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Thyroxine Inner Ring Monodeiodinating Activity in Fetal Tissues of the Rat

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ABSTRACT. We studied thyroxine (T_4) inner ring monodeiodinating activity (5-MA) in various tissues of fetal, maternal, and adult male rats. Tissue homogenates were incubated with 0.26 μM T_4 in 0.1 M phosphate buffer (pH 7.4) containing 10 mM EDTA and 400 mM dithiothreitol (final volume 0.7 ml) for 10 min at 37° C; the 3,3′,5′-triiodothyronine (rT_3) generated was measured by radioimmunoassay of ethanol extracts of incubation mixture and the result was corrected for rT_3 degradation during incubation. Compared to maternal tissues, T_4 to rT_3 5-MA in the 14-day-old fetus was increased about 70 times in skeletal muscle (mean ± SEM, velocity, 5.4 ± 0.9 *versus* 0.08 ± 0.01, pmol rT_3/h/mg protein); ~8 times in intestine (0.72 ± 0.17 *versus* 0.09 ± 0.03); and ~4 times in cerebral cortex (19 ± 0.5 *versus* 4.5 ± 0.9), while it was similar in skin (3.2 ± 0.48 *versus* 2.6 ± 0.52). Hepatic T_4 5-MA approximated 1.1 ± 0.63 in the 14-day-old fetus; it could not be measured reliably in maternal or 19-day fetal tissue because of extensive (>90%) degradation of rT_3 during incubation. Relative to mother, T_4 5-MA in 19-day fetal tissues was increased ~30-fold in intestine, ~20-fold in skeletal muscle, and ~6-fold in cerebral cortex while it was similar in skin. The T_4 5-MA in maternal rat tissues did not differ significantly from corresponding values in adult male rat, except skin, where it was lower in the mother rat (2.6 ± 0.52 *versus* 4.6 ± 0.61, $p < 0.05$). In summary, relative to adult tissues T_4 5-MA is exceedingly active in several fetal tissues, most notably in skeletal muscle followed by intestine and cerebral cortex. (*Pediatr Res* 23: 196–199, 1988)

Abbreviations

T_4, thyroxine
rT_3, 3,3′,5′-triiodothyronine
T_3, 3,5,3′-triiodothyronine
5-MA, iodothyronine inner ring monodeiodinating activity
5′-MA, iodothyronine outer ring monodeiodinating activity
MA, iodothyronine 5′-monodeiodinase activity
DTT, dithiothreiotol
3,3′-T_2, 3,3′-diiodothyronine
RIA, radioimmunoassay
Vmax, maximal velocity

Previous studies (1, 2) have demonstrated that the fetal hypothalamo-pituitary-thyroid system develops and functions independently of the maternal system. Fetal tissues, *e.g.* liver, also show in some species an age-related, progressive increase in 5′-MA accompanied by a reciprocal decrease in 5-MA (3). The pituitary-thyroid axis and tissue metabolism of iodothyronines both begin maturation toward adult levels in the last third of gestation in several species including man, sheep, and chicken (3–5) but not in the rat where maturation occurs in the immediate postnatal period (6, 7). The maturation pattern of tissue 5′-MA has been studied in several tissues, including liver, pituitary gland, kidney, cerebrum, cerebellum, and hypothalamus in several species (8–13). However, there is a paucity of information regarding the maturation of 5-MA in fetal tissues. 5-MA has been observed to be very active in the placenta (14) and in some neuronal tissues of the fetal rat, *e.g.* the cerebrum and the hypothalamus (10, 15, 16). Compared to body fluids of the adult, the concentration of rT_3 is much higher in fetal serum and amniotic fluid (12, 17). To gather insight into the contribution of the various fetal organs to the high rT_3 in fetal serum and amniotic fluid, we have studied T_3 5-MA in various tissues. This information may be important in understanding physiological role of rT_3 either as rT_3 per se or as a route to metabolism of T_4 to inactive metabolites. Our data suggest that the T_4 5-MA is higher in several fetal tissues than in adult tissues, but most notably in skeletal muscle and the intestine.

MATERIALS AND METHODS

Animal tissues. Timed pregnant Sprague-Dawley rats were obtained from Charles River Breeding Laboratories, Inc., Boston, MA. Fourteen or 19 day pregnant Sprague-Dawley rats (pregnancy in rat approximates 21 days) were anesthetized with ether and fetuses were removed from the uterus. Various organs of mothers and fetuses were dissected and homogenized in cold assay buffer (w/v, 10–33%) using a polytron homogenizer (Brinkman Instruments, Westbury, NY). Skeletal muscle tissues used were dissected predominantly from the thigh and the leg. Intestinal and dermal tissues were studied without separation into individual components (*e.g.* epithelium *versus* muscle in intestine or epidermis *versus* dermis in skin).

