Thyrotropin-Releasing Hormone is not Required for Thyrotropin Secretion in the Perinatal Rat

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ABSTRACT To determine the role of thyrotropin-releasing hormone (TRH) in the regulation of thyroid-stimulating hormone (TSH) secretion in the perinatal period, a physiological approach of neutralizing circulating TRH in the fetal and early neonatal rat was employed. TRH-antiserum (TRH-AS) raised in rabbits and administered daily to low iodine-propylthiouracil (LID-PTU)-fed pregnant rats from days 12 to 19 of gestation markedly impaired the rise in serum TSH to LID-PTU when compared with normal rabbit serum-treated controls. In contrast, fetal serum TSH was unaffected by TRH-AS. The binding capacity of TRH-AS in the fetal serum (111 ng/ml) far exceeded circulating TRH in the fetus. Similarly, acute TRH-AS administration to the pregnant rat fed LID-PTU markedly decreased the serum TSH concentration in the mother, but not in the fetus, 60 min after TRH-AS administration. Chronic TRH-AS administration to neonatal rats whose nursing mothers were fed LID-PTU was ineffective in decreasing the elevated serum TSH in the neonate through day 8 of life, whereas a slight but significant decrease in serum TSH was observed on day 10. Chronic daily TRH-AS administration to neonatal rats through day 10 of life had no effect on the later development of the hypothalamic-pituitary-thyroid axis. These findings suggest that TRH does not participate in TSH regulation during the perinatal life in the rat and that thyroid hormones are probably the main regulators of TSH secretion during this period. Placental TRH is not important in regulating TSH secretion in the fetal rat. Furthermore, TRH "deprivation" during neonatal life does not prevent normal later development of the hypothalamic-pituitary-thyroid axis.

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INTRODUCTION

In animals and man, thyroid-stimulating hormone (TSH)[1] secretion is stimulated by the hypothalamic thyrotropin-releasing hormone (TRH), and the TSH response to TRH is modulated by the thyroid hormones, thyroxine and triiodothyronine. Evidence for the TRH control of TSH secretion has been derived mainly from animal studies with hypothalamic lesions, basal hypothalamic deafferentation, or heterotopic pituitary transplantation, all of which result in a decrease in pituitary TSH secretion (1–5). Recently, we and others (6–8) have reported that passive immunization with TRH antibody results in a marked decrease in the basal and cold-stimulated TSH secretion in the normal and hypothyroid adult rat, although the role of endogenous TRH in maintaining increased serum TSH in the hypothyroid rat has been questioned (9).

In the fetus, previous studies have suggested that the hypothalamus and brain are not involved in the regulation of TSH secretion because encephalectomized fetuses with intact pituitaries developed goiters as large as normal controls when pregnant rats were fed antithyroid drugs (10–12). More recently, Tonooka and Greer (13) reported that serum TSH in encephalectomized fetuses was markedly elevated when pregnant rats were fed propylthiouracil (PTU) and that hypothalamic lesions in these PTU-fed pregnant rats did not prevent the TSH rise in the fetuses. Although these studies suggest that fetal and maternal TRH do not regulate TSH secretion in the fetus, this surgically treated model may not be optimal to study the physiological role of TRH. Encephalectomy also eliminates the possible effects of other brain neutrotransmitters

[1] *Abbreviations used in this paper*: LID-PTU, low-iodine-propylthiouracil; NRS, normal rabbit serum; PTU, propylthiouracil; RIA, radioimmunoassay; T_3, triiodothyronine; T_4, thyroxine; TRH, thyrotropin-releasing hormone; TRH-AS, TRH antiserum; TSH, thyroid-stimulating hormone.

on TSH synthesis and release. The recent observation that the rat placenta contains considerable quantities of TRH (14) which probably reaches the fetus and could serve as an extracerebral source of TRH in the encephalectomized fetus raises the possibility that TRH may still be important in TSH regulation in the fetal rat. The present studies, therefore, were carried out under more physiological conditions by administering TRH antiserum (TRH-AS) to the pregnant rat to neutralize circulating TRH in the fetus and thus explore the role of TRH in regulating fetal TSH secretion. The effect of TRH-AS on serum TSH concentration in the hypothyroid neonatal rat was also studied.

