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Role of Thyroid Hormones in Human and Laboratory Animal Reproductive Health

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The highly conserved nature of the thyroid gland and the thyroid system among mammalian species suggests it is critical to species survival. Studies show the thyroid system plays a critical role in the development of several organ systems, including the reproductive tract. Despite its highly conserved nature, the thyroid system can have widely different effects on reproduction and reproductive tract development in different species. The present review focuses on assessing the role of thyroid hormones in human reproduction and reproductive tract development and comparing it to the role of thyroid hormones in laboratory animal reproduction and reproductive tract development. The review also assesses the effects of thyroid dysfunction on reproductive tract development and function in humans and laboratory animals. Consideration of such information is important in designing, conducting, and interpreting studies to assess the potential effects of thyroid toxicants on reproduction and development. *Birth Defects Res B* 68:479–491, 2003. Published 2003 Wiley-Liss, Inc.[†]

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INTRODUCTION

The thyroid gland and thyroid hormones are central to human development. Animal and human studies indicate thyroid hormones play a role in cardiovascular, nervous, immune, and reproductive system development and function (Jannini et al., 1995; Metz et al., 1996; Krassas, 2000). Specifically, numerous studies and reviews have evaluated the effect of thyroid hormones on proper development and function of human reproductive tracts (Jannini et al., 1995; Krassas, 2000). Additionally, numerous studies have focused on evaluating the role of thyroid hormones on reproductive tract development in rodent models. However, there is limited information available in the current literature discussing the comparative reproduction physiology of humans and laboratory animals and the role of thyroid hormones in reproduction and reproductive tract development among species. The present review will discuss (1) similarities and differences in thyroid gland function and the role of thyroid hormones in humans and laboratory animals, (2) the role of thyroid hormones in normal reproductive tract development and function in humans and laboratory animals, and (3) the effects of thyroid hormone dysfunction in humans and laboratory animals on reproductive tract development and function. Consideration of such information is important in designing, conducting, and interpreting studies to assess the potential effects of thyroid toxicants on reproduction and development.

NORMAL THYROID GLAND FUNCTION

General

Located in the neck, just below the larynx, the thyroid gland in humans is a brownish-red organ having two lobes connected by an isthmus and consists of low cuboidal epithelial cells arranged to form small sacs known as follicles. The two principle thyroid hormones are thyroxine (T4 or L-3,5,3′,5′-tetraiodothyronine) and triiodothyronine (T3 or L-3,5,3′-triiodothyronine). These hormones are composed of two tyrosyl residues linked through an ether linkage and substituted with four or three iodine residues, respectively. T3 is the biologically

Abbreviations: FSH, follicle stimulating hormone; GD, gestation day; GnRH, gonadotropin-releasing hormone; GTT, gestational transient thyrotoxicosis; hCG, human chorionic gonadotropin; H-P-T, hypothalamic-pituitary-thyroid; IGF-1, insulin-like growth factor-1; Km, Michaelis-Menton constant; LH, leuteinizing hormone; rT3, reverse T3; SHBG, sex hormone binding globulin; T3, triiodothyronine or L-3,5,3′-triiodothyronine; T4, thyroxine or L-3,5,3′,5′-tetraiodothyronine; TBG, thyroxine-binding globulin; TBPA, thyroid-binding prealbumin; TPO, thyroid peroxidase; TR, thyroid receptor; TRH, thyrotrophin releasing hormone; TSH, thyroid stimulating hormone; TTR, transthyretin; UDP-GTs, uridine diphosphatase glucuronosyl transferases.

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active hormone and T4, the major thyroid hormone that is secreted from the thyroid gland, is considered a precursor or prohormone. Deiodination of T4 in peripheral tissues (e.g., liver) leads to production of T3 (which has two iodines on the inner ring and one iodine on the outer ring of the molecule) and reverse T3 (rT3; which has one iodine on the inner ring and two iodines on the outer ring of the molecule); rT3 has no known biological activity (Fig. 1).

The gross structure of the thyroid gland in laboratory animals, two lobes connected by an isthmus, is similar to that described for humans. However, there are morphological differences in the follicles. Compared to the follicles in primates, which are large with abundant colloid and follicular cells that are relatively flattened (low cuboidal), rodent follicles are relatively small and often surrounded by cuboidal epithelium (U.S. EPA, 1998). It is proposed that the morphological differences, in part, are due to differences in thyroid hormone turnover (see below). The structures of T3 and T4 are the same in laboratory animals and humans.

