Development of the thyroid

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The period of maturation of human thyroid function and metabolism extends throughout gestation and into the newborn period. This maturation represents a complex series of interrelated events in the thyroid and pituitary glands, in the brain and hypothalamus, and in peripheral tissues. In this chapter we review the events of fetal thyroid system maturation in some detail.

Maturation begins during the period of fetal organogenesis (first 12 weeks of gestation) with the appearance and histological development of the thyroid and pituitary glands followed by development of the hypothalamus between 10 and 35 weeks’ gestation. Beginning at approximately 30 weeks the liver and perhaps other tissues begin to develop the capacity to convert thyroxine (T₄) to the most active thyroid hormone analogue, 3,5,3'-triiodothyronine (T₃) for transport to fetal plasma. Superimposed on these events are maturation of thyrotrophin-releasing hormone (TRH) production, first from nonhypothalamic tissues and later from the hypothalamus, maturation of pituitary control of thyrotrophin (thyroid-stimulating hormone; TSH) secretion, and maturation of thyroid follicular cell responsiveness to TSH and iodide. There is a simultaneous maturation of nuclear thyroid hormone receptor binding which is variable among tissues. Integration and synchronization of these events results in the orderly ontogenesis of thyroid hormone secretion and action as outlined in Figure 1 and successful transition of the fetus to the extrauterine environment.

THE PLACENTA AND THYROID FUNCTION

The fetal hypothalamic–pituitary–thyroid axis develops autonomously of maternal influence. The placenta is impermeable to TSH and, while permeable to TRH, the circulating levels of TRH in maternal serum are too low to contribute significantly to fetal thyroid function (Fisher et al, 1977; Roti et al, 1981; Roti, 1988). The placenta actively transports iodide to the fetus; the fetal: maternal plasma gradient of iodide concentration approximates 4–5:1 (Roti et al, 1981). The mechanism and control of this placental iodide transport system have not been characterized. In rats, it has been shown that
there is significant maternal to fetal transfer of thyroid hormones both before (10–17 days' gestation) and after (21 days) the onset of fetal thyroid hormone secretion at 19 days (Obregon et al., 1984; Morreale de Escobar et al., 1988). In humans and sheep, available information suggests that thyroid hormones, including thyroxine (T₄), 3,5,3′-triiodothyronine (T₃) and reverse triiodothyronine (rT₃) have only limited access to the fetal compartment via maternal-to-fetal placental transfer. The T₄ concentration in blood samples of athyreotic neonates at birth ranges from 2 to 5 μg/dl whereas levels in cord blood of normal neonates range from 7 to 14 μg/dl (Vulsma et al., 1989). This T₄ presumably is derived by placental transfer and even though in the hypothyroid range may provide protection to selected fetal organs (Morissette and Dussault, 1986). It is possible that maternal-to-fetal placental T₄ transfer early in pregnancy could supply significant amounts of thyroid hormone to the developing fetus, but evidence of such transfer is not presently available in humans.

Placental tissue and fetal membranes contain an iodothyronine α-ring monodeiodinase enzyme capable of deiodinating T₄ to inactive rT₃ and T₃ to
inactive diiodothyronine (Roti et al. 1981). This enzyme activity may contribute to the placental 'barrier' to iodothyronine transfer and may account, at least in part, for the relatively high levels of rT3 in amniotic fluid (Roti et al, 1981). The commonly used antithyroid drugs of the thioureylene class (propylthiouracil, methimazole, carbimazole) freely cross the placenta and may have important perinatal effects. The placenta is also permeable to the IgG class of immunoglobulins, which circulate in the plasma of women with autoimmune thyroid disease. These immunoglobulins may be either thyroid stimulators or thyroid inhibitors.

EMBRYOGENESIS

Development of the hypothalamus and pituitary gland

The human fetal forebrain is identifiable by three weeks of gestation; the diencephalon and telencephalon are distinguishable by five weeks. Rathke’s pouch, the buccal precursor of the anterior pituitary gland, has separated from the primitive pharyngeal stomatodaeum by five weeks (Falin, 1961; Conklin, 1968). The neural components of the transducer system, the hypothalamus, pituitary stalk and the posterior pituitary gland, are largely developed by seven weeks. The bony floor of the sella turcica which separates the adenohypophysis from the primitive gut also is present by this time. Capillaries develop within the proliferating anterior pituitary mesenchymal tissue around Rathke’s pouch by eight weeks and intact hypothalamic–pituitary portal vessels are present by 12–17 weeks (Thiveris and Currie, 1980). A superficial system of capillaries, the supratriuberal plexus, develops in association with the pituitary gland. Such capillaries, referred to as the secondary plexus of the pituitary portal system, have been identified in the mesenchymal tissue adjoining Rathke’s pouch and the diencephalon in the human fetus as early as seven to eight weeks of gestation. The tufted capillaries of the primary or hypothalamic plexus of the portal vascular system are first visible at 15–16 weeks. There is progressive maturation thereafter, with increasing tortuosity and looping of the tufts and progressive increase in the volume of median eminence capillaries (Thiveris and Currie, 1980). Histological maturation of the pituitary portal system is largely complete by 30–35 weeks’ gestation.

The median eminence of the hypothalamus is evident by nine to ten weeks and cell condensations (which represent the hypothalamic nuclei) and interconnecting neuronal tracts are demonstrable by 15–18 weeks (Raiha and Hjelt, 1957; Hyyppa, 1972). Hypothalamic cells and diencephalic neuronal tracts for the hypothalamic neuropeptides somatostatin (somatotrophin-release inhibiting factor; SRIF), corticotrophin-releasing factor (CRF), growth hormone releasing factor (GRF), and gonadotrophin-releasing hormone (GnRH) are also visible by this time (Bugnon et al, 1977; 1978; 1984; Bresson et al, 1984; 1987). Significant concentrations of dopamine, TRH, GnRH and SRIF have been measured by bioassay or immunoassay in hypothalamic tissue by 10–14 weeks (Kaplan et al, 1976; Gluckman et al, 1981).
The anterior pituitary gland develops as a dorsal derivative of the primitive buccal cavity. By the fifth week after conception this derivative, referred to as Rathke's pouch, makes contact with the infundibular process, a funnel-shaped diverticulum of the third cerebral ventricle, which is destined to become the neurohypophysis or posterior pituitary gland (Falini, 1961; Conklin, 1968; Gluckman et al., 1981). The buccal connection of the anterior lobe is obliterated by the developing sphenoid bone, and by 12 weeks the pituitary gland is already partially encapsulated within the bony sella turcica. Specialized anterior pituitary cell types including lactotrophs, somatotrophs, corticotrophs, thyrotrophs and gonadotrophs appear in the anterior pituitary between 7 and 16 weeks (Gluckman et al., 1981; Mulchahey et al., 1987). Anterior pituitary hormones, including growth hormone, prolactin, TSH, luteinizing hormone (LH), follicle-stimulating hormone (FSH) and adrenocorticotropic hormone (ACTH) are detectable by radio-immunoassay between 10 and 17 weeks. Thus the anatomy and biosynthetic mechanisms comprising the hypothalamic-pituitary neuroendocrine transducer appear functional by 12 to 17 weeks of human gestation.

Development of the thyroid gland

The thyroid of the human embryo is derived from a midline outpouching of the endoderm of the floor of the primitive buccal cavity (Fisher and Dussault, 1974). Lateral ultimobranchial anlagen, derived from portions of the fourth pharyngeal pouches, contribute the calcitonin-producing parafollicular C-cells. The thyroid develops as a flask-like vesicle with a narrow neck attached to the buccal cavity. The vesicle gradually enlarges and becomes bilobed; the stalk ruptures and the gland becomes a solid mass of laterally expanding tissue in the anterior lower neck. By the end of the seventh week after conception the thyroid weighs 1–2 mg and has assumed its definitive shape and position in the anterior lower neck. Histologically, the gland develops in three phases: precolloid, beginning colloid, and follicular growth phases. During the final period of follicle organization (70–80 days' gestation), iodide concentration and thyroid hormone synthesis can be demonstrated (Fisher and Dussault, 1974).