METHODS

Acute and chronic administration of TRH-AS to pregnant rats. Female Sprague-Dawley rats weighing 200–250 g were used in all experiments. The day of conception was accurately assessed by obtaining vaginal smears for identification of spermatozoa. To determine whether TRH-AS crosses the placenta, 0.4 ml i.p. TRH-AS was injected to four pregnant rats on day 21 of gestation, and blood obtained 60 min later from the mothers and fetuses and the presence of TRH-AS in the serum determined. Other rats were fed low iodine (0.03 μg/g)-propylthiouracil (0.15%) diet (LID-PTU) from days 12 to 19 of pregnancy. These rats were injected with 0.3 ml i.p. TRH-AS daily from days 12 to 19 of gestation. Control rats were injected with 0.3 ml normal rabbit serum (NRS). The TRH-AS employed in these experiments displayed a binding capacity of 48 nM/liter and when used in the TRH radioimmunoassay in a dilution of 1:50,000, 30% of [^{125}I]TRH was bound to antiserum (6). Blood was obtained by heart puncture from the pregnant rats under light ketamine anaesthesia, the fetuses were removed through cesarian section, and fetal blood was collected from the trunk, after decapitation. In another experiment, the rats were maintained on LID-PTU diet from day 14 to 21 of gestation, and 0.3 ml of TRH-AS or NRS was injected daily until day 20 of gestation. Blood was obtained on days 14, 17, and 21 of gestation, 24 h after TRH-AS or NRS administration. Maternal blood and pooled blood from fetal siblings were centrifuged, and serum obtained and quickly frozen until assayed for TSH. The presence and binding characteristics of the TRH-AS in fetal serum were determined by Scatchard plot analysis (15). Fetal thyroids, pituitaries, hypothalami, and extra hypothalamic brain tissues were separately pooled, whereas maternal tissues were individually studied. The thyroids were weighed. The pituitaries were frozen on dry ice, weighed, and homogenized in 4 ml 0.01 M PO_4 buffer (pH 7.5) and stored at −20°C until assayed for TSH content. The hypothalami and brains were quickly frozen on dry ice, weighed, and homogenized in 1 and 4 ml 90% methanol, respectively. The methanol extracts were evaporated under nitrogen, kept frozen, and reconstituted in 2 ml 0.01 M PO_4 buffer just before determining TRH content.

The effect of a single dose of TRH-AS on maternal and fetal serum TSH concentrations was evaluated as follows. Pregnant rats fed the LID-PTU diet from days 18 to 21 of gestation were injected with single dose of 0.4 ml i.v. TRH-AS or NRS. Six TRH-AS-treated rats and seven NRS-treated control rats were studied. Blood was obtained from the dams 30 min after intravenous injection. The dams were then sacrificed 30 min later, and maternal and fetal blood obtained. Sera from fetuses obtained from the same dam were pooled.

Acute and chronic TRH-AS administration to neonatal rats. 10-d-old neonatal rats, whose mothers were fed LID-PTU after delivery, received a single injection of 0.1 ml i.p. TRH-AS or NRS and were sacrificed 30, 60, and 120 min later. An adequate quantity of serum could be obtained from each 10-d-old neonate. The lactating mothers were injected with 0.4 ml i.p. TRH-AS, and serum was obtained 30, 60, and 120 min thereafter to determine the efficacy of the antiserum in neutralizing circulating TRH in the hypothyroid, adult rat.

