Minireview: Developmental Regulation of Thyrotropin Receptor Gene Expression in the Fetal and Newborn Thyroid

ROSALIND S. BROWN
Endocrine Division, Children’s Hospital, Boston, Massachusetts 02115

The TSH receptor plays a pivotal role in thyroid gland growth, function, and differentiation in the mature animal, but only recently has its role in the fetus and neonate been examined. Observational studies comparing the developmental regulation of TSH receptor gene expression, with thyroid morphology, and thyroid-specific gene expression in the rodent model, are reviewed in the context of older literature. Together, these data strongly suggest that the TSH receptor is essential for terminal thyroid maturation and growth but is not involved in early thyroid organogenesis or migration. Consistent with the aforementioned studies in rodents, babies born to mothers with potent TSH receptor-blocking antibodies have hypothyroidism and hypoplastic, but normally located, thyroid glands. Because the TSH receptor is probably not expressed in human fetuses before 10–12 wk gestation when thyroid organogenesis and migration are complete, these data provide strong evidence that human chorionic gonadotropin, which peaks in the first trimester of human pregnancy, could not play a role in fetal thyroid development. Similarly, these data imply strongly that maternal TSH receptor antibodies, when present in high titer, are of major importance in influencing fetal thyroid function only after mid-pregnancy when, by analogy with rodents, increased TSH receptor expression is likely to occur. (Endocrinology 145: 4058–4061, 2004)

THYROID HORMONE IS critical for the growth and development of numerous fetal and neonatal tissues, especially the brain and bone (1, 2). The preeminent stimulator of thyroid hormonogenesis and gland growth in the mature animal is pituitary TSH, which initiates its action by binding to a specific heterotrimeric receptor located at the cell membrane (3, 4). TSH exhibits transcriptional control of the genes for the major thyroid proteins thyroglobulin (Tg), thyroid peroxidase (TPO), and the sodium-iodide symporter (NIS) and stimulates an array of cellular events, including iodine uptake and organification, as well as thyroid hormone synthesis and secretion (3–6). Despite major advances in knowledge of the structure, function, and molecular biology of the TSH receptor in the adult, only recently has information been obtained about its expression and regulation in fetal life and its role in fetal thyroid gland development. In this minireview, evidence will be provided that TSH, acting through its receptor, plays a major role in terminal thyroid gland maturation and growth but is not involved in early events involving commitment to a thyroid-specific phenotype, thyroid organogenesis, or cell migration. The implications of these findings to human disorders involving the TSH receptor will be discussed.

Thyroid Development: the Rodent Model

Organogenesis and migration

The thyroid gland is derived from fusion of a medial outpouching from the floor of the primitive pharynx, the precursor of the Tc-producing follicular cells, and bilateral evaginations of the fourth pharyngeal pouch, which give rise to the parafollicular, or calcitonin (C)-secreting cells. Three transcription factors, thyroid transcription factor 1 (TTF-1), TTF-2, and PAX-8, are expressed in the rat before or just after the first appearance of the thyroid diverticulum on fetal day 9.5–10 (7–10). Organogenesis and migration of the thyroid bud caudally to the neck is complete by fetal day 15. Both in vitro experiments and in vivo studies of animals with a targeted disruption in gene expression have documented that TTF-1, and PAX-8, acting coordinately, are of major importance in early thyroid gland embryogenesis, whereas TTF-2 is essential for migration.

Morphological and functional maturation

Evidence of weak TSH receptor gene expression is not observed until fetal day 15 (11). At this time, Tg gene expression is also detectable, but the thyroid gland is difficult to distinguish from the surrounding structures, and neither iodine organification, thyroid hormonogenesis, nor evidence of a follicular structure is present (11–15). Thus, TTF-1 and PAX-8 are necessary but not sufficient for the expression of the fully differentiated thyroid phenotype. On fetal day 17, TSH receptor gene expression is dramatically up-regulated, accompanied by significant growth and rapid development in both structural and functional characteristics (11). Expression of both Tg and TPO mRNA increase, thyroid follicles develop, thyroid colloid can be demonstrated, TPO enzyme function can be demonstrated, and there is evidence of thyroid hormonogenesis (11, 12, 14, 15) (Figs. 1 and 2). After fetal day 17, there is continuing maturation of thyroid gland morphology and function until the first 2–3 wk postnatally.

