Minimal Placental Transfer of L-Thyroxine (T₄) in the Rat

J.H. DUSSAULT⁽²⁰⁾ AND P. COULOMBE

Service d'Endocrinologie et Métabolisme, Le Centre Hospitalier de l'Université Laval, Quebec, Canada

Summary

Studies of L-thyroxine T₄ kinetics and placental transfer were conducted in pregnant rats during the last days of gestation using radioiodine labeled and unlabeled T₄. The maternal T₄ secretion rate was 53.0 ± 6.9 ng/hr/100 g body wt. The placental transfer rate was $0.463 \pm 0.196 \times 10^{-3}$ /hr at 18 days and $1.516 \pm 0.147 \times 10^{-3}$ /hr at 20 days. From these results, we calculated that at 20 days of gestation, 80 ± 8 pg/hr were transferred to the fetus, less than 1% of the fetal production rate. Inasmuch as we have demonstrated that little placental transfer of T₄ occurred during these studies, we conclude that the fetal rat hypothalamo-pituitary-thyroid axis develops autonomously.

Speculation

The present data plus the fact that the rats are hypothyroid at birth support the concept of an autonomous development of the hypothalamic-pituitary-thyroid axis. It suggests that the rat can serve as a useful model for development of this axis in the human.

EXTRACT

Placental transfer of L-thyroxine (T₄) was measured after the administration of 2 μ Ci of [¹²⁵I]T₄ to 16, 18, and 20 days pregnant animals. Three hr after the administration of the hormone, which corresponds to the equilibrium time determined by a method of constant infusion, the pregnant rats and their fetus were killed. The [¹²⁵I]T₄ was extracted from the serum by butanol extraction and alkaline washes. The transfer rate was calculated using a two-compartmental analysis. At 18 days of gestation, the transfer rate is $0.463 \pm 0.196 \times 10^{-3}$ /hr and significantly increases to $1.516 \pm 0.147 \times 10^{-3}$ /hr at 20 days of gestation. The maternal serum T₄ concentration significantly decreases in pregnant animals ($P < 0.05$) and is minimum at 20 days of gestation (21.6 ± 0.53 ng/ml). However, fetal serum T₄ concentration progressively increases to 7.46 ± 0.52 ng/ml at 20 days of gestation. Maternal T₄ production rate was 53.0 ± 6.9 ng/hr/100 g body wt. Based on these findings, we calculated that 80 ± 8 pg T₄ per hr was transferred to the fetus, less than 1% of the fetal T₄ production rate. Administration of 100 μ g T₄ to 16, 18 and 20 days pregnant rats induced a significant increase in maternal serum T₄ concentrations (627 ± 82 ng/ml versus 21.6 ± 0.53 ng/ml) and a modest increase in the fetal serum T₄ concentration (23.9 ± 1.5 ng/ml versus 7.46 ± 0.52 ng/ml) at the 20th day of pregnancy. From these results, we conclude that there is a minimal transfer of T₄ in the last days of pregnancy in the rat and that the hypothalamo-pituitary-thyroid axis develops autonomously.

INTRODUCTION

The placental transfer of T₄ and/or L-triiodothyronine (T₃) has previously been reported in the pregnant rat. Knobil and Josimovich (11) reported that T₄ and T₃ could cross the placental barrier and reach the fetus, by measuring the inhibition of the

fetal pituitary gland's secretion of thyroid-stimulating hormone after the administration of T₄ or T₃ to the mother. In the guinea pigs receiving antithyroid drugs, the administration of T₄ or T₃ to the pregnant animal reduced fetal goiter only when relatively large quantities of hormone were used (2), suggesting that the transplacental passage of thyroid hormones was low. In the sheep, Dussault *et al.* (5) have not been able to demonstrate a significant placental transfer of [¹²⁵I]T₄. Finally, Dubois *et al.* (4) recently demonstrated that there was minimal or no placental transfer of T₃ in the rat and that hypothalamo-pituitary-thyroid axis of the fetus develops autonomously.

To study the placental transfer of L-T₄, we measured T₄ kinetics to detect the presence or absence of placental transfer of T₄ in the rat.

MATERIALS AND METHODS

Virgin Sprague-Dawley rats were matched at the supply house (18) and shipped 2 weeks after mating. Pregnant animals were kept in separate cages in a sound-attenuated and temperature- and light-controlled room ($24 \pm 1^\circ$, 10 hr of darkness, 14 hr of light) and had free access to lab chow and water.