The control of thyroid gland maturation is not well understood. It is clear that TSH is not necessary for fetal thyroid growth during the first half of gestation (Fisher and Dussault, 1974; Smith et al., 1986). Recent studies suggest that insulin-like growth factors, epidermal growth factor, or other related factors are involved in the replication and growth of thyroid follicular cells (Thorburn et al., 1981; Smith et al., 1986; Brenner-Gati et al., 1988; Heldin and Westermark, 1988).

MATURATION OF FETAL TSH AND THYROXINE CONCENTRATIONS

Pituitary TSH is detectable at 8–10 weeks in the human fetus (Fisher et al., 1977; Fisher and Klein, 1981). The concentration remains low until 16–18
weeks then increases to a plateau level by 28 weeks’ gestational age. Pituitary TSH content also increases early in gestation, but values continue to increase rather than reaching a plateau (Klein et al, 1982). TSH is detectable in human fetal serum by 10 weeks of gestation, but concentrations are <2 µU/ml until 20 weeks. Serum TSH values then increase to a mean level of approximately 15 µU/ml between 20 and 30 weeks; by 40 weeks the mean fetal serum TSH level decreases to a value of approximately 10 µU/ml (Figure 2). Fetal serum total T₄ concentrations are low prior to 16–18 weeks’ gestation and increase progressively thereafter to plateau values at 34–36 weeks. This increase is accompanied by progressive increases in serum thyroxine-binding globulin concentrations derived from hepatic production,

![Fractional Thyroid System Maturation](image)

**Figure 2.** The ontogenesis of thyroid function in the human fetus. Fetal age in weeks is shown on the upper horizontal axis. Thyroid system maturation is complete by one month of postnatal age (1.0 of thyroid maturation). Fractional system maturation is shown relative to this scale. Fetal serum TSH and thyroid hormone levels (T₄, T₃ and rT₃) are shown in the upper or lower panels. Pancreatic, hypothalamic and serum TRH concentrations are plotted in the middle panel.
presumably stimulated by placental oestrogens. However, fetal serum free \( T_4 \) concentrations also increase during the last half of gestation, suggesting a progressive maturation of thyroid hormone \( (T_4) \) secretion during this period (Figure 2) (Klein et al, 1982).

**MATURATION OF EXTRAHYPOthalamic AND HYPOTHalamic TRH CONCENTRATIONS AND PITUITARY TRH RECEPtORS**

TRH has been detected in the human fetal hypothalamus as early as 10–12 weeks’ gestation and levels have been thought to increase progressively to term. TRH concentrations are high in fetal rat and sheep serum at midgestation and are derived largely from extrahypothalamic tissues (Engler et al., 1981; Polk et al., 1988a; Fisher, 1989b). In newborn rats and midgestation fetal sheep, TRH levels are higher in the placenta, pancreas and gut tissues than in the hypothalamus; in the sheep, hypothalamic TRH concentrations increase only during the last third of gestation. Hypothalamic ablation experiments, TRH antiserum administration and studies of TRH augmentation of propylthiouracil-induced increases in serum TSH in neonatal rats have suggested that pituitary TSH release becomes TRH dependent between five and ten days of age (equivalent to about 0.5 of thyroid system ontogenesis in the human fetus) (Strbak and Greer, 1979; 1981; Theodoropoulous et al., 1979a).

Extrahypothalamic tissue TRH levels and serum TRH concentrations are thyroid hormone suppressible in the midgestation ovine fetus, suggesting that extrahypothalamic TRH in the mammalian fetus may be involved in the regulation of TSH release from the fetal pituitary prior to the maturation of hypothalamic TRH secretion (Polk et al., 1988a). Pancreatic TRH levels are high in the human fetal and neonatal pancreas and plasma and there is a generally reciprocal pattern of ontogenesis of pancreatic and hypothalamic TRH in the human fetus (Figure 2) compatible with this hypothesis (Kovusalo, 1981; Perelman et al., 1981; Leduque et al., 1986). There is limited data regarding maturation of human fetal TRH receptors. Studies in the rat have demonstrated TRH receptors at the time of birth (equivalent to midgestation for the human thyroid system development (Banerji and Prasad, 1982). TRH will stimulate TSH secretion in the premature infant born at 20 weeks’ gestation, indicating the presence of pituitary TRH receptors; the TSH response to exogenous TRH is quantitatively similar in premature and term infants (Jacobsen et al., 1977).

**MATURATION OF THYROID SYSTEM CONTROL**

**The pituitary thyrotroph cell**

A primary focus of thyroid system control is the pituitary thyrotroph cell (Figure 3). One major factor modulating pituitary TSH release is TRH. The binding of TRH to its receptor increases intracellular free calcium concent-
Figure 3. Details of the pituitary thyrotroph cell. TRH binding to its receptor on the cell membrane stimulates a second messenger system, probably inositol triphosphate/diacylglycerol, which acts to increase intracellular free calcium (Ca\(^{++}\)) by mobilization from intracellular pools and by increasing transport via cell membrane calcium channels. Increased free Ca\(^{++}\) stimulates TSH release. T3 derived from T4 deiodination or via membrane transport binds to the nuclear receptor to inhibit TSH α- and β-chain mRNA production. T3 also inhibits TRH receptor binding.

Intimations both by mobilization from intracellular pools and by increasing transport via cell membrane calcium channels (Gershengorn, 1986). The increased cytoplasmic calcium activates TSH release. Cyclic AMP (cAMP) may play a role: both TRH and cAMP increase calcium inflow into the thyrotroph and mobilize calcium from intracellular pools. However, cAMP does not appear to be the primary mediator of the TRH effect; rather, stimulation of membrane inositol phospholipid metabolism with production of inositol triphosphate and diacylglycerol as second messengers may be involved (Gershengorn, 1986). In addition to secretion, TRH stimulates glycosylation of TSH but does not increase production of the messenger RNA (mRNA) species for either the α or β subunits of TSH (Lippman et al, 1986).

The second major factor controlling pituitary TSH secretion is thyroid hormone. T3 binding to its nuclear receptor in the thyrotroph inhibits both α- and β-chain TSH mRNA production and T3 decreases TRH receptor binding (Morley, 1981; Hinkle and Goh, 1982; Gershengorn, 1986). Intrapituitary T3 is derived from T4 by local monodeiodination as well as by transport from serum. The T4 outer ring monodeiodinase (5'MDI) in pituitary tissue is a type II enzyme, in contrast to the type I hepatic 5'MDI. The pituitary deiodinase differs from the hepatic enzyme in having a lower \(K_m\),
being insensitive to propylthiouracil (PTU) inhibition and being suppressed rather than induced by thyroid hormone (Cheron et al., 1980; Polk et al., 1988b).

The hypothalamic–pituitary axis

TRH is widely distributed in the mature hypothalamus and highly concentrated in the median eminence. Synthesis and release of hypothalamic TRH into the pituitary portal vascular system is regulated by several factors including environmental temperature, neurotransmitters, and adrenal and thyroid hormones (Figure 4) (Morley, 1981). Both peripheral and preoptic neuronal thermal receptor systems monitor environmental and core body temperature. These thermal receptors modulate preoptic neuronal outflow to the paraventricular nucleus and other TRH-synthesizing neurones in the hypothalamus, thus modulating TRH secretion (Morley, 1981). Decreasing environmental or core body temperature increases TRH output and

![Figure 4. Hypothalamic control of TRH production and TSH release. The level of TRH in pituitary portal blood provides a tonic stimulus to TSH release. Environmental temperature is an important factor modulating TRH release. TRH production in the hypothalamus is stimulated by cold via thermal receptors in the preoptic area of the anterior hypothalamus. Neural input from skin thermal receptors similarly stimulates TRH production. SRIF and dopamine can inhibit TSH release via actions at the pituitary level. See text for details.](image-url)
increases the tonic level of TSH release. SRIF and dopamine can inhibit TSH release by actions at the pituitary level and these inhibitory transmitters contribute to central nervous system modulation of TSH release. Administration of SRIF antiserum to adult rats increases basal TSH levels and potentiates the TSH response to cold, suggesting a modulatory role for SRIF in TSH control (Oliver et al., 1982). There is evidence that serotonin may affect TSH release in the adult rat, but this does not seem to be the case in other species. Noradrenaline (norepinephrine) also may be inhibitory. Glucocorticoids inhibit TSH release via hypothalamic pathways, but the mechanism is not known. The exact roles of TRH and non-TRH regulatory factors in TSH control are not clear. Inhibitory factors probably also play a role in the diurnal variation in TSH secretion and in the thyroid reactions to stress (Morley, 1981).