Neonatal rats, 5 d old, whose mothers were fed LID-PTU diet after delivery were injected with 0.1 ml i.p. TRH-AS or NRS daily for 5 d. The neonatal rats were sacrificed by decapitation at 5, 8, and 10 d of age, 24 h after the last injection, and blood was collected. Serum was frozen until assayed for TSH. The TRH binding capacity in sera from rats treated with TRH-AS was also assessed.

To determine whether the presence of TRH during neonatal life is important for the later development of the hypothalamic-pituitary-thyroid axis, neonatal rats fed Purina chow (Ralston Purina Co., St. Louis, Mo.) were injected with 0.1 ml i.p. TRH-AS or NRS on days 1, 2, 3, 4, 6, 8, and 10 of age. They were then studied at age 40 d. Basal serum thyroxine (T_4), triiodothyronine (T_3), and TSH concentrations, the thyroid ^{131}I-uptake, the serum TSH response to TRH, and the serum TSH response to a LID-PTU diet were assessed.

Measurement of immunoreactive TRH in fetal serum. 10 separate pools of blood obtained from 21-d-old fetuses from normal pregnant rats were extracted immediately with 90% methanol. The extraction efficiency was calculated from the recovery of [^{125}I]TRH added to the blood. The volume of blood in each pool was estimated by the addition of the blood to known volumes of methanol in graded centrifuge tubes. The methanol extract was dried under nitrogen and reconstituted with 0.1 ml of 0.01 M PO_4 buffer, pH 7.5. Five of the extracted pools were incubated with 0.2 ml fresh normal adult rat serum at 37°C for 1 h which deactivates immunoreactive TRH. The other five pools were also incubated with 0.2 ml adult rat serum whose TRH deactivating activity was destroyed by preheating the serum at 56°C for 2 h. The TRH content in 50 μl of the incubate was then measured by radioimmunoassay (RIA). The standards were incubated with 50 μl of preheated rat serum to equalize the quantity of protein in the unknown samples.

Hormone measurements. Serum TSH was measured by RIA with material kindly distributed by the National Pituitary Agency, National Institute of Arthritis, Metabolism, and Digestive Diseases (Dr. A. Parlow). Hypothalamic and serum TRH was assayed by RIA by the method of Bassiri and Utiger (16–18) as modified in our laboratory (19). Serum T_3 and T_4 concentrations were measured by RIA. Statistical analysis was carried out by the Student's *t* test and, when indicated, by the paired *t* test.

RESULTS

Evidence that TRH-AS crosses the placenta. TRH-AS administered intravenously or intraperitoneally to the pregnant rat crosses the placenta. Fetal serum obtained 60 min after the administration of 0.4 ml TRH-AS to pregnant rats bound ^{125}I-labeled TRH added in vitro. 10 μl fetal serum bound 44±4% (mean±SE), whereas 10 μl maternal serum bound 60±10% of ^{125}I-TRH (final dilution, 1:500).

Serum TRH in the fetal rat. The immunoreactive TRH concentration in the methanol extract of fetal

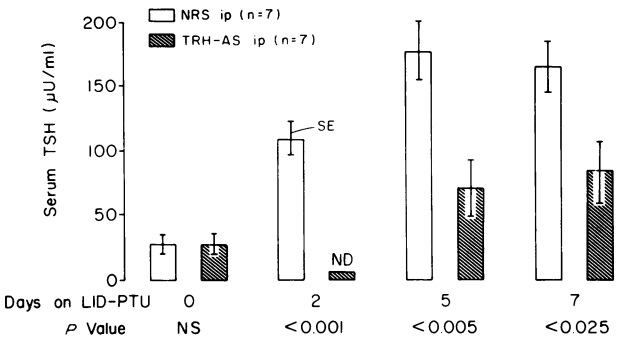

FIGURE 1 Effect of TRH-AS or NRS administration on serum TSH concentration in pregnant rats. Rats were maintained on LID-PTU diet from days 12 to 19 of gestation, and were injected daily with 0.3 ml i.p. of TRH-AS or NRS from days 12 to 18 of gestation. Blood was obtained on days indicated in the figure, 24 h after the administration of TRH-AS or NRS. Bars and vertical lines represent group mean±SE. ND, not detectable.