EQUILIBRIUM TIME

The equilibrium time of T₄ for pregnant rats was first determined by a method of constant infusion. Four pregnant rats (16 to 18 days of gestation) were injected through an in-dwelling jugular cannula for 3 hr with a purified solution of [¹²⁵I]T₄ (~ 10 μ Ci/hr; New England Nuclear; specific activity, ~ 1000 μ Ci/ μ g) at a rate of 1.0 ml/hr using a model 355 syringe pump from Sage Instruments.

Blood, 0.5 ml, was collected by cutting the tail at 0, 30, 60, 90, 120, 150, and 180 min after the onset of the infusion. The blood samples were centrifuged, and the serum was frozen (-20°) until extraction. The butanol extraction was performed in duplicates according to the method described by Fisher *et al.* (7) which allows recovery of over 95% of organic iodine and less than 0.5% of inorganic iodine. The butanol fraction was counted in an Auto-Logic gamma counter (Abbott Laboratories).

The percentage of injected dose/ml of serum was then calculated for each point and plotted.

T₄ KINETICS IN THE PREGNANT RATS

The volume of distribution (VD), the fractional removal rate (K), the production rate (PR), and the metabolic clearance rate (MCR) of [¹²⁵I]T₄ were calculated in pregnant rats (16 to 18 days of age) after an IV bolus of the labeled hormone was administered.

Six pregnant rats were studied. Two μ Ci of purified [¹²⁵I]T₄ were injected through the tail vein under light either anesthesia. Each rat also received Lugol IP. Blood samples (0.5 ml) were collected by cutting the tail under light either anesthesia 1, 2, 4, 6, 8, 12, 24, 30, 36, and 48 hr after the injection. The blood was centrifuged and the serum was frozen (-20° C) until butanol extraction (7). The percentage of the injected dose/ml serum was calculated for each time and plotted on a semilogarithmic paper.

PLACENTAL TRANSFER

Placental transfer of T₄ was studied in pregnant rats at 16, 18, and 20 days of gestation. At the indicated stage of gestation, six rats were given injections through the tail vein under light ether anesthesia with purified solution of [¹²⁵I]T₄ (3 μCi); they also received Lugol solution IP to prevent recycling of the labeled iodine.

Three hours later, the time which corresponds to the equilibrium time, the rats were killed, and serum was collected. The fetuses were delivered by hysterectomy and decapitated. The serum from a single litter was pooled. The maternal and fetal sera were frozen (-20°C) until butanol extraction (7).

In addition, similar groups of pregnant rats received an IV injection of 100 μg unlabeled T₄. Prior to the injection, blood, 0.5 ml, was collected to measure basal serum T₄ concentration in the mother. Three hr after the injection, the mothers and their fetuses were killed by decapitation, and the serum was frozen until assay. The maternal and fetal serum T₄ concentrations were measured by the method of Chopra (1).

CALCULATIONS

The half-life, the volume of distribution, the production rate and the MCR were calculated from the T₄ disappearance curve (Fig. 1) by the single compartment method described by Sterling and Chodos (15). Least-squares regression analysis was used to fit the linear portion of the disappearance curve (from $T = 4$ hr to $T = 48$ hr).

$$VD = \frac{100}{\% \text{ dose/ml}} (t = 0) \quad (1)$$

$$T_{0.5} = (y - b)/m \quad (2)$$

$$y = [\% \text{ injected dose/ml } (t = 0)]/2$$

$$b = \% \text{ injected dose/ml } (t = 0)$$

$$m = \text{slope of the regression line}$$

$$K = \frac{\ln 2}{T_{0.5}} \quad (3)$$

$$MCR = VD \times K \quad (4)$$

$$PR = [T_4] \times VD \times K \quad (5)$$

The volume of distribution and the MCR were also calculated using the noncompartmental analysis recently described by Oppenheimer *et al.* (13). The T₄ placental transfer rate (k_f) from the mother to the fetus was calculated according to the model previously described by Dussault *et al.* (5). The rate of placental transfer in the direction mother-fetus is represented by the following equation (Fig. 2):

$$k_F = \frac{VF}{VM} \times \frac{Y_F(3)}{Y_M(3)} \times (k_R + K_{FO}) \quad (6)$$

where: k_F = T₄ transfer rate (per hr);

V_F = volume of distribution of the fetus (ml/100 g body wt);

V_M = volume of distribution of the mother (ml/100 g body wt);

$Y_F(3)$ = % injected dose/ml serum at $t = 3$ hr in the fetus;

$Y_M(3)$ = % injected dose/ml serum at $t = 3$ hr in the mother;

K_R = T₄ transfer rate from the fetus to the mother;

K_{FO} = fractional removal rate of T₄ from the fetal compartment.