Maturation of hypothalamic–pituitary control

The events of pituitary thyrotroph and hypothalamic maturation have been studied to various degrees in the rat and sheep and to a lesser extent in humans (Fisher et al., 1977; Roti, 1988; Fisher, 1989b); these data are summarized in Tables 1 and 2. The TSH response to TRH is present at birth in the rat and early in the third trimester in man and sheep (Jacobsen et al.,

Table 1. Maturation of the pituitary thyrotroph.

<table>
<thead>
<tr>
<th>Event</th>
<th>Time of appearance*</th>
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<tbody>
<tr>
<td>TRH receptor present</td>
<td>Man</td>
</tr>
<tr>
<td>TSH response to TRH</td>
<td>&lt;0.6</td>
</tr>
<tr>
<td>T₃ 5'-deiodinase activity present</td>
<td>&lt;0.8</td>
</tr>
<tr>
<td>T₃ receptor present</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>T₃ stimulation of T₃ receptor binding</td>
<td>&lt;0.7</td>
</tr>
<tr>
<td>TSH synthesis</td>
<td>&lt;0.3</td>
</tr>
<tr>
<td>T₃ inhibition of TSH synthesis and release</td>
<td>&lt;0.65</td>
</tr>
<tr>
<td>T₃ inhibition of pituitary TRH binding</td>
<td>&lt;0.6</td>
</tr>
<tr>
<td>TRH effect on TSH glycosylation</td>
<td>&gt;0.6</td>
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</tbody>
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* Fractional proportion of thyroid system maturation time; complete maturation time (= 1.0) is 10 months in man, 5½ months in sheep and 50 days in rats.

Table 2. Maturation of hypothalamic control of TSH release.

<table>
<thead>
<tr>
<th>Event</th>
<th>Time of appearance*</th>
</tr>
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<tbody>
<tr>
<td>TRH synthesis</td>
<td>Man</td>
</tr>
<tr>
<td>TRH stimulation of TSH</td>
<td>&lt;0.3</td>
</tr>
<tr>
<td>T₃ inhibition of TRH synthesis</td>
<td>&gt;0.8</td>
</tr>
<tr>
<td>TSH response to cold</td>
<td>&lt;0.6</td>
</tr>
<tr>
<td>Somatostatin inhibition of TSH secretion</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td>Dopamine inhibition of TSH secretion</td>
<td>&gt;1.0</td>
</tr>
</tbody>
</table>

* Fractional proportion of thyroid system maturation time; complete maturation time (= 1.0) is 10 months in man, 5½ months in sheep and 50 days in rats.
The pituitary iodothyronine 5’-monodeiodinase (M5’-DI) enzyme which allows for intrapituitary conversion of T4 to T3 is present at birth in the rat and has been measured during the mid-third trimester in the fetal sheep pituitary (Cheron et al., 1980; Segall-Blank et al., 1982). Pituitary nuclear T3 receptors are present in near-adult concentrations in the five-day-old neonatal rat and PTU inhibition of pituitary T3 receptor binding was observed at 14 days of postnatal age (about 0.7 of thyroid system maturation) (Coulombe et al., 1983). The capacity for T3 modulation of TSH synthesis and release is present at five days of age in neonatal rats and as early as 26 weeks’ gestation in the human premature infant (Walker et al., 1980; Delange et al., 1984). T3 inhibition of TRH receptor binding has been observed in the ten-day-old neonatal rat (Hinkle and Goh, 1982). A TRH effect on glycosylation of TSH in vivo was not observed at five days, but was easily observed by 56 days in the rat (Gyves et al., 1987). These results indicate that the pituitary cellular mechanisms for control of TSH release are present by 0.4–0.6 of thyroid system maturation; this corresponds to the mid or late second trimester of development in the human fetus.

The TSH response to cooling has been observed in the sheep fetus at 106 days’ gestation (0.6 of system ontogenesis) (Fraser et al., 1985). In the human neonate a T4 response to extraterine cooling has been observed at term (Fisher and Odell, 1969); moreover, the TSH response of premature infants to extraterine exposure presumably also reflects a cold response (Fisher and Klein, 1981). In the neonatal rat, a TSH response to cold is not observed until three to four weeks of age (Theodoropoulos et al., 1979b; Frankel and Lange, 1980). SRIF inhibition of TRH-stimulated TSH secretion has been demonstrated in the neonatal rat using SRIF antiserum as early as three days of age (0.4 of thyroid development) (Oliver et al., 1982); however, no effect on basal TSH levels was observed during the first 60 days of age (Oliver et al., 1982). Exogenous SRIF inhibits the TSH response to TRH in neonatal lambs (Sack et al., 1977). Finally, dopamine receptor blockade in neonatal rats had no effect on serum TSH levels during the first six weeks of life and no effect in human infants at birth (Becu and Libertun, 1982; Roti et al., 1983).

In the human fetus, the period of increasing serum T4 concentrations between 20 and 35 weeks’ gestation marks the critical period of maturation of thyroid system control. Hyponoamidemia is common in preterm infants and the degree is inversely proportional to gestational age; the prevalence in infants <30 weeks’ gestation is 50% (Hadeed et al., 1981; Klein et al., 1982; Delange et al., 1984). Preterm newborns with hyponoamidemia demonstrate low serum TSH values and normal TSH and T4 responses to TRH, observations characteristic of a state of hypotalamic hypoamidemia (Hadeed et al., 1981; Delange et al., 1984). The data of Table 1 suggest that TRH binding and post-receptor responsiveness are reasonably well developed at this time and are not contributing to the immature function. The progressive increase in hypotalamic TRH concentrations observed in sheep and rats would support the hypothesis of progressively maturing hypotalamic TRH secretion during this period.
There is a progressive maturation of T₃ negative feedback control of pituitary TSH release during the last half of thyroid system development. In the neonatal rat this is reflected by a progressive decrease in the dose and serum level of T₃ necessary to suppress serum TSH or inhibit the serum TSH response to TRH (Walker et al., 1980). Pituitary T₃ receptors and pituitary T₄-to-T₃ conversion capacity are not rate limiting (Table 1). Thyroid hormones also increase T₃ receptor binding in the developing pituitary gland (Coulombe et al., 1983). These data suggest that the maturation of pituitary sensitivity to negative feedback suppression of TSH by T₃ is a complex process involving: (a) a T₃-induced decrease in TRH receptors, (b) a T₃-induced augmentation of T₃ receptor binding, and (c) T₃ inhibition of hypothalamic TRH synthesis (Hinkle and Goh, 1982; Coulombe et al., 1983; Segerson et al., 1987).

Finally, there is a progressive maturation of the thyroid gland responsiveness to TSH. This has been most clearly demonstrated in the fetal sheep, where a progressive increase in the T₄ response to TRH-stimulated endogenous TSH release has been observed during the third trimester of gestation (Klein and Fisher, 1980). This maturation probably involves: (a) an increase in TSH glycosylation which augments the biological potency of TSH, and (b) an increased thyroid follicular cell response to TSH. The progressive increase in serum free T₄ levels in the human fetus in the face of relatively elevated but constant serum TSH concentrations would support this hypothesis (Klein et al., 1982) (Figure 2).