blood averaged 765±40 pg/ml (n = 7). Because the extraction efficiency was 95%, as judged from the recovery of ^{125}I-TRH, no correction for recovery was made. Incubation of the methanol extract with fresh adult rat serum for 1 h at 37°C reduced the immunoreactive TRH activity by 87±5% when compared with the methanol extract or synthetic TRH treated with 56°C preheated rat serum. Furthermore, the TRH immunoreactivity in the fetal serum extract exhibited parallelism with the synthetic TRH standard curve. These findings strongly suggest that immunoreactive TRH in fetal serum is TRH.

Effect of chronic TRH-AS administration on maternal and fetal serum and pituitary TSH in LID-PTU-fed rats. On the basis of the above experiments, 0.3 ml i.p. TRH-AS was injected daily to LID-PTU-fed pregnant rats. Inasmuch as serum TSH in the fetal rat was not sufficiently elevated when pregnant rats were fed normal chow, the dams were fed LID-PTU diet to obtain an elevated fetal serum TSH. Daily injections of TRH-AS from days 12 to 18 of pregnancy prevented the elevation in serum TSH concentration observed in the NRS-treated control dams (Fig. 1). In contrast, fetal serum TSH remained elevated after daily injections of TRH-AS for 7 d to the pregnant rat and was almost identical to that obtained in fetuses from control rats (n = 7) treated with NRS (TRH-AS 86±24 vs. NRS 88±16 μU/ml). 24 h after the last injection of TRH-AS to the dams, the affinity constant (K) of the pooled fetal serum was 1.78×10^{-9} liters/mol and the binding capacity (C) was 0.41 nM/liter, clearly exceeding the circulating serum, hypothalamic, and brain TRH content. Pituitary TSH content was increased in LID-PTU-fed dams treated with TRH-AS (TRH-AS 80±12 vs. NRS 21±3.9 mU/mg pituitary, $P < 0.001$). In contrast, fetal pituitary TSH was not significantly affected by the administration of TRH-AS to the pregnant rat (TRH-AS 50±10 vs. NRS 35±6 μU/pituitary). Similar results were obtained in another experiment. The serum TSH in NRS-treated pregnant rats (n = 6) was increased from basal values of 13.2 ±1.5 to 217±50 μU/ml 3 d after the institution of the LID-PTU diet (day 17) and remained elevated (160±26 μU/ml) on day 21. In contrast, in the TRH-AS-treated group (n = 4), serum TSH was 68±8 (day 17) and 93±10 μU/ml (day 21), significantly different from the control NRS-treated rats ($P < 0.02$ and < 0.05, respectively). Fetal serum TSH was not significantly different (TRH-AS 256±7 vs. NRS 165±24 μU/ml). The brain and hypothalamic TRH content was not affected by the TRH-AS in either the dam or the fetus. Similarly, thyroid weights in the dams and fetuses were identical in both groups (Table I).

Serum T_4 in the dams was barely detectable 7 d after the institution of LID-PTU diet, whereas T_3 was low in both groups (TRH-AS 25±1 vs. NRS 22±3 ng/dl). Serum T_4 and T_3 in the fetuses were undetectable in all groups.