The pattern of thyroid development among rodents, sheep, and humans is similar. However, the timing of various perinatal developmental events differs among species. Rats are born relatively immature. Thus, late developmental events that occur in utero in humans occur postnatally in rats. Thyroid development in sheep, comparatively, appears to occur mostly in utero. The developmental life stage at which thyroid receptor (TR) binding first occurs is one example of the differences among species in thyroid development. TR binding occurs mid- to late-gestation (average gestation is 3 weeks) in rats, during the latter two-thirds of gestation (average gestation is 20.5 weeks) in sheep, and between gestational weeks 10 and 16 (average gestation is 39 weeks) in humans (Fisher and Brown, 2000).

Thyroid Hormone Synthesis, Secretion, and Transport

Thyroid gland follicles play a critical role in compartmentalizing the necessary components for thyroid hormone synthesis. Thyroglobulin, a glycoprotein that comprises 134 tyrosine residues and is one of the starting molecules for thyroid hormone synthesis, fills the follicles. Epithelial cells of the thyroid gland have a sodium-iodide symporter on the basement membranes that concentrates circulating iodide from the blood. Once inside the cell, iodide is transported to the follicle lumen. Thyroid peroxidase (TPO), an integral membrane protein present in the apical plasma membrane of thyroid epithelial cells, catalyzes sequential reactions in the formation of thyroid hormones. TPO first oxidizes iodide to iodine, then iodinates tyrosines on thyroglobulin to produce monoiodotyrosine and diiodotyrosine. TPO finally links two tyrosines to produce T3 and/or T4.

In rodents and humans, the peptide linkage between thyroid hormones and thyroglobulin is enzymatically

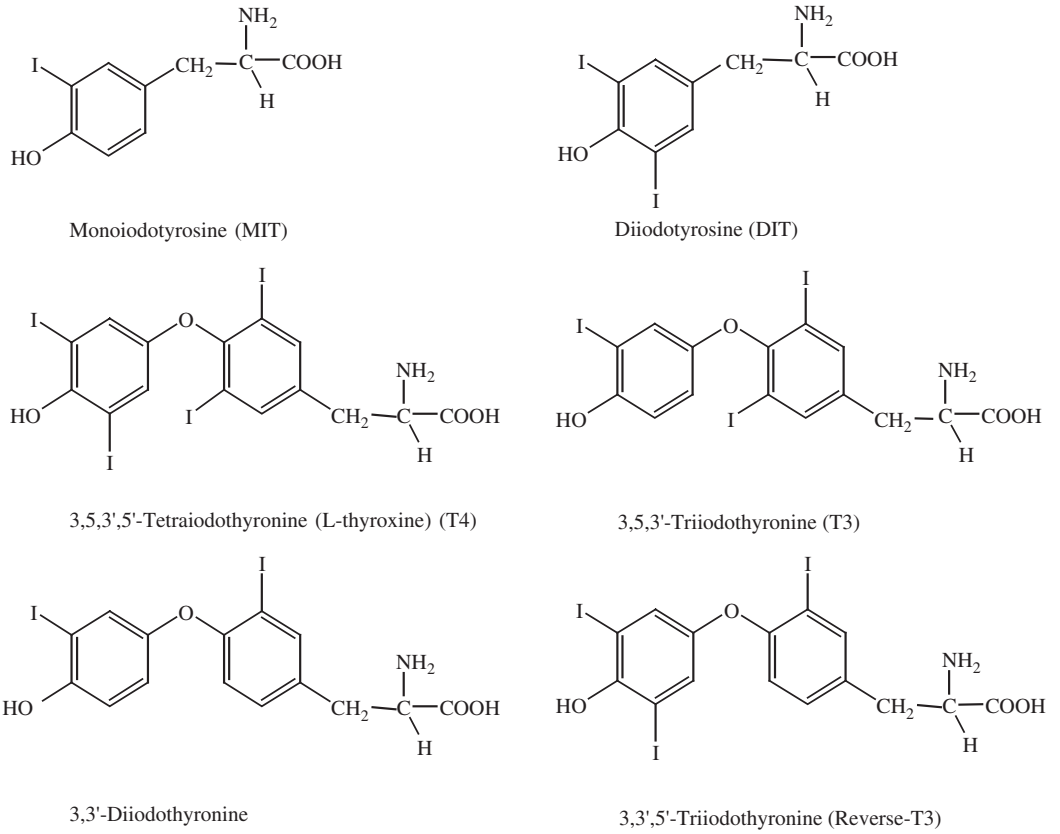

Fig. 1. Structural formulas of thyroid hormones and related compounds.