**THYROIDAL AUTOREGULATION**

The mature thyroid follicular cell can modify iodine transport or uptake relative to dietary iodine intake, exclusive of variations in serum TSH (Penel et al., 1987). The developing thyroid gland lacks this autoregulation mechanism and is susceptible to iodine-induced inhibition of thyroid hormone synthesis (Castaing et al., 1979; Theodoropoulos et al., 1979c). Thyroid follicular cell autoregulation of iodide transport develops after 36 to 40 weeks of gestation in the human fetus (about 18 days of age in the rat) (Castaing et al., 1979; Theodoropoulos et al., 1979c). This maturation involves the capacity of thyroid follicular cells to decrease iodide trapping and thus prevent the high intracellular iodide concentrations that produce the Wolff-Chaikoff (iodide) blockade of hormone synthesis. The responses of thyroid follicular cells to an increase in plasma iodide availability are complex and include both structural and functional alterations: membrane transport of iodide is inhibited, as are adenylate cyclase activity, thyroglobulin iodination and thyroglobulin turnover (Penel et al., 1987). The membrane autoregulatory mechanism is not well characterized but preliminary evidence suggests that the failure of the immature thyroid follicular cell to exhibit autoregulation relates to the absence or reduced iodination of an 8000 to 10000 Mr protein component of the thyroid follicular cell (Price and Sherwin, 1986; Sherwin and Price, 1986).
MATURATION OF TISSUE METABOLISM

Thyroid hormones in the vascular compartment are derived from thyroid secretion as well as peripheral tissue metabolism of T₄. T₄ (tetraiodothyronine) is derived exclusively from thyroid gland synthesis and secretion. The triiodothyronines T₃ (3,5,3′-triiodothyronine) and rT₃ (3,3′,5′-triiodothyronine), in contrast, are produced largely in peripheral tissues via deiodination of T₄ (Chopra et al, 1978; Kaplan, 1983; 1986; Leonard and Visser, 1986). Only small amounts of T₃ and rT₃ are secreted from the thyroid gland – perhaps 10–20% and <5%, respectively, of the total T₃ circulating in euthyroid adults on a normal iodine intake.

Thyroid hormones undergo several types of biochemical transformations in tissues (Burger, 1986). These include deiodination, side-chain metabolism and conjugation (with sulphate or glucuronide). Sequential monodeiodination of the iodothyronines is the most important pathway of thyroid hormone metabolism. The first step in thyroxine deiodination involves the removal of an iodine atom from either the outer ring (the β or hydroxyl ring) of the T₄ molecule to form T₃, or from the inner ring (the α or tyrosyl ring) to form rT₃ (Figure 5). T₃ is the most biologically active iodothyronine, having three to four times the metabolic potency of T₄; rT₃ has a very low affinity for the thyroid nuclear receptor and is essentially inactive. Further monodeiodinative steps sequentially degrade the triiodothyronines to the diiodothyronines (T₂), then to monoiodothyronines, and finally to the noniodinated thyronine skeleton.

Two types of β or outer-ring iodothyronine 5′MDI have been described (Kaplan, 1986; Leonard and Visser, 1986). Type I 5′MDI activity, predominantly expressed in liver and kidney, is a high $K_m$ enzyme, inhibited by PTU and stimulated by thyroid hormone. Type II 5′MDI activity, predominantly located in brain, pituitary and brown adipose tissues, is a low $K_m$ enzyme insensitive to PTU and inhibited by thyroid hormone. Type I 5′MDI activity in liver, kidney and perhaps muscle probably accounts for most of the peripheral deiodination of T₄. The type I enzyme also deiodinates rT₃ to T₂, and rT₃ is the preferred substrate for the enzyme. It thus has an important degradative function deiodinating rT₃ to T₂ in addition to its role in activating thyroxine (to T₃). The type II 5′MDI acts primarily to increase intracellular levels of T₃ in the brain and pituitary and is important to brown adipose tissue function during the immediate postnatal period.

Both the type I and the type II outer-ring 5′MDI are present in the third trimester fetus. In sheep, during the last third of gestation, hepatic type I 5′MDI (T₄ to T₃ conversion) activity increases about 100%, and brain type II 5′MDI activity increases about 50% (Polk et al, 1986; 1988b). Both deiodinase species in the fetal sheep are thyroid hormone responsive but in opposite directions (Polk et al, 1988b). Brain type II activity is responsive (increases with hypothyroidism) throughout the final third of gestation, whereas hepatic type I 5′MDI activity becomes thyroid hormone responsive (activity decreases with hypothyroidism) only during the final weeks of gestation. The type II deiodinase probably plays an important role in providing intracellular T₃ to those tissues which are dependent on T₃ during
Figure 5. Initial monodeiodination steps in the metabolism of T₄. The upper panel shows the T₄ molecule with the outer or hydroxyl ring and the inner or tyrosyl ring each containing two iodine atoms. β-Ring monodeiodination at the 5' carbon produces 3,5,3'-triiodothyronine or T₃; α-ring monodeiodination at the 5 carbon produces 3,3',5'-triiodothyronine or reverse T₃ (rT₃). In the fetus the predominant deiodinative pathway is inner ring monodeiodination to produce rT₃ (lower panel). β-Ring monodeiodination is limited. See text for details.

fetal life (pituitary, brain and brown fat), while the activity of the type I enzyme to provide increased serum T₃ levels increases only during the final weeks of gestation and during postnatal life. Similar data are available for the developing rat (Harris et al., 1978; Silva and Leonard, 1985).

The inner (tyrosyl) ring iodothyronine 5'MDI (type III 5'MDI) is present in fetal liver, brain, skin and placenta (Chopra et al., 1975; Wu et al., 1978; Kaplan, 1983; 1986). This enzyme system catalyses the conversion of T₄ to rT₃ and T₃ to 3,3'-diiodothyronine. Studies of the ontogenesis of this enzyme system in rodents and sheep have shown a predominance of type III enzyme activity in the fetal period, particularly in placenta and fetal mem-
branes, and it is believed that this activity accounts for the high levels of rT₃ in the fetal serum and amniotic fluid (Figure 3) (Kaplan, 1983; 1986). However, the persistence of high circulating rT₃ levels for several weeks in the human newborn indicates that T₄ to rT₃ conversion in nondecidual tissues is also important to the maintenance of high circulating rT₃ levels (Oddie et al, 1979).

In the human fetus, serum T₃ levels are very low before 30 weeks of gestation. After this time, T₃ concentrations increase to a mean of about 50 ng/dl near term (Fisher and Klein, 1981). During the first four to six hours after birth, serum T₃ levels increase another three to six-fold (Figure 3). In the human fetus, serum rT₃ concentrations exceed 250 ng/dl early in the last trimester and decrease steadily to term. In contrast to T₃ concentrations, serum rT₃ remains essentially unchanged in term infants during the early neonatal period, gradually falling to levels characteristic of infancy during the second week (Fisher and Klein, 1981). The patterns of ontogenesis of the iodothyronine deiodinases have not been studied in man, but the patterns of change in iodothyronine metabolism in the human fetus presumably reflect similar patterns of change in 5’MDI activity as observed in the fetal sheep and developing rat. These would include a predominance and early appearance of type III MDI activity in liver, placenta, fetal membranes and perhaps skin, low levels of type I MDI activity in liver and kidney with an increase in the perinatal period, and the earlier appearance of type II MDI activity in brain, pituitary and brown adipose tissue.

In fetal and newborn sheep, serum T₃ levels increase gradually during the week immediately preceding parturition (the prenatal T₃ surge) and then abruptly increase during the first two to four hours after birth (the postnatal surge) (Klein et al, 1978; Nwosu et al, 1978). The prenatal T₃ surge correlates with the prenatal increase in fetal serum cortisol concentrations. Moreover, cortisol administration to the near-term sheep fetus increases fetal serum T₃ concentrations over a period of two to three days (Thomas et al, 1978), and cortisol administration or the onset of spontaneous labour is associated with a marked increase in hepatic conversion of T₄ to T₃ in vitro (Wu et al, 1978). In the human fetus the prenatal increases in serum T₃ occur over several weeks (Figure 3) and may be induced by cortisol. Osathanondh et al (1978) reported that dexamethasone administration to women at term (3–48 h before elective caesarean section) increases cord-blood serum T₃ concentrations three-fold.