Effect of acute TRH-AS administration to the LID-PTU-fed pregnant rat on maternal and fetal TSH. We have previously reported (6) that in the hypothyroid rat, acute TRH-AS administration resulted in a decreased serum TSH concentration 30, 60, and 120 min later, but that this effect was no longer seen after 120

TABLE I
Hypothalamic and Brain TRH Content and Thyroid Weight in Pregnant Rats Fed LID-PTU and their Fetuses after Chronic TRH-AS Administration

	Hypothalamic TRH		Brain TRH		Thyroid weight	
	Maternal	Fetal	Maternal	Fetal	Maternal	Fetal
	ng/hypothalamus		*ng/brain*		*mg*	
TRH-AS (4)*	8.4±1.1‡	0.37±0.1	16±2.3	0.58±0.09	36±4	3±0.4
Control (6)	7.6±1.4	0.45±0.1	19±4.4	0.46±0.1	37±5	4±0.5

* Number of rats given in parentheses.
‡ Mean±SE.

min. To exclude the possibility that an early inhibitory effect of TRH-AS on TSH secretion, as observed in adult rats, might have been overlooked, 0.4 ml i.p. TRH-AS or NRS was administered to pregnant rats fed LID-PTU on day 21 of gestation. Maternal blood was taken at 30 min, and fetal and maternal blood at 60 min after TRH-AS or NRS administration.

Fetal serum TSH concentration was not significantly affected by TRH-AS (TRH-AS 148±27 vs. NRS 182 ±24 μU/ml), whereas maternal serum TSH concentration was significantly decreased at 30 min (TRH-AS 26±6 vs. NRS 100±21 μU/ml, $P < 0.01$) and 60 min (TRH-AS 35±11 vs. 100±24 μU/ml, $P < 0.025$) (Fig. 2). The calculated in vitro binding capacity of fetal serum varied from 35 to 50 ng TRH/ml, verifying the presence of a high concentration of TRH-AS.

Effect of acute TRH-AS administration on neonatal and maternal serum TSH in LID-PTU-fed lactating rats. Serum TSH concentration in neonatal rats whose mothers were fed LID-PTU since delivery was elevated as observed in primary hypothyroidism. The increased serum TSH concentration was not affected by the administration of TRH-AS (Fig. 3). The presence of TRH-AS in the neonatal rat serum was verified as described previously. The calculated TRH binding capacity of the neonatal serum in the TRH-AS-treated group varied from 80 to 100 ng TRH/ml.

In contrast to the findings in the neonatal rat, when lactating mothers were injected with 0.3 ml i.p. TRH-AS, a marked decrease in serum TSH concentration occurred at 30, 60, and 120 min later ($P < 0.001$) when compared with NRS-treated controls (Fig. 4). In rats receiving NRS, an unexplained significant rise in serum TSH concentration was observed 30 min after the injection of NRS as compared with pretreatment values ($P < 0.001$, paired t test), but serum TSH concentration was identical to the initial value at 120 min. In rats receiving TRH-AS, serum TSH concentration was markedly decreased at 60 and 120 min as compared with pretreatment values ($P < 0.001$; paired t test).

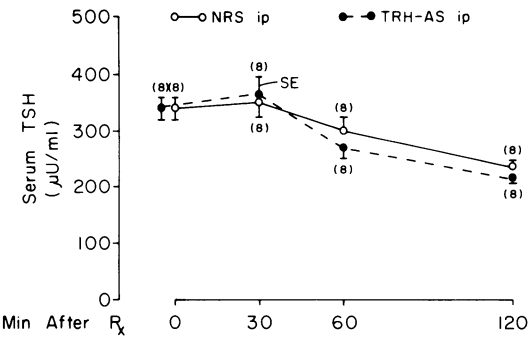

FIGURE 3 Serum TSH concentration after acute TRH-AS administration (0.1 ml i.p.) to 10-d-old neonatal rats. Mothers were maintained on LID-PTU diet after delivery for 10 d. Numbers in parentheses represent the number of rats used in each group.

Effect of chronic TRH-AS administration on serum TSH in neonatal rats whose mothers were fed the LID-PTU diet. Chronic TRH-AS administration to neonatal rats whose mothers were fed LID-PTU for 10 d beginning on the day of delivery did not decrease the elevated serum TSH on day 8. However, a slight but significant decrease was observed on day 10 (Fig. 5).