cleaved. Thyroid hormone-containing colloid then is internalized at the apical surface of the thyroid epithelial cells by endocytosis. Lysosomes, which contain hydrolytic enzymes, fuse with the endosomes and release the hormones. Free thyroid hormones diffuse into blood where they reversibly complex with liver-derived binding proteins for transport to other tissues.

The chemical nature of these liver-derived binding proteins and the proportion of T3 and T4 binding to these proteins vary considerably among animal species. T3 and T4, in different species, can reversibly bind to three different liver-derived binding proteins: thyroxine-binding globulin (TBG), transthyretin (TTR; also called thyroid-binding prealbumin, TBPA), and albumin (Robbins, 2000). Lipoproteins also bind a small fraction of the available thyroid hormones. TBG is a monomer that is a member of the serine protease inhibitor (serpin) superfamily of proteins (Flink et al., 1986; Robbins, 2000). TTR is a tetramer that is composed of four identical subunits that are each composed of 127 amino acids (Power et al., 2000). Albumin is a monomer that has substantial sequence homology with α-fetoproteins and vitamin D-binding proteins (Robbins, 2000). There is little overall amino acid sequence homology between the three binding proteins.

In normal human plasma, the T4 binding distribution is roughly 80% bound to TBG, 15% to TTR, and 5% to albumin and lipoproteins. For T3, human plasma binding distribution is 90% bound to TBG and the remainder to albumin and lipoproteins. T4 and T3 binding distribution correlates with affinity of the hormones for the binding proteins; T4 and T3 affinity for TBG is much higher than their affinities for albumin or TTR (Kaneko, 1989; Robbins, 2000).

As noted above, thyroid hormones also interact with TBG, TTR, and albumin in rodents and other animals. There is moderate to high amino acid sequence homology of the proteins among species (Imamura et al., 1991; Tsykin and Schreiber, 1993; Power et al., 2000). For example, TTR sequence homology among humans and other mammals, birds, reptiles, and fish ranges from 67 to 92% (Power et al., 2000). Compared to humans, albumin appears to be the major binding protein in adult rodents. Rodents contain a gene that can encode the TBG protein, but it is expressed at very low levels in adult animals (Vranckx et al., 1990; Rouaze-Romet et al., 1992; Tani et al., 1994). Developmental studies show TBG protein levels increase during the early postnatal period in rodents, but then decline to very low levels by weaning and remain low through the remainder of the animal's life span (Savu et al., 1987, 1991; Vranckx et al., 1990). As in humans, T3 and T4 have higher affinity for TBG than TTR or albumin in rodents. However, since TBG is expressed at low levels, almost all T4 and T3 bind to TTR and albumin in adult rodents (Keneko, 1989).

Experimental manipulations (e.g., increases in sample volume) have enabled the detection of TBG levels in different rodent species and have shown there are differences in TBG levels among different species of adult rodents. Trends in rat TBG levels appear to closely mimic those seen in humans, whereas trends in mice TBG levels appear to be opposite of what is seen in humans. For example, TBG levels are higher in adult female rats and humans when compared to adult male rats and humans. In contrast, TBG levels are higher in adult male mice when compared to adult female mice (Vranckx et al., 1990). Another example is seen when evaluating TBG levels during pregnancy. TBG levels increase in humans and rats during pregnancy, while TBG levels decrease in mice during pregnancy (Savu et al., 1989). The basis for this observed species difference during pregnancy is unclear. However, steroid-induced alterations in TBG synthesis or clearance are proposed to play a role.

Thyroid stimulating hormone (TSH), which is secreted by the anterior pituitary gland, regulates thyroid hormone synthesis and secretion in humans and laboratory animals. Thyrotrophin releasing hormone (TRH) is secreted by the hypothalamus and regulates pituitary TSH secretion. Control of circulating concentrations of thyroid hormone is regulated by negative feedback loops within the hypothalamic-pituitary-thyroid (H-P-T) axis (Scanlon and Toft, 2000). In general, blood concentrations of thyroid hormones above normal levels inhibit the release of TRH and TSH. When thyroid hormone serum levels are decreased, TRH and TSH release is stimulated. Increased TSH levels are associated with increased thyroid cell proliferation and stimulation of T3 and T4 production (Fig. 2).

