buffer, pH 7.5, with 0.25 *M* sucrose and 5 m*M* EDTA). After centrifugation at 2000*g* for 30 min at 4°C, the supernate (referred to hereafter as homogenate) was incubated with T_4 (1.3 μM) for 30 min and the amount of T_3 generated was measured by radioimmunoassay (RIA). Each incubation tube contained 0.4 ml homogenate and 0.6 ml assay buffer with dithiothreitol (DTT, 2 m*M* final concentration). Incubation was terminated by addition of 2 ml 100% ethanol. Samples were centrifuged and the resulting supernates were kept at −20°C until T_3 was determined. Each incubation assay included a blank tube to which T_4 was added at the end of incubation. The amount of T_3 in blank tubes was subtracted from T_3 in samples. Generation of T_3 due to incubation of homogenate with T_4 was expressed as nanograms of T_3 per hour of incubation per milligram of protein. Each homogenate was assayed in duplicate; the values agreed within 5–10%.

Hormone determination. Concentrations of T_4 and T_3 were determined in duplicate using a commercially available radioimmunoassay kit (Immuchem Corp., Carson, CA) and standards were prepared in rat T_4- and T_3-free serum. All samples were analyzed in the same assay for each hormone to eliminate interassay variation. Mean intraassay coefficients of variations were 4.2 and 7.8% for T_4 and T_3 assays. The amount of T_3 produced during incubation of T_4 with tissue homogenate was measured in the ethanol extract of the incubation mixture, using the same RIA kit with modifications as previously described (18).

Statistical evaluation of data. Data are expressed as the means and standard errors of the mean (SEM). Student's *t* test was applied to compare groups of lactating and postpartum nonlactating rats at particular times after delivery and to compare pregnant and nulliparous rats. Analysis of variance followed by Duncan's multiple-range rest was used to make comparisons among groups of nonlactating rats after delivery and virgin rats. Data were analyzed using the general linear model and *t* test procedures of the Statistical Analysis System (19).

Results. Pregnant rats (2 days prepartum) had serum T_4 and T_3 concentrations 25% ($P < 0.001$) and 67% ($P < 0.05$) of the concentrations observed in virgin females (Fig. 1). As a result, T_4/T_3 molar ratio in serum of pregnant rats was lower ($P < 0.001$) than that of virgin rats (50.5 ± 4.6 vs 21.3 ± 3.1). After delivery, concentrations of T_4 in the serum of nonlactating rats increased to those of virgin rats within 7 days (Fig. 1A). Serum T_3 concentrations returned from a low during pregnancy to concentrations equal to those of virgin rats on the day of delivery with a transient increase ($P < 0.05$) on Day 2 (Fig. 1B). In lactating rats, serum T_4 increased after parturition but remained significantly lower than in the nonlactating group throughout the period of lactation (Fig. 1A, Days 2–19). On the day of parturition, the concentration of T_3 in serum of lactating rats was greater than that of pregnant rats (Fig. 1B); however, 7 days later

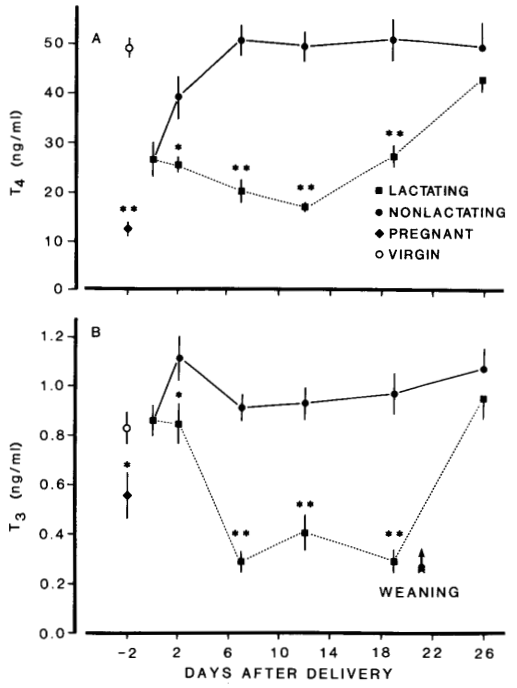

FIG. 1. Serum thyroxine (T_4; A) and triiodothyronine (T_3; B) concentrations in lactating, postpartum nonlactating, pregnant, and virgin rats. Values are means ± SEM; $n = 6$. *$P < 0.05$, **$P < 0.001$, lactating compared with nonlactating rats at particular days after parturition or pregnant compared with virgin rats.