Reagents. T_4 and DTT were obtained from Sigma Chemical Co., St. Louis, MO. rT_3 and 3,3′-T_2 were obtained through the courtesy of Dr. Paul Block, Jr., of River Research, Toledo, OH. Radioactive T_4 and rT_3 were obtained from New England Nuclear, Boston, MA.

Study of T_4 to rT_3 MA. Homogenates of various tissues (~3 to 13 mg protein) were incubated in duplicate with 0.26 μM (200 ng/ml) T_4 in 0.1 M phosphate buffer (pH 7.4) containing 10 mM EDTA and 400 mM DTT (total volume, 0.7 ml) for 10 min at 37° C; the rT_3 generated was measured by RIA of ethanol extracts of incubation mixture as previously described (15, 18, 19). T_4 cross-reated 0.06% in rT_3 RIA. The intrassay and interassay coefficient of variation for rT_3 measurement was 6 and 9%, respectively. Protein concentration was measured by the

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method of Bradford (20). Previous studies with adult cerebral cortical and skin tissues (15, 19) and pilot studies with fetal skeletal muscle tissues had shown that T_4 to rT_3 conversion was near maximal under the above mentioned conditions. The results of T_4 5-MA were expressed as pmol of rT_3 produced per h/mg protein after correction for rT_3 degradation during the incubation. The latter correction was made by dividing rT_3 produced during incubation with (100% minus degradation of rT_3 during incubation studied as described below).

In some experiments, Km and Vmax of T_4 5-MA were measured in certain tissues. For this purpose, maternal or pooled fetal tissue aliquots were incubated for 30 min at 37° C with 0.04 to 2.5 μM T_4 in the presence of 400 mM DTT and rT_3 produced during incubation was measured by the RIA. The results of rT_3 generated during incubation were corrected for degradation of rT_3 during incubation and the data on T_4 5-MA were computed in terms of pmol of rT_3 produced per h/mg protein. Km and Vmax were calculated from the Lineweaver-Burk plot of the data after the data had been subjected to linear regression analysis by the method of least mean squares (21, 22).

Degradation of rT_3 during incubation. When rT_3 degradation was to be studied, the tissue homogenates were incubated as described above, with 7.7, 15, or 30 pmol rT_3 and the percent rT_3 remaining at the end of incubation was determined by RIA. Percent degradation of each amount of rT_3 added was calculated and the results were expressed as an average of various determinations for each tissue. Pilot studies had shown that rT_3 was degraded by various tissues mainly by 5′-monodeiodination to 3,3′-diiodothyronine.

Other statistical analyses. The data on rT_3 degradation or T_4 5-MA in different groups were reduced to the mean ± SEM and the results were compared using Student's two tailed *t* test for unpaired variates. For some studies, Bonferroni's correction for multiple comparisons was applied to the *t* test (22).

RESULTS

Table 1 shows the results of rT_3 degradation in maternal, adult male, and fetal tissues. Maternal and adult male rat liver degraded rT_3 very actively; approximately 90% of rT_3 was lost during a 10-min incubation. Other tissues of the adult rat degraded rT_3 modestly. The degradation of rT_3 approximated ~5% for intestine, ~10% for skeletal muscle, and <5% for cerebral cortex and skin. Fourteen-day-old fetal liver degraded only about 20% of substrate rT_3 during the 10-min incubation, whereas 19-day-old fetal liver degraded rT_3 as actively as did adult tissue. Fetal intestine degraded ~12% rT_3 at 14-day gestation and ~29% at 19-day gestation. Fetal skeletal muscle demonstrated a moderate ~11% degradation of rT_3 at 14-day gestation but little (<5%) degradation at 19-day gestation. The cerebral cortical or skin tissues of adult and fetal rat demonstrated less than 5% degradation of rT_3 for up to 1 h of incubation.