The alanine side-chain of the iodothyronines may undergo decarboxylation or transamination. Although the acetic acid derivatives of thyroxine have some biological activity in vitro, their rapid degradation in vivo limits their physiological significance. Pyruvate and lactate derivatives also have been isolated, both with minimal biological activity (Burger, 1986). Thyroid hormones may also be excreted as both free or glucuronide or sulphate conjugates in urine and stool; the conjugated forms can undergo hydrolysis and enterohepatic recirculation. In general, gut excretion accounts for less than 15% of the total amount of metabolized T₃ or T₄ after birth (Burger, 1986). There is little information regarding side-chain cleavage or conjugation reactions in the fetus.
ONTOGENESIS OF THYROID HORMONE RECEPTORS AND ACTIONS

With the advent of widespread neonatal screening programmes for congenital hypothyroidism it has become clear that athyrotic human infants are born with few if any signs of their hypothyroid state (Fisher and Klein, 1981; Letarte and LaFranchi, 1983; Fisher, 1985). Length, weight and head circumference are normal for gestation age and IQ and neurological function are normal in the vast majority of such infants treated during the first 45 days of life. Selected intrauterine effects of the hypothyroid state are observed in the human neonate, including an increased serum TSH and variable retardation of bone maturation. Transient neonatal hypothermia also may occur. These manifestations of the neonatal hypothyroid state are mild and subtle, however, and the classic manifestations of cretinism only develop during the early months of life. Deficiencies in thermogenesis and metabolism characteristic of the hypothyroid state in adults are then observed, as well as profound effects on growth and development, including deficient statural growth and growth of lean body mass, delayed epiphyseal maturation, deficiencies of brain growth and development, and delayed development and maturation of a variety of organs and tissues (Fisher, 1985).

A number of investigators have studied the timing of appearance of thyroid hormone effects in developing rodents. These altricial species (in particular the rat and mouse) are born relatively immature with an undeveloped hypothalamic–pituitary–thyroid system and are poikilothermic (Fisher and Dussault, 1974). They have a pattern of thyroid system development analogous to that of humans, except that the late ontogenic events occur after birth (Fisher et al, 1977). Thyroid nuclear receptor maturation has been characterized in several tissues including brain and liver (Perez-Castillo et al, 1985). There appear to be two thyroid hormone receptor genes in the rat (Lazar et al, 1988; Hodin et al, 1989). They are expressed with variable abundance in most tissues. The α-gene receptor is most abundant in brain, hypothalamus, skeletal muscle and brown fat; the β-gene receptor is prominent in liver, kidney, heart, brown fat and pituitary gland. Receptor binding activity is detectable at the time of birth in most rat tissues; it is greatest in brain tissue, but increases gradually during the first postnatal weeks in most other tissues (Perez-Castillo et al, 1985).

The ontogenesis of a variety of thyroid actions have been characterized in these altricial species (Fisher and Polk, 1989). These include tissue thermogenesis, hepatic enzyme activities, β-adrenergic receptor binding (in the heart, lung and brain), body weight gain, carcass and muscle growth, skeletal maturation, skin maturation (including eye opening and tooth eruption) and brain maturation. Influences of thyroid status on pituitary and serum growth hormone concentrations, submandibular gland nerve growth factor (NGF) and epidermal growth factor (EGF) concentrations, EGF levels in skin, eye, kidney and urine, and EGF receptor binding in skin and liver have also been characterized during development. Some of these effects represent thyroid hormone actions on specific gene products medi-
ated via thyroid hormone receptor control of gene transcription. These include effects on hepatic enzymes, pituitary growth hormone synthesis, and EGF or NGF receptor binding in skin and liver. Other thyroid hormone actions represent complex events, the mechanisms of which are not yet clear. Such actions include thyroid hormone stimulation of growth, skeletal maturation and brain development. Recent reviews of the role of thyroid hormones in these events are available (Schwartz, 1983; Walker, 1984; Fisher and Polk, 1989).

All of these effects in the rodent appear in the neonatal period, in general during the second and third postnatal weeks (Figure 6). Thyroid hormone stimulation of pituitary growth hormone content, skin and eye EGF levels, and skin EGF receptor binding appear during the first few days of life.

Effects on various aspects of brain maturation and liver enzymes have been described between three and ten days of age. Thyroid hormone effects on thermogenesis and kidney and urine EGF concentrations appear during the second week. The stimulatory effects of thyroid hormone on lung and heart adrenergic receptors, submandibular gland NGF and EGF concentrations, and liver EGF receptor binding appear during the third and fourth weeks of extrauterine life. Thus, much of the variation in timing of appearance of thyroid hormone actions in the rodent relates to maturation of events beyond the hormone-receptor binding step. What these postreceptor mechanisms represent for a nuclear receptor is not yet clear but they may

Figure 6. The pattern of maturation of hepatic thyroid nuclear receptors, serum T₃ concentrations (and production) and selected thyroid hormone effects in the developing rodent. The time of appearance of thyroid hormone actions varies among and within tissues and may be delayed relative to the time of appearance of nuclear receptors and circulating T₃. See text for details.
DEVELOPMENT OF THE THYROID

relate to the methylation status of responsive genes (Wong et al, 1989).

The sheep (in contrast to the rodent) is a precocial species born homeo­

thermic with relatively advanced brain maturation (Fisher et al, 1977). The

pattern of thyroid system ontogenesis is comparable in rodents and sheep; however, in sheep most of thyroid system maturation occurs in utero. Thus, the period of central nervous dependency on thyroid hormones in this species begins during the second trimester of gestation. Thyroid hormone receptor binding in brain tissue is present at newborn levels in the fetal sheep during the late second trimester (Ferreiro et al. 1987; Polk et al, 1989). In contrast, thyroid hormone receptor binding in liver matures during the third trimester, reaching adult levels at term.

The timing of appearance of thyroid hormone actions in the developing sheep is quite variable from tissue to tissue. Effects on carcass growth, bone and skin maturation and brain maturation first become detectable in the thyroidectomized fetus at 90–110 days’ gestation (McIntosh et al, 1983; Fisher and Polk, 1989). Fetal thyroidectomy at 99–107 days in the sheep significantly increases type II iodothyronine 5’MDI activity in fetal brain tissue but does not decrease type I activity in liver (Polk et al, 1988b). In contrast, after fetal thyroidectomy at 129–132 days, both activities are altered; liver type I iodothyronine 5’MDI activity decreases and brain type II activity increases (Polk et al, 1988b). The ontogeny of other specific thyroid hormone effects during development have also been described. Atrial natriuretic factor (ANF) levels in adult cardiac tissue are known to be thyroid-hormone responsive. A significant reduction in ANF levels in fetal cardiac atria was observed when fetal sheep were thyroidectomized at 115 days and measurements conducted at 130 days (Castro et al, 1988). Decreased cardiac output at birth also has been demonstrated in fetal sheep thyroidectomized at 128–129 days (Breall et al, 1984). Thyroid hormone effects to increase malic enzyme activity and increase EGF receptor binding in liver do not occur after late fetal thyroidectomy but are observed after thyroidectomy of the two-month-old neonatal lamb (D. H. Polk and D. A. Fisher, unpublished data). The effect of thyroidectomy to decrease β-adrenergic receptor (BAR) binding in heart and lung tissue in the sheep was not observed after late fetal thyroidectomy, whereas a decrease in BAR binding activity did occur after early neonatal (one to two days) thyroidectomy (Padbury et al, 1986). Moreover, T₃ treatment significantly increased BAR binding in thyroidectomized neonates (Padbury et al, 1986).

These results in the developing sheep, although less comprehensive, resemble those in developing rodents (Figure 7). In both species relatively early effects of thyroid hormones on various parameters of brain development appear at 0.5–0.6 of thyroid system development. Thyroid effects on skin and growth parameters also appear relatively early, whereas selected effects on heart, lung, kidney and liver are delayed. Also in the sheep, as in the rodent, the delay in appearance of selected thyroid hormone actions, such as the effects on liver malic enzyme and liver EGF receptor, are not accounted for by the delayed appearance of thyroid hormone nuclear receptors (Polk et al, 1989). This also applies to the delayed appearance of lung β-adrenergic receptors. Thus, the timing of maturation of thyroid hormone
actions is variable in both species and relates both to the ontogenesis of nuclear thyroid hormone receptors and to the maturation of post-nuclear receptor response mechanisms.