Because it is not technically feasible to study the T₄ kinetics in the fetal rat or to study the T₄ placental transfer in the direction fetus-mother (K_R), the following assumptions were made in the calculations of K_F . The T₄ volume of distribution of the fetal rat was given the value of 24.0 ml/100 g body wt, which is the T₄ volume of distribution measured in 5-day-old rats and K_{FO} , the fractional removal rate of T₄ from the fetal compartment, has been assigned the value of 0.004/hr, which is also the fractional removal rate of T₄ in 5-day-old rats (4). These assumptions appear valid in view

Fig. 1. Curve of the disappearance of ¹²⁵I-labeled T₄ in serum of pregnant rats ($N = 6$). Points, mean $\pm$ S.E.

Fig. 2. A simplified two-compartment model for the transplacental passage of T₄ in the rat.

of the minor changes affecting VD and K_{FO} during early postnatal days in the rat (4). The value of K_R , the placental transfer in the direction fetus-mother, has been assumed equal to K_F .

RESULTS

Figure 1 illustrates the [¹²⁵I]T₄ disappearance curve obtained from six pregnant rats between 16 and 18 days of gestation. From this curve, we calculated the values of $T_{0.5}$, VD, K, the production rate, and the MCR. Individual values for the parameters are listed in Table 1. The VD was 24.7 ± 3.1 ml/100 g body wt, the T₄ fractional removal rate (K) was 0.061 ± 0.006 /hr. The serum T₄ concentration in pregnant rats was 37.6 ± 5.3 ng/ml, whereas the PR and the MCR averaged 53.0 ± 6.9 ng/hr/100 g body wt and 1.43 ± 0.115 ml/hr/100 g body wt, respectively. It is interesting to note the significant reduction in serum T₄ concentration in pregnant rats when compared to nonpregnant female rats (55.1 ± 0.28 ng/ml $N = 33$; $P < 0.01$). The calculation of VD and MCR by noncompartmental analysis gave the following results: $VD = 22.4 \pm 3.7$ ml/100 g body wt and $MCR = 1.33 \pm 0.1$ ml/hr/100 g body wt (mean $\pm$ S.E.; $N = 6$). Therefore, the single compartment analysis and the noncompartmental approach result in similar estimation of VD and MCR in agreement with previous results in human (13).

The equilibrium time as calculated by constant infusion technique was 3.0 hr, a value similar to what we previously calculated for T₃ (Fig. 3) (3).

Table 2 summarizes the results for the maternal-fetal transfer

rate after the administration of [^{125} I]T₄. The percentage of injected dose/ml remains fairly stable during late pregnancy in the rat (16 days, 1.045 ± 0.161 ; 18 days, 0.946 ± 0.130 ; 20 days, 1.340 ± 0.120 % dose/ml). On the other hand, in the fetus, the percentage of injected dose/ml increases significantly from 18 days (0.009 ± 0.004 % dose/ml) to 20 days (0.0416 ± 0.0016 % dose/ml) of gestation ($P < 0.01$). The fetal-maternal ratio also increases from $8.0 \pm 2.0 \times 10^{-3}$ at 18 days of gestation to $31.0 \pm 3.0 \times 10^{-3}$ at 20 days of gestation. Similarly, the T₄ placental transfer rate significantly increases from 0.463 ± 0.196 /hr at 18 days of gestation to $1.516 \pm 0.147 \times 10^{-3}$ /hr at 20 days of gestation.

EQUILIBRIUM TIME OF [^{125} I]-T₄ IN PREGNANT RAT

Fig. 3. Equilibrium time of ^{125} I-labeled T₄ in serum of pregnant animals. Equilibrium is achieved within 3 hr. Points mean $\pm$ S.E. ($N = 4$).

Table 3 illustrates the effects of the administration of $100 \mu\text{g}$ T₄ on the maternal and fetal serum T₄ concentrations. Serum T₄ concentrations significantly decrease with advancing gestational age ($P < 0.05$; 31.2 ± 0.17 ng/ml at 18 days versus 21.6 ± 0.53 ng/ml at 20 days). However, fetal serum T₄ concentrations rise from 5.37 ± 0.53 ng/ml at 18 days to 7.46 ± 0.52 ng/ml at 20 days of gestation. As expected, the administration of $100 \mu\text{g}$ T₄ resulted in a significant increase in serum T₄ concentrations in the mothers of the three groups studied. On the other hand, the serum T₄ concentrations measured in the fetus were markedly lower than the one measured in the mothers, but progressively rose with advancing gestational age (3.1 ± 0.2 ng/ml at 16 days, 6.0 ± 1.2 ng/ml at 18 days and 23.9 ± 1.2 ng/ml at 20 days). When we express the results in terms of the fetal-maternal ratio, we observed an excellent agreement between isotopic data and radioimmunoassay data.