Table 2 shows the data on T_4 5-MA in various tissues of maternal and fetal (14 and 19 day old) rats after correction for rT_3 degradation during incubation. Fetal skeletal muscle, intestine, and cerebral cortex demonstrated more active T_4 5-MA than the corresponding maternal tissues, even when Bonferroni's correction for multiple comparisons was applied to the *t* test. Skeletal muscle showed the largest (~70-fold) increase at 14-day gestation and intestine showing the largest (~30-fold) increase at 19-day gestation. Skin T_4 5-MA was similar in the fetus and the mother. Fetal hepatic T_4 5-MA of 1.1 ± 0.63 pmol/h/mg protein at 14-day gestation was similar to or lower than that in other fetal tissues of comparable gestation. Hepatic T_4 5-MA in 19-day-old fetal, maternal, and adult rat was computed to be 15 ± 4.6, 20 ± 6.8, and 17 ± 5.1 pmol/h/mg protein, respectively. However, the reliability of these values is uncertain. These liver tissues degraded rT_3 extensively during incubation (90–94%) (Table 1) and this factor necessitated a very large correction in the calculation of T_4 5-MA in terms of rT_3 produced per h/mg protein. T_4 5-MA in maternal skin was lower than that in the adult male skin ($p < 0.05$). T_4 5-MA in other maternal tissues studied was comparable to that in tissues of the adult male rat. Similar results were obtained in another experiment using 10-min incubation and two other experiments using incubation of 1 h instead of 10 min.

The Km and Vmax of fetal skeletal muscle T_4 5-MA were measured at 14-day gestation and approximated 0.66 μM and 5.0 pmol/h/mg protein, respectively. The reaction rate for T_4 to

Table 1. *Degradation of rT_3 during incubation for 10 min with homogenates of tissues of maternal, fetal, and adult male rats*

Group	Tissue (% of added rT3 degraded)				
	Cerebral cortex	Skin	Intestine	Skeletal muscle	Liver
Mother	n†	n	5.0 ± 3.0*	10 ± 3.8	94 ± 1.5
Fetus‡ (14 day old)	n	n	12 ± 4.9	11 ± 6.8	20 ± 11§^{b,y}
Fetus‡ (19 day old)	n	n	29 ± 2.6^{a,d,x}	n	91 ± 1.0^{e}
Adult male	n	n	n	n	94 ± 0.9^{e}

* Mean ± SE; n = 3–5.
† Negligible, <5%.
‡ Fetal tissues were pooled as needed to obtain appropriate protein concentration (two to four/incubation vessel).
§ *cf* mother: $^{a}p < 0.01$; $^{b}p < 0.001$.
cf 14-day fetus: $^{d}p < 0.05$; $^{e}p < 0.001$.
cf adult male: $^{x}p < 0.01$; $^{y}p < 0.001$.

Table 2. *T_4 to rT_3 monodeiodinating activity in homogenates of various tissues of maternal, fetal, and adult male rats*

Group	Tissue (pmol/h/mg protein)				
	Cerebral cortex	Skin	Intestine	Skeletal muscle	Liver
Mother	4.5 ± 0.90*	2.6 ± 0.52†^{x}	0.09 ± 0.03	0.08 ± 0.01	
Fetus (14 day old)	19 ± 0.49^{b,z}	3.2 ± 0.48	0.72 ± 0.17^{a,y}	5.4 ± 0.90^{b,z}	1.1 ± 0.63
Fetus (19 day old)	28 ± 1.8^{b,d,z}	2.3 ± 0.26^{y}	2.8 ± 0.20^{b,e,z}	1.7 ± 0.25^{b,d,z}	
Adult male	7.1 ± 1.2	4.6 ± 0.61	0.08 ± 0.02	0.12 ± 0.05	

* Mean ± SEM; n = 3–5. Fetal tissues were pooled as needed to obtain appropriate protein concentration (~2–4 tissues/incubation vessel).
† *cf* mother: $^{a}p < 0.01$; $^{b}p < 0.001$.
cf 14-day fetus: $^{d}p < 0.01$; $^{e}p < 0.001$.
cf adult male: $^{x}p < 0.05$; $^{y}p < 0.01$; $^{z}p < 0.001$.

rT_3 in maternal skeletal muscle homogenate was too low to measure Km or Vmax accurately.

The Km and Vmax of T_4 5-MA in fetal cerebral cortical homogenate at 14-day gestation approximated 1.1 μM and 69 pmol/h/mg protein, respectively. The corresponding values of Km and Vmax in maternal cerebral cortical tissue approximated 1.6 μM and 6.5 pmol/h/mg protein, respectively.

The Km and Vmax of T_4 5-MA in fetal intestinal homogenates measured at 19-day gestation approximated 0.48 μM and 7.6 pmol/h/mg protein, respectively. The rate of T_4 to rT_3 conversion in maternal intestinal homogenate was too low to measure Km or Vmax accurately.