Effect of TRH-AS administered during the neonatal period on the later development of the hypothalamic-pituitary-thyroid axis. Basal serum TSH and TRH-induced TSH release assessed at 40 d of age were not affected when TRH-AS was injected chronically during early neonatal life (Table II). Similarly, when these rats were challenged with LID-PTU diet, no difference in the increase in serum TSH was observed between the previously treated TRH-AS and NRS groups. Basal serum T_4 and T_3 concentrations and the 3-h thyroid radioactive iodine uptake were also similar in the TRH-AS-treated and NRS-treated rats (Table II).

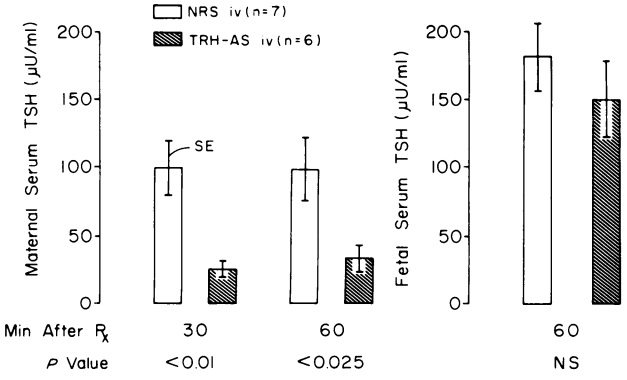

FIGURE 2 Effect of a single dose of TRH-AS (0.4 ml i.v.) to the pregnant rat on maternal and fetal serum TSH. Mothers were maintained on LID-PTU diet from days 18 to 21 of gestation.

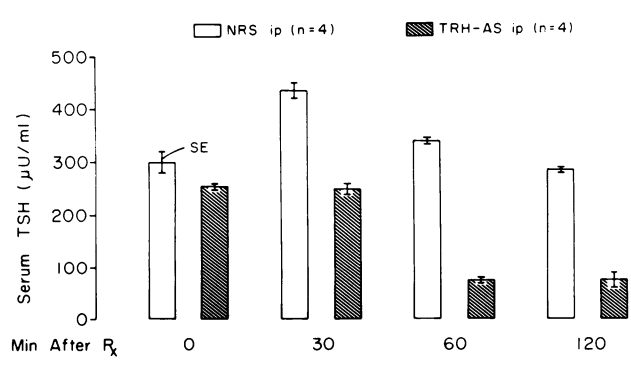

FIGURE 4 Serum TSH concentration in the lactating mothers of the neonates in Fig. 3 after a single dose of TRH-AS (0.3 ml i.p.).

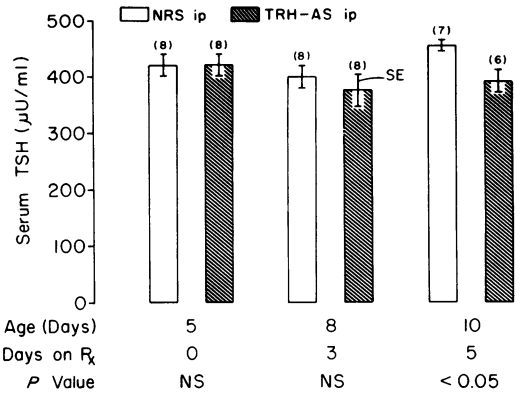

FIGURE 5 Serum TSH concentration in nursing neonatal rats whose mothers were maintained on LID-PTU diet after delivery for 10 d. Neonates were injected daily with 0.1 ml TRH-AS or NRS from days 5 to 9 of age and sacrificed on days 5, 8, and 10 as indicated in the figure. Numbers in parentheses represent the number of rats used in each group.