The TSH response to hypothyroxinaemia appears relatively early in both rodent and sheep species. In adult animals this negative feedback effect of thyroid hormones on pituitary TSH release is mediated via nuclear thyroid receptors in pituitary thyrotroph cells as well as modulation of hypothalamic TRH synthesis (Segerson et al., 1987). In neonatal rodents and fetal sheep, TRH is present in relatively high concentrations in extrahypothalamic tissues, including pancreas, gut and placenta, before TRH appears in significant concentration in hypothalamic tissue (Engler et al., 1981; Polk et al., 1988a). Moreover, in fetal sheep, TRH in these extraneural sites and in serum is thyroid hormone responsive, increasing markedly in thyroidectomized animals (Polk et al., 1988a). These data suggest that at this time of development (0.4–0.5 of thyroid system ontogenesis) pituitary and serum TSH are dependent on extrahypothalamic TRH. These extrahypothalamic TRH production sites presumably express nuclear thyroid hormone receptors, and TRH synthesis in these tissues may be thyroid hormone responsive at this early period of development.

The human fetus is intermediate between the altricial rat and precocial sheep at birth, being homeothermic but with a relatively immature central nervous system. There is limited information about the ontogenesis of

**Figure 7.** The pattern of maturation of hepatic thyroid nuclear receptors, serum T₃ levels (and production) and selected thyroid hormone effects in the developing sheep. The time of appearance of thyroid receptors and thyroid hormone effects is variable among and within tissues. In this species, as in the rat, selected thyroid effects are delayed relative to the appearance of nuclear receptors and circulating T₃ levels. See text for details.
thyroid nuclear receptors in the human fetus. Bernal and Pekonen (1984) studied human fetal tissue from 10–18 weeks estimated gestational age. There was an increase in brain T₃ binding capacity from low levels at 10 weeks to levels in the 350–500 fmol/mg DNA range by 16–18 weeks. Liver, heart and lung receptors were measured in one or two fetuses each at 16–18 weeks, with receptor concentrations in the 200–600 fmol/mg DNA range. Gonzales and Ballard (1981) assessed thyroid hormone receptor binding in human fetal lungs obtained between 13 and 19 weeks’ gestation. A single class of high-affinity receptors was characterized, with an increase in receptor concentration from 200–300 fmol/mg DNA at 12–13 weeks to 350–500 fmol/mg DNA at 16–19 weeks. There are no data in term infants, but these available data suggest significant concentrations of thyroid hormone nuclear receptors in human fetal brain, liver, heart and lung by mid-gestation.

As indicated earlier, development of the human fetus is largely independent of thyroid status. However, some systems are responsive to thyroid hormones at term. The TSH response to hypothyroxinaemia appears relatively early in human development, as in the rodent and sheep. This early TSH response may relate to increased extrahypothalamic as well as hypothalamic TRH production in response to hypothyroxinaemia; relatively high concentrations of TRH have been reported in the human fetal pancreas during the first half of gestation (Leduque et al., 1986). Bone maturation is also responsive to thyroid hormone in some human fetuses; one-third to one-half of athyroid human infants are born with a modest retardation of epiphyseal maturation (Letarte et al., 1980; Fisher and Klein, 1981). Quantitatively this amounts to two to six weeks and is quickly corrected with treatment. There also may be some delay in cranial fontanelle closure in athyroid infants at birth. Linear bone growth and weight gain become thyroid responsive soon after birth, and by six weeks of age a significant reduction in growth can be detected in most athyroid infants. Athyroid infants generally show no metabolic signs of hypothyroidism at birth, but a few infants manifest prolonged jaundice and/or hypothermia in the neonatal period.

Brain development in infants with congenital hypothyroidism has been studied carefully during the nearly 15 years since neonatal screening for congenital hypothyroidism was introduced in the USA. Several hundred infants have been evaluated at six to eight years of age with Stanford Binet or WISC intelligence tests and with careful neurological and hearing testing (Glorieux et al., 1985; New England Congenital Hypothyroid Collaborative, 1985). The mean and range of IQ values in these infants have been similar to simultaneously studied control infants, and to date there has been no evidence of consistent neurological abnormalities or learning disorders in properly treated infants. A few patients with low IQ values at six to eight years have been reported retrospectively at birth to have had higher neonatal serum TSH levels, lower serum T₄ values, delayed bone maturation and/or treatment delayed beyond 45 days (Rovet et al., 1987; Glorieux et al., 1988). These correlations have been observed only in programmes in which the initial dose of replacement thyroxine was relatively low (<10 μg/kg...
daily) (Fisher and Foley, 1989). Current information suggests that a dose of replacement thyroxine of 10–15 µg/kg daily begun before 45 days of age will assure normal brain maturation in infants with congenital hypothyroidism (Fisher and Foley, 1989). This indicates that any brain dysfunction due to thyroid hormone deficiency in utero is corrected by early adequate treatment at birth. The time of onset of a thyroid hormone effect on brain development in human infants, therefore, would appear to be the perinatal period (three to four weeks before or after birth).

NEONATAL ADAPTATION

In general, much of fetal thyroid system development is preparatory, providing for the relatively large amounts of thyroid hormones required for normal postnatal development. The production of active thyroid hormones is markedly increased in association with the events of parturition (Figure 3). During the first hours after birth, there is an abrupt increase in circulating T4 and T3 levels, coincident with an increase in serum TSH concentration (Fisher and Klein, 1981). The initial increases in circulating thyroid hormone levels are due largely to increased hormone secretion from the thyroid gland (Fisher and Odell, 1969; Polk et al, 1986). However, the TSH surge (which is likely a response to the thermal stimuli coincident with birth) can be obtunded in the newborn sheep by warm bath immersion without complete inhibition of the increments in T3 or T4 (Fisher et al, 1977). Other substances which might modulate the acute increases in circulating thyroid hormones include catecholamines. A postnatal increase in serum catecholamine concentrations also occurs at the time of parturition (Padbury et al, 1985) and the thyroid gland is adrenergically innervated. Stimulation of thyroidal adrenergic receptors may augment TSH-induced changes in the T4/T3 ratio of secreted thyroid hormones.

Because thyroid hormone binding globulin concentrations remain relatively constant throughout the newborn period, free T4 and T3 levels rise abruptly after birth in association with increases in hormone production rates. The cold-stimulated TSH surge is short-lived, and the decrease in TSH which follows during the 72–96 h after birth is due to feedback inhibition by T4 at both hypothalamic and pituitary levels (Fisher and Klein, 1981; Roti, 1988). The serum TRH concentration is elevated in cord blood and falls in the days following birth. A clear increase in the serum TRH value coincident with the increase in TSH after parturition has not been reported, but the parallel increases in both TSH and prolactin levels in the early hours after birth support the view that the TSH surge is mediated by TRH (Fisher and Klein, 1981; Roti, 1988). Thyroid hormone levels in the newborn gradually decrease to adult levels by about one month of age. The high level of circulating rT3 characteristic of the fetus persists following birth, gradually declining to the adult range by four to six weeks of age (Oddie et al, 1979).

The metabolic significance of the neonatal thyroid hormone surge is not entirely clear. Physiological processes known to be modulated by thyroid
hormone in adults, such as thermogenesis and cardiovascular responses, clearly are important in the transition from intrauterine to extrauterine life, and it is tempting to link these processes with the changes in thyroid hormone metabolism which occur during this transition. Several studies have attempted to establish such a link. Brown adipose tissue (BAT) is the major site for newborn thermogenesis (Polk, 1988). Hypothyroidism induced during the final weeks of gestation is associated with impaired BAT thermogenesis, largely due to the effects of T4 on BAT iodothyronine 5'MDI activity and mitochondrial uncoupling protein (thermogenin) (Polk et al., 1987). However, obtundation of the postnatal T3 surge (by acute thyroidectomy in newborn sheep) does not accentuate transient neonatal hypothermia, indicating that the prenatal T4 level is more important in neonatal thermogenesis than the early postnatal T3 surge.