DISCUSSION

Previous studies have indicated that the thyroid gland becomes functional in the rat between the 16th and the 17th days of gestation. At this stage, it has been shown to synthesize labeled T₄ from tracer doses of ^{131}I (10). Therefore, placental transfer of thyroxine was studied at the 16th and subsequent days of gestation.

Serum T₄ concentrations progressively decrease during gestation in the rat in contrast with normal serum T₃ concentrations and kinetics (3). However, this fall in serum T₄ concentration can be explained on the basis of the modifications in T₄ kinetics that we observed in the pregnant animal. Indeed, in the rat, gestation is associated with a 38% increase in the fractional removal rate of T₄ and a 50% increase in the apparent volume of distribution (Table 1) when compared to nonpregnant animals (4). Similar results are also obtained with noncompartmental analysis, suggesting that T₄ kinetics are fairly approximated by both methods. Fetal serum T₄ concentrations were also measurable in a significant amount at 18 and 20 days of fetal life, but were markedly lower than were the serum T₄ concentrations measured in the maternal serum, confirming the relative state of hypothyroidism in the fetal rat. However, it was impossible to measure the T₄ kinetics in the fetal animal.

To study the maternal-fetal placental transfer rate of T₄, we used the two-compartment model previously described by Dussault *et al.* (5). Because serum T₄ concentrations are measurable in the fetal animal (Table 3) and it is not technically feasible to study

Table 1. Volume of distribution, fractional removal rate, serum concentration, production rate, and metabolic clearance rate of thyroxine in pregnant rat

RAT	VD ml/100 g body wt	K (per hr)	T ₄ (ng/ml)	PR (ng/hr/100 g)	MCR (ml/hr/100 g body wt)
1	30.2	0.049	37	54.7	1.48
2	22.3	0.063	56	78.7	1.41
3	27.4	0.059	34	54.9	1.62
4	15.8	0.086	23	31.2	1.36
5	17.2	0.058	46	45.9	1.00
6	33.0	0.053	30	52.5	1.75
Mean $\pm$ S.E.	24.7 ± 3.1	0.61 ± 0.006	37.6 ± 5.3	53.0 ± 6.9	1.43 ± 0.115

Table 2. Placental transfer of [^{125} I]L-thyroxine in rats at different period of gestation

MATERNAL				FETAL			
Gestational age	Wt (g)	Fetus (n)	% dose/ml	Wt (g)	% dose/ml	F-M ¹ $\times 10^{-3}$	K _F ² $\times 10^{-3}$
16	239 ± 10^3	9 ± 1	1.045 ± 0.161	0.27 ± 0.020	0.003 ± 0.001	2.8 ± 0.3	0.131 ± 0.015
18	281 ± 8	9 ± 1	0.946 ± 0.130	0.75 ± 0.090	0.009 ± 0.004	8.0 ± 2.0	0.463 ± 0.196
20	330 ± 16	10 ± 2	1.340 ± 0.120	4.04 ± 0.250	0.042 ± 0.002^4	31.0 ± 3.0^4	1.516 ± 0.147^4

¹ F-M = % dose/ml at 3 hr in the fetus/% dose/ml at 3 hr in the mother.

² K_F = placental transfer of [^{125} I]thyroxine, from the mother to the fetus assuming that K_R, the placental transfer of thyroxine from the fetus to the mother, equals K_F.

³ Mean $\pm$ S.E. ($N = 6$).

⁴ $P < 0.01$ versus 18 days values (14).

Table 3. Placental transfer of unlabeled T₄ (100 µg) in pregnant rats at 16, 18 and 20 days of gestation

Gestational age	Maternal				Fetal			
	Wt (g)	Fetus (n)	T ₄ (ng/ml)		Wt (g)	T ₄ (ng/ml)		F-M × 10 ⁻³
			T = 0	T = 3 hr		T = 0	T = 3 hr	
16	263 ± 11 ¹	11 ± 1	30.1 ± 1.5	576 ± 53	0.263 ± 0.04		3.1 ± 0.2	5.0 ± 0.2
18	281 ± 3.6	9 ± 2	31.2 ± 0.17	683 ± 44	0.800 ± 0.80	5.37 ± 0.53	6.0 ± 1.2	8.8 ± 1.0
20	297 ± 10	8 ± 1	21.6 ± 0.53 ²	627 ± 82	3.760 ± 0.35	7.46 ± 0.52	23.9 ± 1.5 ³	38.0 ± 2.0 ³

¹ Mean ± S.E. (N = 6).² P < 0.05 versus 18-day pregnant rat and P < 0.05 versus 16- and 18-day pregnant rats (14).³ N = 17.

the T₄ kinetics in the fetal rat, assumptions were made for the fetal compartment, based on our previous studies of the T₄ kinetics in the neonatal rat (4).