DISCUSSION

The present study clearly demonstrates that the circulating immunoreactive TRH in the fetal and early neonatal rat is not involved in the regulation of TSH secretion. Although similar conclusions were made from earlier studies with fetal encephalectomy and maternal hypothalamic lesions (10–13), the present report differs from these studies in many respects. First, all previous studies involving fetal encephalectomy and maintenance of an isolated pituitary island cannot be considered physiological because extensive surgical manipulation is involved. Second, possible remnant neural connections between residual hypothalamic tissue and the pituitary gland after encephalectomy or hypothalamic lesions cannot be excluded. Third, a possible role of placental TRH in rat (14) and man (20) in regulating fetal TSH synthesis and release could not be excluded in these studies. It is possible that the failure to observe a decrease in serum TSH in the fetus after encephalectomy, with or without hypothalamic lesions in the mother, may be due to the passage of placental TRH into the fetal circulation which could stimulate the fetal pituitary gland. Although there is no definitive evidence that placental tissue releases TRH into the fetal circulation, our studies suggest that whether or not this occurs, circulating TRH in the fetus, whatever its source, is not involved in fetal TSH secretion under physiological conditions. This conclusion is further strengthened by the finding that the pituitary thyrotroph is not dependent upon TRH during early neonatal life, because TRH-AS administration did not decrease serum TSH concentration in the hypothyroid neonatal rat but was effective in decreasing serum TSH concentration in their LID-PTU-fed lactating mothers. The slight but significant decrease in serum TSH concentration in the 10-d-old neonatal rats whose mothers were fed a LID-PTU diet suggests that the neonatal pituitary is responsive to endogenous TRH by 10 d of age and indicates the initiation of the dependence of TSH regulation upon TRH secretion.

Several possibilities are raised, however, in an attempt to explain the failure of TRH-AS to decrease serum TSH in the fetal and early neonatal rat. First, it may be argued that the quantity of TRH-AS administered to the pregnant rat which reached the fetus was inadequate to neutralize circulating TRH in the fetus or that its binding efficiency was lost because of degradation during its passage through the placenta. However, this is most unlikely because fetal serum from mothers injected with TRH-AS was found to bind

TABLE II

Serum T_4 and T_3 Concentrations and Thyroid ^{131}I-Uptake and the Serum TSH Response to TRH and LID-PTU Diet in 40-d-Old Rats Treated with TRH-AS during Early Neonatal Life

	Serum TSH post-TRH			Serum TSH post-LID-PTU						
	0*	10	20	0‡	3	6	9	Serum T_4	Serum T_3	3-h ^{131}I-uptake
	μU/ml			μU/ml				μg/dl	ng/dl	%
Females										
TRH-AS (6)§	51±20‖	571±124	628±104	15±2	138±37	443±74	483±39	3.8±0.3	60±4	4.1±0.7
NRS (7)	77±19	700±214	717±158	23±5	223±38	561±57	413±33	3.0±0.4	56±6	4.2±0.3
Males										
TRH-AS (7)	31±11	512±80	742±42	57±21	214±43	431±58	372±30	3.7±0.2	48±8	3.0±0.3
NRS (7)	59±48	701±100	735±129	23±4	236±18	530±57	424±49	3.7±0.2	57±7	3.3±0.3

* Time (minutes) after TRH administration.
‡ Number of days on LID-PTU diet.
§ Number of rats given in parentheses.
‖ Mean±SE.

TRH with a binding capacity far exceeding the TRH content in the extrahypothalamic brain, hypothalamus, and serum in the fetus. Second, the possibility that the effect of the antiserum occurred early and disappeared during the 24-h period after the last injection of TRH-AS to the mother is unlikely because serum TSH was significantly decreased in the mother but not in the fetus. Furthermore, serum TSH concentration in mother and fetus assessed at earlier time intervals after a single large dose of TRH-AS was not affected in the fetus, but was markedly decreased in the mother. Similarly, TRH-AS was effective in decreasing TSH in the lactating mother but not in the nursing neonate, despite the presence of large quantities of circulating TRH-AS in the serum. Thus, the failure of TRH-AS to decrease perinatal TSH cannot be explained by inadequate neutralization of circulating TRH because of lack of TRH-AS present in perinatal serum, loss of TRH-AS biological activity, or by the time-course of TSH sampling.