Physiological Effects of Thyroid Hormones

The mechanism of cellular T3 uptake is an area that continues to be under study. Cellular entry of T3 through a carrier-mediated process is one proposed mechanism of action (Hennemann et al., 2001). In vitro studies show the presence of specific T3 and T4 binding sites/carriers in different laboratory animal and human tissues (Hennemann et al., 2001). An alternative mechanism of cellular transport is the presence of selective and specific interaction of thyroid hormone binding proteins with cell surface receptors. Reports have noted the presence of receptors for TBG and TTR on some cells (Robbins, 2000). The function of these receptors is unclear, but it is proposed they could be involved in targeting thyroid hormones to specific subcellular sites. Potential species and sex differences in cellular T3 uptake are currently not defined.

Upon entry into the cell, T3 is transported to the nucleus for interaction with TR. Results of current studies suggest a combination of mechanisms (diffusion, cytosolic binding proteins, interaction with cytosolic receptors) play a role in transporting T3 from the cytosol to the nucleus. Species and sex differences in intracellular transport of T3 are not completely understood currently.

TR function as hormone-activated transcription factors and act by modulating gene expression. Similar to other nuclear receptors, the TR consists of a transactivation domain, a DNA-binding domain, and a ligand-binding and dimerization domain (O'Shea and Williams, 2002). TR bind DNA in the absence of hormone, usually leading to transcriptional repression. Hormone binding is associated with a conformational change in the receptor that leads to transcriptional activation. Mammalian TR (TRα and TRβ) are encoded by two genes. The encoded mRNAs are alternatively spliced to produce nine mRNA isoforms (O'Shea and Williams, 2002). Studies indicate that of the nine expressed TR in humans, only four