Therefore, in equation 6, the fetal T₄ volume of distribution and fractional removal rate were given the values measured in the 5-day-old animals (24 ml/100 g body wt and 0.044/hr, respectively) (4). Because these parameters do not vary significantly during early postnatal days, they do represent good estimates for the fetal volume of distribution and fractional removal rate. Finally, in our calculations, the rate of placental transfer rate from the fetus to the mother was assumed equal to the placental transfer rate from the mother to the fetus. This assumption is based primarily on the data available in the sheep where no placental transfer of T₄ was observed in both directions (6, 8, 9).

Based on these assumptions, we calculated that the rate of placental transfer of T₄ (K_F) increases with advancing gestational age reaching a maximum near term (Table 2). However, calculations of the amount of T₄ reaching the fetus at 20 days of gestation show that, based on a maternal production rate of 53 ng/hr/100 g body wt (Table 1) and a K_F of 1.516 × 10⁻³/hr (Table 2), 80 pg/hr of T₄ are transferred to the fetus. Unless the fractional removal rate of T₄ in the fetal rat is significantly lower than the one we observed at 5 days of postnatal life, the amount of T₄ transferred (80 pg/hr) represent only 1% of the fetal T₄ secretion rate (7.95 ng/hr/100 g body wt). However, one must point out that our results are approximations which might underestimate the amount of T₄ reaching the fetus during late gestation. Indeed, recent studies suggest that the volume of distribution of T₄ in newborn animals is twice the one measured in 10-day-old rats, and the fractional removal rate of T₄ is more rapid in newborn animal than in 10-day-old rats (16, 17). Based on the values reported in this study, one can calculate that the amount of T₄ transferred to the fetus represents 3% of the fetal T₄ secretion rate, still an insignificant amount over total fetal T₄ production. Therefore, the placental transfer of T₄ increases during pregnancy in the rat but remains a minimal source of T₄ in the fetal animal.

Confirmation of a minimal transfer rate of T₄ is illustrated in the last experiment where 100 µg T₄ were injected in pregnant rats. As seen on Table 3, this dose of T₄ markedly increases the serum T₄ concentration in the mothers and moderately but significantly increases the serum T₄ concentration in the fetus. The calculated fetal-maternal ratio shows a good agreement with isotopic data, indicating that the assumptions made for the calculation of K were valid.

Previous studies have suggested that the placental transfer of thyroid hormones could permit the access of physiological amounts of thyroxine and triiodothyronine to the fetus. However, these conclusions were based primarily on indirect measurements. Knobil and Jasimovich (11) demonstrated a significant effect of 15 µg T₄/day for 10 days on the pituitary thyroid-stimulating hormone secretion of the fetal rat. Based on the T₄ kinetics and placental transfer rate reported in this study, one can conclude that the serum T₄ concentrations achieved at the end of this treatment would result in high serum T₄ concentrations both in the mothers and their fetuses (>100 and >20 ng/ml, respectively). Therefore, indirect studies based on the administration of large

quantities of hormone are not relevant to the physiological role of thyroid hormones derived from maternal pool. Our results also support recent findings by McGuire and Berman (12) who demonstrated that the fetal T₄ system was largely autonomous and that the maternal exchange was not significantly modifying the fetal T₄ economy.

The present findings indicate that a minimal placental transfer of T₄ occurs in the rat during the last days of gestation, but the amount of T₄ transferred to the fetus is minimal compared to the quantity of T₄ secreted by the fetal thyroid at this stage of development. Therefore, we conclude that the fetal rat hypothalamo-pituitary-thyroid axis develops autonomously.

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- Requests for reprints should be addressed to: Dr. J. H. Dussault, Laboratoires de Recherches en Endocrinologie-Metabolisme, Le Centre Hospitalier de l'Université Laval, 2705, Boul. Laurier, Ste-Foy, Qué. G1V 4G2 Canada.
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