T_3 concentration sharply decreased and remained significantly lower than that in nonlactating rats ($P < 0.001$). Five days after weaning (Day 26), serum T_4 and T_3 concentrations were not different ($P > 0.05$) from the nonlactating group. Throughout lactation (Days 2–19), the overall T_4/T_3 ratio was significantly higher in lactating than in nonlactating rats (51.9 ± 5.5 vs 41.1 ± 2.0, $P < 0.05$).

Changes in T_4 to T_3 conversion are shown in Fig. 2. The livers of pregnant rats exhibited T_4-5′-monodeiodinase activity which was two times the levels observed in virgin rats ($P < 0.001$). Within 2 days after parturition, T_4-5′-monodeiodinase activity in liver decreased in all females to the level in virgin rats (Fig. 2A). In nonlactating rats, whose litters were removed after delivery, monodeiodinase activity in livers remained at virgin levels although a slight depression of activity was observed 7 days after parturition ($P < 0.05$). In lactating rats, monodeiodination activity in liver remained at a significantly lower level than in nonlactating rats 7 ($P < 0.05$), 12 ($P < 0.001$), and 19 ($P < 0.001$) days after delivery. The activity of T_4-5′-monodeiodinase in kidneys of pregnant rats was not different from that of virgin rats (Fig. 2B). In kidney homogenates, T_3 generation decreased below those levels ($P < 0.05$) in all females within 2 days after parturition. However, in nonlactating rats it returned to the range of virgin and pregnant animals by Day 7 postpartum. In contrast, a further decrease in T_4-5′-monodeiodinase activity was observed in lactating rats, resulting in lower T_3 generation as compared to nonlactating rats ($P < 0.001$). Five days after weaning, T_4-5′-monodeiodinase activity in livers and kidneys of lactating rats increased and was not significantly different from those in nonlactating rats ($P > 0.05$).

Because lactating rats had higher body and liver weights and lower protein concentration

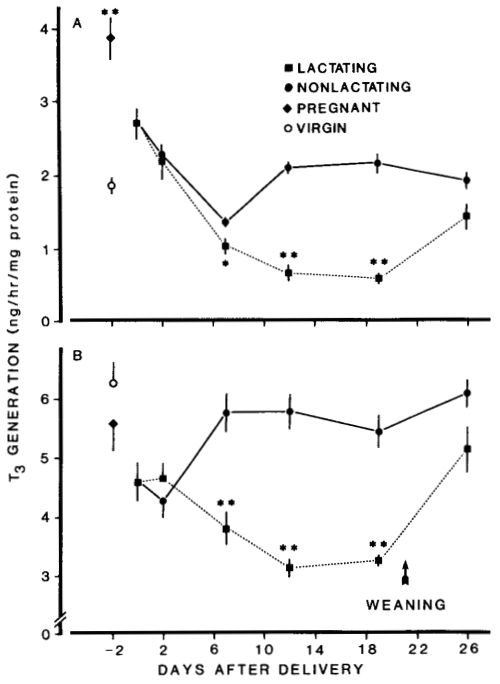

FIG. 2. Thyroxine-5′-monodeiodinase activity in liver (A) and kidney (B) homogenates in lactating, postpartum nonlactating, pregnant, and virgin rats. Values are means ± SEM; $n = 6$. *$P < 0.05$, **$P < 0.001$, lactating compared with nonlactating rats at particular days after parturition or pregnant compared with virgin rats.

in kidney homogenates than nonlactating rats (Table I), we also calculated total T_3 generation from liver or kidney per gram of metabolic body weight. As shown in Table I, the overall T_4-5′-monodeiodinase activity in liver and kidney in lactating rats (Days 2–19) was lower ($P < 0.001$) than in nonlactating rats, whether T_3 generation was measured per milligram of tissue protein of per gram of metabolic body weight. This indicates a specific decrease in deiodinase activity in liver and kidney during lactation.