A similar relationship between thyroid system function and neonatal cardiovascular adaptation has been described in neonatal sheep; normal fetal thyroid function in the final weeks of gestation is required for the increases in myocardial performance associated with the transition to extrauterine life. However, obtundation of the acute increase in serum T3 at birth does not alter neonatal cardiovascular adaptation (Breall et al., 1984). These observations in the sheep support the view that the level of thyroid function during the final weeks of gestation is more important than the neonatal increases in T3 and T4 for successful neonatal transition in the sheep. The situation in the human neonate may be somewhat different since the human neonate is less mature than the sheep and fetal hypothyroidism is not associated with prominent clinical manifestations. However, mild transient hypothermia may occur in the human neonate and it is likely that BAT thermogenesis is thyroid hormone dependent to some degree.

THYROID DISORDERS IN THE NEONATE

Transient hypothyroxinaemia

As described earlier, cord blood T4 concentrations increase progressively with gestational age. Thus, all premature infants have some degree of hypothyroxinaemia (Hadeed et al., 1981; Delange et al., 1984). The prevalence of serum T4 values <6.5 μg/dl is approximately 50% in infants delivered before 30 weeks' gestation, and the prevalence in all premature infants is approximately 25%. Infants with hypothyroxinaemia (T4 <6.5 μg/dl) also have low levels of free T4 (Hadeed et al., 1981; Delange et al., 1984). However, the levels are not as low as in neonates with congenital primary hypothyroidism, and are similar to values in normal adults; term infants have free T4 concentrations two-fold greater. Basal serum TSH values are normal, as is the response to TRH. These features characterize a state of hypothalamic (or tertiary) hypothyroidism or immaturity that represents a normal stage of thyroid system development. The hypothyroxinaemia is transient, correcting spontaneously (over four to eight weeks) with progressive maturation and does not require treatment.
Transient primary hypothyroidism

This disorder, characterized by low serum T\textsubscript{4} and high TSH concentrations, is more common in Europe than in North America (Delange et al, 1984). The prevalence in Belgium is approximately 20% of premature infants, with the incidence inversely proportional to gestational age. Cord blood T\textsubscript{4} and TSH levels are normal in these infants; the primary hypothyroid state develops during the first one to two weeks of extrauterine life and is superimposed on the usual state of transient hypothyroxinaemia characteristic of prematurity. Affected infants develop hypothyroxinaemia, and serum TSH concentrations increase into the primary hypothyroid range. Urinary iodine excretion and thyroid iodine content are reduced, suggesting that the acquired primary hypothyroid state is the result of limited iodine substrate relative to the increased thyroid hormone needs of early infancy. The hypothyroidism is transient, but may persist for two to three months so that treatment with either iodine or thyroid hormone is recommended.

Transient hypothyroidism may occur in term infants exposed to iodine, especially in areas of iodine deficiency (Delange et al, 1984; Fisher, 1987; 1989a). In iodine-sufficient areas, including North America and Japan, the prevalence of transient hypothyroidism is low, perhaps 1 in 50,000 infants. In these areas, the mechanism is likely to be iodine overload, exposure to antithyroid medications, or placental transfer from mother to fetus of TSH-receptor blocking antibodies which produce a hypothyroid state lasting until the maternal immunoglobulin is degraded.

Premature infants are particularly susceptible to iodine-induced hypothyroidism; exposure may occur in utero or during the neonatal period (Fisher, 1987; 1989a). These infants may develop a goitre, and are characterized by low serum T\textsubscript{4} and free T\textsubscript{4} concentrations and high levels of TSH. Treatment of these infants at birth is indicated and should be continued for two to three months or until the goitre disappears.

The low T\textsubscript{3} syndrome

In the normal preterm infant, thyroid function parameters in the perinatal period, although qualitatively similar to those in term infants, are relatively obtunded (Fisher, 1987; 1989a). The early 30-min peak of the TSH surge and the 24–36 h postnatal T\textsubscript{4} peak progressively decrease in amplitude with decreasing gestational age. The early T\textsubscript{3} peak is also reduced in amplitude, and in small premature infants serum T\textsubscript{3} levels increase to values comparable to term infants only after several weeks. The high serum rT\textsubscript{3} values normalize by three to four weeks, as in term infants. These low postnatal serum T\textsubscript{3} levels in premature infants presumably reflect a reduced T\textsubscript{3} production rate, a result of a relatively reduced rate of hepatic T\textsubscript{4} to T\textsubscript{3} conversion.

Premature infants have an increased susceptibility to neonatal morbidity, including respiratory distress, trauma, intravascular haemorrhage, hypoxia, hypoglycaemia, hypocalcaemia and infection, as well as relative malnutrition. All of these factors tend to further inhibit hepatic type IMDI activity.
in the neonatal period and aggravate the extent of the low T<sub>3</sub> state (Fisher, 1987; 1989a). Serum T<sub>3</sub> values may remain low in these infants for one to two months; T<sub>4</sub> given to such infants increases rT<sub>3</sub> but not T<sub>3</sub> concentrations. Features of the low T<sub>3</sub> syndrome in the premature infant resemble those in older children or adults and include a low serum T<sub>3</sub> concentration, variable serum rT<sub>3</sub> levels, and normal or low total serum T<sub>4</sub> concentrations with free T<sub>4</sub> levels in the range of values for healthy premature infants of matched gestational age and weight. The low T<sub>4</sub> is due to low thyroxine-binding globulin (TBG) levels with or without an inhibitor of T<sub>4</sub> binding to TBG as described in adults with the low T<sub>3</sub> syndrome. Serum TSH concentrations are normal and no treatment is indicated.

**Thyroid dysgenesis**

Thyroid dysgenesis is the term used to describe infants with ectopic or hypoplastic thyroid glands or total thyroid agenesis. The prevalence is approximately 1 in 4000 newborns. Some thyroid tissue probably is present in 40–60% of these infants, so that they represent a spectrum of severity of thyroid hormone deficiency (Fisher, 1987; 1989a). Thyroid scanning and uptake tests may not be sensitive enough to detect small amounts of residual functioning thyroid tissue. In such infants, a normal or near-normal circulating level of T<sub>3</sub> in the face of a low T<sub>4</sub> value suggests the presence of residual thyroid tissue. A measurable level of serum thyroglobulin also indicates the presence of thyroid tissue.

The pathogenesis in most cases is unclear (Fisher, 1987; 1989a). Thyroid dysgenesis is more prevalent in female than in male infants, the female-to-male ratio being approximately 2:1. The vast majority of cases are sporadic, but a few familial cases have been described. The prevalence is increased in infants with Down’s syndrome. A seasonal incidence with a peak during summer months has been reported from Japan. In rare instances, thyroid dysgenesis has occurred in association with maternal autoimmune thyroiditis; the disorder in these instances has been attributed to transplacentally acquired antithyroid factors. However, there usually is no correlation between thyroid dysgenesis and the presence of maternal autoimmune thyroiditis or circulating thyroid autoantibodies. Recently, TSH-blocking antibodies or cytotoxic antibodies have been reported in both maternal and newborn blood of cases of sporadic congenital hypothyroidism and the authors suggest a role for such immunoglobulins in the pathogenesis of congenital hypothyroidism.

Infants usually are asymptomatic in the neonatal period and develop signs of hypothyroidism during the early weeks of life (Fisher, 1987; 1989a). Few infants are detected by clinical criteria before the chemical screening diagnosis. Most affected infants have low serum T<sub>4</sub> and high TSH concentrations in cord blood or in filter-paper blood spots collected at two to five days of age. An additional group of infants have been identified who have T<sub>4</sub> levels in the low-normal or normal range with increased TSH values. These infants usually have ectopic thyroid tissue on scanning and may constitute 15–20% of infants with congenital thyroid dysgenesis. An additional group, perhaps
comprising 5% of the total, have a delayed increase in serum TSH and thus can be missed by the screening programmes.