There is no doubt that immunoreactive TRH is present in the circulation of the fetus. It was readily detected in extracted blood and displayed parallelism with synthetic TRH in the TRH immunoassay. Furthermore, it was deactivated by fresh rat serum, suggesting that the immunoreactive TRH-like substance is TRH. The presence of TRH in fetal serum is not surprising. In contrast to the adult rat serum, fetal and neonatal serum obtained from rats up to 16 d of age does not deactivate TRH because of the absence of TRH deamidases and peptidases (21–23). Thus, even a small amount of TRH from the portal system or extrahypothalamic tissue reaching the systemic circulation is more easily detected in the fetal and neonatal rat than in the adult rat.

It is not clear why endogenous TRH, under physiological conditions, is not involved in the regulation of TSH secretion in the perinatal rat. The circulating TRH may be immunologically active but biologically inactive, although this possibility seems unlikely. It is also possible that fetal hypothalamic TRH may not be transported to the pituitary via the median eminence neurovascular link because capillary loops apparently do not penetrate the median eminence until late in the first postnatal week (24). However, capillaries with the characteristics of primary portal vessels are present along the ventral surface of the median eminence very early in fetal life (24). The finding that corticotrophin and growth hormone secretion are markedly impaired after hypothalamic lesions in rat fetuses (25–27), whereas TSH secretion is unaffected, suggests that TRH, corticotrophin-releasing factor, and growth hormone-releasing factor are transported to the pituitary through the median eminence and that TRH does not regulate TSH secretion. This may be due to a decrease in the number of TRH receptor sites in the pituitary thyrotroph during perinatal life although direct experimental evidence is lacking. The present findings and those of Tonooka and Greer (13) suggest that the perinatal pituitary thyrotroph is exquisitely sensitive to the inhibitory effects of thyroid hormones. This may explain, at least in part, the low serum TSH in the perinatal rat in the presence of very low concentrations of thyroid hormones and the increased serum TSH response after thyroid hormone deprivation. This is reminiscent of the increased sensitivity of the hypothalamic-pituitary axis to the inhibitory effects of the gonadal steroids during prepubertal life in man and the increased sensitivity of the pituitary thyrotroph to the inhibitory effect of thyroid hormones in adult rats with hypothalamic lesions (5). Thus, in the perinatal rat, TSH secretion is primarily regulated by the thyroid hormones acting unopposed on a pituitary with a low set point. The higher threshold of TSH secretion is developed later in life under the influence of TRH.

The biological inactivation of TRH during early neonatal life does not appear to influence the later development of a normal hypothalamic-pituitary-thyroid axis because prolonged administration of TRH-AS, and presumably neutralization of circulating TRH during neonatal life, had no effect on basal and stimulated TSH secretion in adult life. This is in contrast to the essential role of luteinizing hormone-releasing hormone during the neonatal period which appears to be important for the normal development of gonadal function in the adult rat (28).

We have previously reported that TRH is an important modulator of TSH secretion in the normal and hypothyroid adult rat (6). The present studies confirm and extend these previous observations and suggest that TRH contributes substantially to the increased TSH secretion in hypothyroidism. The rapidity of the reduction of serum TSH and the sustained effect of TRH-AS on lowering serum TSH concentration in the hypothyroid, pregnant and lactating rat observed in the present study suggest that TRH secretion is required to maintain the marked increase in serum TSH concentration in adult hypothyroidism.

Addendum. When this study was completed, Strbak and Greer reported in abstract form (54th Annual Meeting of the American Thyroid Association) that hypothalamic lesions in the perinatal, hypothyroid rat did not effect TSH secretion until 12 d of age. Their findings are thus in agreement with those of this study.

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