The kinetics of dermal T_4 to rT_3 MA were measured in tissues of 19-day fetal and the nonpregnant adult rat. The Km and Vmax values were 0.21 μM and 2.3 pmol/mg protein, respectively, in the fetus and 0.39 μM and 6.0 pmol/h/mg protein, respectively, in the adult.

DISCUSSION

Previous studies have described an increased T_4 5-MA in fetal cerebral cortex (10, 15, 16). We support this finding and in addition, demonstrate for the first time that the T_4 5-MA is markedly increased in fetal skeletal muscle (20- to 70-fold the activity in maternal tissue) and intestine (20- to 30-fold the activity in maternal tissue). The progression of gestation from 14 to 19 days was associated with a reduction in T_4 5-MA in skeletal muscle, whereas there was an increase in the activity in the case of intestine and possibly in the liver. However, the data in the case of liver in the 19-day old fetal rat (or the adult rat) were not entirely reliable as a large correction was necessary for an extensive (>90%) degradation of the product (rT_3) even during a brief (10 min) incubation (Table 1). The fetal dermal T_4-5 MA was similar to that in the mother and both these values were less than those in the nonpregnant (male) adult rat (19) (Table 2). Inasmuch as 5′-MA has been shown to be low in fetal tissues (8–13) and rT_3 degradation is quite limited in several fetal tissues, especially at 14-day gestation, active T_4 5-MA would be associated with accumulation of rT_3 in fetal tissues. However, actual contribution of the various organs to fetal production of rT_3 is not known. The placenta contains a very active T_4 5-monoadiodinase and is probably a major contributor to fetal rT_3 (14). Our data suggest that fetal cerebral cortex, skeletal muscle, and intestine also produce rT_3 and may contribute rT_3 to tissues, at least locally. Similar local production of rT_3 has been demonstrated in cerebral cortex of the adult rat (23).

There is ample evidence suggesting that thyroid hormones are important in fetal differentiation and development (24–28), even before development of the fetal thyroid gland (28–32). However, maternal T_4 and T_3 are poorly transported across the placenta and furthermore are degraded by a very active placental inner-ring deiodinase (14); thus only minute amounts of T_4 and T_3 would reach fetal tissues until the fetal thyroid becomes sufficiently productive. Because of active inner-ring and relatively inactive outer-ring deiodination, the major iodothyronine available to fetal tissues before thyroidal activity at around 17 days of gestation will be rT_3 derived from metabolism of maternal T_4. Some workers (33) suggest that small amounts of T_4 and T_3 contributed by the mother are physiologically relevant for the embryo and fetus in the rat. Others (34) find that even mild or moderate hyperthyroidism is harmful to the fetus. It is possible that active inner-ring deiodination serves as a measure to protect the fetus from the effects of T_3. rT_3 is known to be a potent inhibitor of the 5′MA of T_4 to T_3 (35) and has also been shown to antagonize the induction of T_4 5′-MA by insulin, cortisol, and T_3 in cultured fetal mouse liver cells (36). We do not know of another biological purpose of rT_3 at this time. It is possible that it plays a role in fetal differentiation or development, or both.

It is interesting to note that T_4 5-MA and T_4 and/or rT_3 5′-MA (*i.e.* degradation of rT_3) increase during the final week of gestation in the intestine while they both decrease in skeletal muscle (Tables 1 and 2). The similarly in maturational pattern of 5′-MA and 5-MA is consistent with the notion that they may be a function of the same enzyme in several tissues as suggested in the liver (37–39). However, the magnitude of changes in 5′-MA and 5-MA differed suggesting that different factors regulate the two activities or that the enzymes involved are distinct. Glucocorticoids have been shown to regulate the maturation of hepatic T_4 5′-MA (4, 8, 36). Whether glucocorticoid has a role in T_4 5-MA maturation process needs further study. The data on T_4 5-MA in the various tissues suggest the possibility that the maturation of 5-MA and 5′-MA may be under local regulation and that it may change to a different degree or even a different direction among the various tissues.

Our finding of active T_4 5-MA in fetal skeletal muscle and the finding of active ^{125}I-T_4 uptake in sheep fetal muscle (~3 times that of liver in ewes of 100–140 days gestation) (40) suggest that fetal muscle is active in the metabolism of thyroid hormones. It has been shown that thyroid hormone is critical in the development and growth of muscle in the chicken embryo (27). Whether rT_3 contributes to this role is an interesting subject for further study.

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