Because the fetal rat thyroid can respond to both TSH and...
forskolin by fetal d 15 (14, 16), the reason that evidence of thyroid maturation is not observed until fetal d 17 is not merely a lag in translation into functional protein. Rather a more likely reason is the appearance of pituitary TSH in the fetal circulation on fetal d 17, accompanied by up-regulation of the TSH receptor (11). This pattern is reminiscent of the LH receptor, which is up-regulated by its homologous hormone LH in fetal life but down-regulated in the adult (17).

It is of interest that Tg gene and protein can first be detected on fetal d 15 (13, 15), 2 d earlier than TPO and NIS and coincident with the first appearance of the TSH receptor. This finding is consistent with other data demonstrating that the regulation of Tg expression is both TSH-dependent and TSH-independent (18, 19). Both insulin and IGF-1 are known to regulate Tg expression (18, 19), but their developmental expression within the thyroid gland is unknown. Other candidate genes are TTF-1 and PAX-8 that, in addition to their role in thyroid cell commitment and organogenesis, also play a role in thyroid-specific gene expression (10, 20). Similarly, mutant mice lacking a functional TSH receptor nonetheless have some evidence of a follicular structure, suggesting that factors other than TSH may be involved in folliculogenesis (5, 21). However, the follicular structure in these mutant mice is poorly developed, follicles are fewer in number and there are more non-follicle-associated cells than in thyroid glands from wild-type animals. Thus, TSH is necessary for the development of a mature thyroid architecture. As might be predicted, if TSH played an important role in terminal thyroid growth and maturation but was not involved in organogenesis or gland migration, mutant animals lacking a functional TSH receptor have hypothyroidism and a hypoplastic, but normally located, thyroid gland (5, 21).

**Implications for Human Thyroid Gland Development and Disease**

Analogous studies of TSH receptor gene expression in human fetuses have not been performed, but it is possible to apply knowledge gained in the rodent to human development and disease. In the human fetus, thyroid gland em-
bryogenesis and descent are largely complete by 10–12 wk of gestation, equivalent to 15 d in the rat fetus. At this stage, tiny follicle precursors can be seen, iodine uptake can be identified, and Tg is present in the follicular spaces (22–24). At 18–20 wk of gestation, equivalent to fetal d 17 in the rat, fetal thyroid gland iodine uptake and serum T4 concentrations begin to increase accompanied by a progressive increase in fetal serum TSH concentration (25, 26). In addition, the free T4:TSH ratio rises progressively after 20 wk, suggesting increasing thyroid gland responsiveness in the second half of pregnancy (26). Extrapolating the aforementioned data obtained in rodents, it is likely that the TSH receptor gene is first expressed in human fetuses at the end of the first trimester and that expression begins to increase in mid-pregnancy, coincident with pituitary-hypothalamic maturation. Similar to findings in mutant mice, human infants with loss of function mutations of the TSH receptor as well as in infants born to mothers with potent TSH receptor blocking antibodies have hypothyroidism and small but normally located thyroid glands (27, 28).

The aforementioned developmental studies have important implications in terms of the timing of perturbations of thyroid function in babies born to mothers with antibodies to the TSH receptor. For example, it may be predicted that fetuses of mothers with potent TSH receptor-stimulating antibodies are not at risk for the development of fetal thyrotoxicosis before the second half of pregnancy and are most vulnerable during the third trimester of pregnancy when up-regulation of the TSH receptor is likely to occur. Similarly, it may be inferred that maternal TSH receptor-blocking antibodies do not affect fetal thyroid function to any significant extent early in pregnancy and consequently, antibody-induced congenital hypothyroidism is a model of maternal hypothyroidism alone in the first half of pregnancy and of combined maternal and fetal hypothyroidism in the second half. Finally, the demonstration that the TSH receptor gene is not expressed until relatively late in gestation provides further evidence that placental factors with thyrotropic activity, such as human chorionic gonadotropin, do not play a significant role in early fetal thyroid gland development.

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Address all correspondence and requests for reprints to: Rosalind S. Brown, Endocrine Division, Children’s Hospital, 300 Longwood Avenue, Boston, Massachusetts 02115. E-mail: Rosalind.Brown@childrens.harvard.edu.

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