Discussion. In the present study, liver and kidney homogenates were chosen to test the effect of lactation on extrathyroidal T_4 to T_3 conversion. Although the T_4-5′-monodeiodinase system is present in almost all tissues, liver and kidney are known to have, at least *in vitro,* the highest T_4 to T_3 conversion activity (17). Moreover, T_3, which is generated within these tissues, enters the circulation and becomes a substantial part of the body T_3 pool (12). In the present study, the T_4-5′-monodeiodinase activity in tissues homogenates was determined in the presence of an excess of the thiol cofactor DTT. Because the thiol dependence of T_4-5′-monodeiodination is well established (11), the alterations observed in our study appear to result from changes in overall T_4-5′-monodeiodinase content in tissue rather than from changes in concentration of SH-reducing cofactors.

TABLE I. EFFECT OF LACTATION ON BODY AND TISSUE WEIGHTS, HOMOGENATE PROTEIN CONCENTRATION, AND T_4-5′-MONODEIODINASE ACTIVITY

	Nonlactating rats	Lactating rats
Weight (g)		
Body	255.7 ± 5.7[a]	271.0 ± 6.7*
Liver	9.5 ± 0.2	12.9 ± 0.5**
Kidney	1.76 ± 0.03	1.84 ± 0.04
Protein in homogenate (mg/ml)		
Liver	46.3 ± 0.5	46.2 ± 0.9
Kidney	34.4 ± 0.4	32.4 ± 0.4**
T_3 generation (ng/hr/mg protein)		
Liver	1.98 ± 0.09	1.14 ± 0.15**
Kidney	5.34 ± 0.19	3.74 ± 0.16**
T_3 generation (ng/hr/g body $wt^{0.75}$)		
Liver	55.2 ± 3.1	38.1 ± 4.3**
Kidney	20.2 ± 0.6	13.5 ± 0.7**

[a] Values are means ± SEM of all lactating or postpartum nonlactating rats (Parturition Days 2–19, $n = 24$).

* $P < 0.05$, ** $P < 0.001$, as compared to nonlactating rats (pups removed after delivery).

Results of the present study clearly demonstrate that lactation in the rat results in a significant decrease in T_4-5′-monodeiodinase activity in liver and kidney homogenates as compared to nulliparous virgin females or nonlactating primiparous females dried off immediately after parturition. The observed decrease was closely related to lactation because 5 days after weaning or 7 days after parturition (when pups were removed), T_4-5′-monodeiodinase activity was restored to normal ranges. Changes in deiodinase activity in lactating rats were accompanied by diminished serum concentrations of T_4 and T_3. Our observations of sequential changes in serum T_4 and T_3 are in close agreement with an earlier report of Fukuda *et al.* (10) and support previous suggestions (2) that lactation induces a functional hypothyroid state in rats. Decreases in thyroidal iodine uptake (20), thyroid secretion rate (21), and serum T_4 (6, 9) and T_3 (10) concentrations were reported earlier in lactating rats. The reason for a functional hypothyroid state in lactating rats is not well understood. However, transfer of iodine (22), iodinated nonhormonal compounds (23), and thyroid hormones (10) through the mammary gland into milk have been postulated by Fukuda *et al.* (10) as one cause of the decreased serum thyroid hormone concentrations. Although in the present study the T_4-5′-monodeiodinase activity was estimated in tissue homogenates using an *in vitro* method, a preferential decrease in T_3 serum concentration, as reflected by the increased T_4/T_3 molar ratio in lactating rats, supports our conclusion that lactation diminishes extrathyroidal T_4 to T_3 conversion.

The cause and physiological significance of the marked reduction in T_4-5′-monodeiodinase activity during lactation in the rat is not clear. However, several factors could be involved. First of all, reduction in T_4-5′-monodeiodinase activity may result from the hypothyroid state itself. Previous studies using

kidney and liver slices (24), liver homogenate (13) or microsomes (14, 15), and perfused liver (16) have shown decreased T_4-5′-monodeiodinase activity in thyroidectomized rats. Recently, decreased T_4 to T_3 conversion in liver and kidney associated with decreased serum T_4 and T_3 concentrations and increased serum TSH were reported in rats after chronic treatment with graded doses of methimazole (25).