**Thyroid dyshormonogenesis**

Several hereditary defects in thyroid hormone synthesis or metabolism have been described (Fisher, 1987; 1989a). The combined prevalence of these disorders is approximately 1 in 30,000–40,000 births. Female infants only slightly outnumber males. Congenital goitre may occur at birth in association with thyroid dyshormonogenesis, but more commonly develops during the early months and years of extrauterine life. Thyroid radio-iodine uptake is normal or increased in these infants (except for the rare infant with a defect in iodine-concentrating ability) in contrast to most infants with thyroid dysgenesis. These infants present with low $T_4$ and high serum TSH concentrations, but some may be partly compensated with low serum $T_4$, normal $T_3$ and elevated TSH values. A few may have normal $T_4$ and $T_3$ concentrations maintained at the expense of an elevated TSH level.

**Diagnosis and treatment of congenital hypothyroidism**

Routine neonatal screening for congenital hypothyroidism is ongoing throughout the industrialized world (Fisher, 1987; 1989a). Filter-paper blood spots are collected in the neonatal period and eluates utilized for measurement of TSH concentration. Infants with elevated TSH concentrations are reported as presumptive-positive for primary hypothyroidism. In North America, screening for hypothyroidism is conducted using follow-up TSH measurement of those samples with $T_4$ values in the lower ten percentile. Primary TSH screening is predominant in Europe and Japan. All infants with suspected hypothyroidism by screening tests require follow-up measurements of serum $T_4$ and TSH. Confirmed cases should have a bone age determination (knee films to detect decreased size or absence of the distal femoral/proximal tibial epiphyses), and a nuclear thyroid scan to identify those infants with thyroid dysgenesis. The absence of serum thyroglobulin indicates thyroid agenesis or a defect in thyroglobulin synthesis. Infants with abnormal thyroid hormone levels and normal radio-iodide scans have thyroid dyshormonogenesis until proved otherwise. Work-up of these infants is usually delayed two to three years, until after the period of brain dependency on thyroid hormones. Transient hypothyroidism due to TSH receptor antibody can be detected by measurement of receptor antibody in maternal and/or neonatal blood when there is a maternal history of autoimmune thyroid disease.

Treatment is begun promptly with $L$-thyroxine in all infants. The initial dose is 10–15 $\mu$g/kg body weight; full term infants can be begun on 50 $\mu$g daily (Fisher and Foley, 1989). The dose of replacement thyroxine is adjusted to produce serum $T_4$ values in the upper half of the normal range during the first two to three years of life. Some infants with congenital hypothyroidism have an alteration in the pituitary threshold for TSH secretion and demonstrate persistently elevated TSH levels in the face of
normal or high-normal levels of serum T₄. Relatively large doses of T₄ may be required to normalize the serum TSH level and the TSH response to TRH in such infants; the resulting high serum T₄ concentrations may produce signs of mild thyroid toxicity (Fisher, 1987; 1989a). Thus, the serum T₄ level is the most important criterion of dosage adjustment. In general, after three to four months of treatment the serum TSH should be less than 20μU/ml.

**Deficient TSH secretion or effect**

Permanent congenital hypothyroidism resulting from defective TSH stimulation of thyroid hormone secretion can result from various abnormalities in TSH synthesis and metabolism (Fisher, 1987; 1989a). Several syndromes have been described including hypothalamic hypothyroidism with TRH deficiency or insensitivity (or both), isolated TSH deficiency, familial panhypopituitarism, congenital absence of the pituitary, and panhypopituitarism with absence of the sella turcica. The combined prevalence is approximately 1 in 70,000–100,000 births. Infants with hypothalamic (tertiary) hypothyroidism resulting from TRH deficiency have persistently low serum T₄, T₃ and free T₄ values with low or normal range serum TSH concentrations, and have a normal or prolonged TSH response to exogenous TRH. Infants with pituitary TSH deficiency have low serum T₄, T₃ and free T₄ levels associated with low or unmeasurable serum TSH concentrations, and do not manifest a TSH response to TRH. Affected infants will be missed by screening programmes which rely on measurements of TSH. Treatment of these infants includes T₄ replacement as for infants with primary hypothyroidism. Some of these infants may have associated pituitary hormonal defects requiring additional therapies.

**Neonatal thyrotoxicosis**

Neonatal Graves' disease is an uncommon disorder occurring in perhaps 1 in 40,000 neonates (Fisher, 1987; 1989a). Usually the disease is due to transplacental passage of thyroid-stimulating TSH receptor antibody (TSA) from a mother with active or inactive Graves' disease or Hashimoto's thyroiditis. In a recent report all women with TSA titres (measured by stimulation of cAMP in human thyroid slices) exceeding 500% of control values delivered thyrotoxic infants whereas those with lower titres delivered euthyroid infants. Neonatal thyrotoxicosis is manifested by irritability, tachycardia, poor weight gain, thyroid enlargement and exophthalmos. Hepatosplenomegaly and thrombocytopenia also have been observed. Arrhythmias, cardiac failure and death may occur if the thyrotoxicity is severe and the treatment is inadequate; mortality approaches 25% in disease severe enough to be diagnosed. The onset of symptoms and signs may be delayed as long as seven to ten days after birth due to the presence of antithyroid drugs acquired from the mother and to the fact that there is an increased production of active T₃ shortly after birth which gradually aggravates the thyrotoxic state. The diagnosis is confirmed by measuring high levels of T₄, free T₄ and T₃ and a low TSH value in postnatal blood;
cord-blood values may be normal or near normal, while levels at two to five
days may be markedly increased. Neonatal Graves' disease resolves spontane­
ously as maternal TSA in the newborn is degraded; the half-life is approxi­
mately 12 days and the usual clinical course of neonatal Graves' disease extends for 3 to 12 weeks.

The treatment of neonatal thyrotoxicosis includes antithyroid drugs and
iodide to decrease thyroid hormone secretion (Fisher, 1987; 1989a). These
drugs have additive effects with regard to inhibition of hormone synthesis; in
addition, iodide will rapidly inhibit hormone release. With adequate
therapy a favourable response should be observed within 24–36 h. If not, the
dose of antithyroid drug and iodide can be increased by 50%. Sedatives and
digitals may be helpful, as well as adrenal corticosteroids in anti­
inflammatory doses and propranolol. Radiographic contrast agents also may
be useful in treatment (100 mg/day or 0.5 g every three days) either alone or
in conjunction with antithyroid drug treatment.

SUMMARY

The fetal hypothalamic–pituitary–thyroid axis develops autonomously of
maternal influence. System ontogenesis begins with the appearance and
histological development of the thyroid and pituitary glands followed by
development of the hypothalamus and the pituitary portal vascular system.
Hypothalamic–pituitary control of thyroid function matures during the last
half of human fetal development. Thyroid hormones undergo several types
of biochemical transformations in tissues, including deiodination, side-chain
metabolism, and conjugation with sulphate or glucuronide. Enzyme­
mediated monodeiodination is the most important pathway. The first step in
T₄ metabolism is either outer-ring monodeiodination to active T₃ or inner­
ring monodeiodination to inactive rT₃. Most T₄ is metabolized to rT₃ in fetal
tissues and/or placenta and rT₃ is the major circulating T₄ metabolite in the
fetus. Selective tissues, such as brain, can monodeiodinate T₄ to T₃, and this
T₃ is available for local action. Nuclear thyroid hormone receptors mature at
different times in different tissues. Receptors appear earlier in brain than in
liver and local T₃ production and action may be important in fetal brain
development. Most thyroid hormone actions, however, appear in the perinatal
period, and infants with thyroid agenesis appear normal at birth and
develop normally with prompt neonatal diagnosis and treatment.

Premature infants, particularly those less than 30–32 weeks' gestational
age, have an immature thyroid system and manifest a state of transient
hypothalamic–pituitary TSH deficiency. This does not require treatment.
Infants with primary hypothyroidism, either due to thyroid dysgenesis or to
thyroid dyshormonogenesis, by contrast, require prompt diagnosis and
treatment. Rarely an infant is born with permanent TSH deficiency with or
without other pituitary hormone deficiencies. These infants also require
prompt treatment. Mothers with thyroid disease or a history of thyroid
disease and with IgG autoantibodies to thyroid gland TSH receptors may
deliver infants with hypothyroidism or hyperthyroidism due to transplacen-
tal passage of the receptor-blocking or receptor-stimulating autoantibodies. These infants also require careful evaluation and management.

REFERENCES


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