The second explanation for the decreased T_4-5′-monodeiodinase activity in lactating rats may involve an effect of glucocorticoids. Although no differences in basal plasma corticosterone between lactating and nonlactating rats were observed (26), suckling stimulates the secretion of corticosterone in rats (27). There are reports indicating that dexamethasone (28, 29), a synthetic glucocorticoid or corticosterone acetate (30), decreases T_4-5′-monodeiodinase activity in rat liver homogenate. Thus, despite the large doses of dexamethasone used in the above studies, we cannot exclude the possibility that increased corticosterone output caused by nursing during lactation also plays a role in reducing T_3 generation in extrathyroidal tissues.

Finally, the decreased T_4-5′-monodeiodinase activity observed in lactating rats may be a physiological adaptation to increased demands due to the great output of energy and protein secreted into the milk (31). Decreased extrathyroidal T_4 to T_3 conversion was previously suggested (11) as an adaptive mechanism in circumstances where overactive metabolism is undesirable. In a situation such as fasting, the decreases in T_4-5′-monodeiodinase activity in liver and serum T_3 concentrations were reported in rats (13) and described as adaptations to reduce the metabolic rate and perhaps conserve protein (12). Morgan (31) has shown that in the rat, rates of catabolism of all proteins were increased significantly during lactation due to loss into milk, but at the same time, rates of synthesis also were increased. We thus speculate that decreased T_4-5′-monodeiodinase activity observed during lactation in rats is also a homeostatic mechanism for the conservation of protein and perhaps of other nutrients for use by the mammary gland.

Nevertheless, a considerably different explanation of our data is also possible. Despite decreased 5′-monodeiodinase activity, the low T_4 and T_3 serum concentrations during lactation may reflect faster turnover of T_4 and T_3 at the cell level. Increased thyroid secretion rate, as measured by the substitution method (21), and higher TSH blood concentrations in lactating rats (10) suggest that increased demand for thyroid hormone, to satisfy higher metabolic needs for milk production, cannot be met because the iodine is in short supply (22). Iodine deficiency should result in a preferential secretion of T_3 by the thyroid and hence lower serum T_4/T_3 ratios (32). Thus, the higher serum T_4/T_3 ratios observed in the present experiment in lactating rats indicate a preferential increase in peripheral T_3 utilization. Increased tissue metabolism of T_3 of thyroid origin in situations where serum T_4 is reduced could result from a decreased conversion of T_4 to T_3 via T_4-5′-monodeiodination.

Decreased serum concentrations of T_4 observed in the present experiment in pregnant rats, 2 days before the expected time of delivery, are in accordance with several earlier reports (10, 33–35). Moreover, as previously reported by Fukuda *et al.* (10), the decrease in serum T_4 was much more dramatic than in serum T_3 concentration, suggesting changes in extrathyroidal metabolism of thyroid hormones. To our knowledge, this is the first report in which increased T_4-5′-monodeiodinase activity was directly demonstrated in extrathyroidal tissues of pregnant rats. Previously, Feldman (33) and Galton (34) observed, in pregnant rats, an acceleration in the disappearance rate of labeled T_4 from serum and an increase in urinary excretion of iodine, suggesting increased intracellular deiodinating activity in extrathyroidal tissues and/or decreased binding of T_4 to blood plasma proteins. Although Galton (34) was not able to demonstrate any differences in T_4-deiodinating activity of liver homogenates between pregnant and nonpregnant rats, the studies of Chen and Walfish (36) indirectly indicate that estrogen increases extrathyroidal T_4 to T_3 conversion. They found that estradiol benzoate increased plasma concentrations of T_3 and decreased plasma T_4 in ovariectomized and thyroidectomized female rats treated with T_4. Because serum concentrations of estrogens are increased near term in the rat (37), the observation of Chen and Walfish (36) together with the present *in vitro* study of T_4-5′-mono-

deiodinase activity suggests increased T_4 to T_3 conversion in extrathyroidal tissues of pregnant rats, despite decreased serum concentrations of thyroid hormones. This increased T_3 generation possibly would explain the increased efficiency of energy utilization in pregnant rats reported recently by Baik *et al.* (38).

In conclusion, the dramatic changes in T_4-5′-monodeiodinase activity observed in extrathyroidal tissues of lactating and pregnant rats are not due merely to a hypothyroid state but also reflect a possible metabolic adaptation to milk production and pregnancy.

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