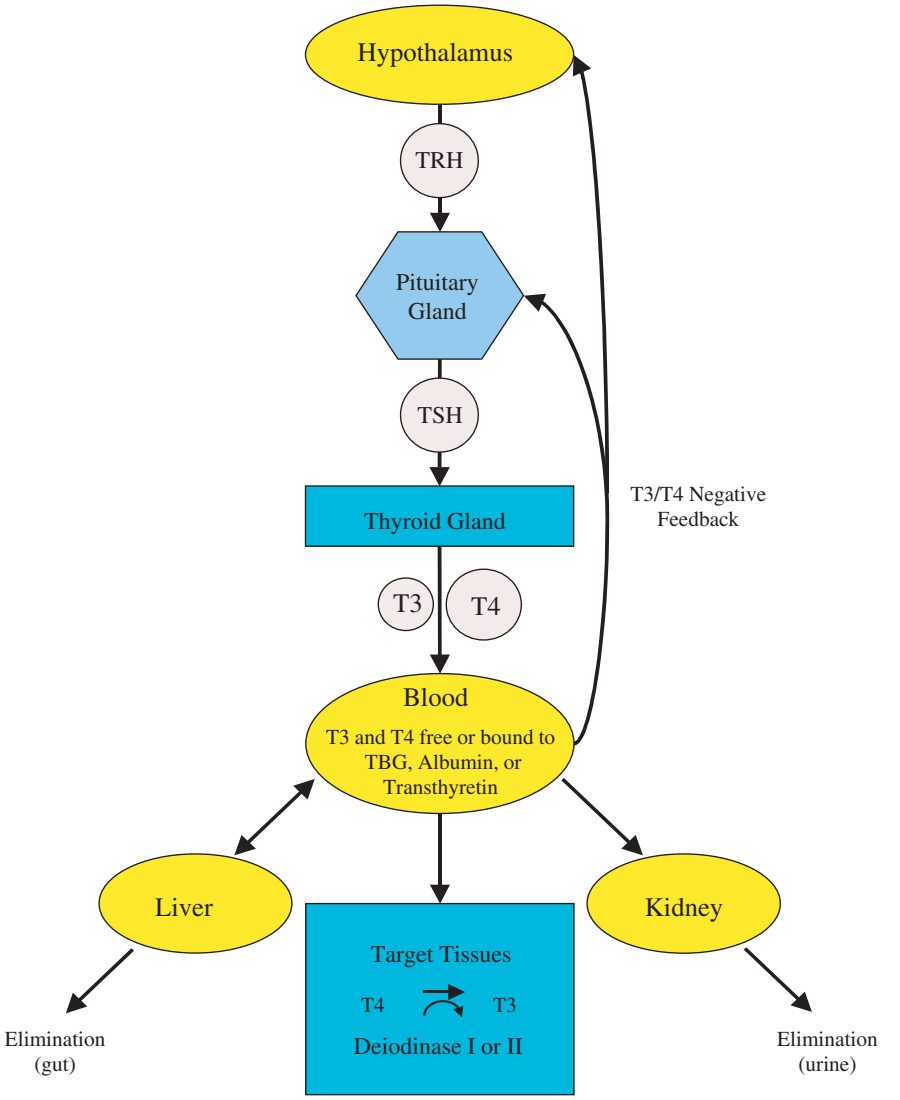

Fig. 2. Thyroid system diagram.

appear to bind to T3: TRα1, TRβ1, TRβ2, and TRβ3 (Harvey and Williams, 2002). Homologs to these receptors also appear to be expressed in rodents (O'Shea and Williams, 2002). TRα2, which is encoded by the TRα gene, fails to bind T3 and acts as a weak antagonist in vitro. TRα3, ΔTRα1, and ΔTRα2 are encoded by the TRα gene and act as dominant negative antagonists. The ΔTRβ3, encoded by the TRβ gene, also lacks the DNA binding domain and is a potent repressor in vitro. These receptors are developmentally regulated and are present in characteristic concentration ratios in various adult tissues (Oppenheimer and Schwartz, 1997; Harvey and Williams, 2002).

The primary functions of T3 are to regulate carbohydrate and protein metabolism in all cells. Thus, changes in T3 can affect all organ systems of the body with profound effects on the cardiovascular, nervous, immune, and reproductive systems. In the developing animal and human, the thyroid regulates growth and metabolism and plays a critical role in tissue development and differentiation. For example, T3 affects perinatal development of α-adrenergic receptors and is important for cardiac β-adrenergic receptor development (Metz et al., 1996; Tan et al., 1997). T3 also may interact with and modulate the action of other hormonal systems such as growth hormones and steroids.

Metabolism and Excretion of Thyroid Hormones

Thyroid hormone activity can be regulated by three separate enzymatic pathways: deiodination, glucuronidation, and sulfation. Deiodination in humans is typically associated with production and metabolism of T3 and plays a major role in metabolism of thyroid hormones.

Approximately 80% of the intracellular production and metabolism of thyroid hormones proceeds by sequential enzymatic removal of iodine from the molecules (Kelly, 2000). Type I and type II deiodinases, which remove iodine from the 5′ position on thyroid hormones, convert

Table 1
Properties of Deiodinases Present in Laboratory Animals and Humans

Property	Deiodinase Type I (5 and 5′ deiodinase activity)	Deiodinase Type II (5′ deiodinase activity)	Deiodinase Type III (5 deiodinase activity)
Limiting Km	0.5 μM	1–2 nM	5–20 μM
Reaction catalyzed	T4 to rT3 or T3	T4 to T3	T4 to rT3 T3 to T2
Inhibitors	Thiouracils, iopanoate, halogenated aromates, propranolol	Iopanoate, flavonoids, high T4 levels, rT3	Iopanoate, flavonoids
Tissue distribution	Thyroid, kidney, liver, euthyroid pituitary, CNS, skeletal muscle, placenta	CNS, pituitary, brown adipose tissue, placenta	Almost all tissues except liver, kidney, thyroid, pituitary; high in rat fetus
Hyperthyroidism	Increase	Decrease	Increase
Hypothyroidism	Decrease	Increase	Decrease

T4 to T3 in peripheral tissues. Type I deiodinases also may remove iodine substituents from the 5 position on thyroid hormones, which leads to the formation of rT3 from T4. Approximately 85% of T3 in the blood is produced by the action of Type I deiodinase in a variety of organs (Crantz and Larsen, 1980). Type III deiodinases, which remove iodine from the 5 position on thyroid hormones, catalyze the conversion of T4 and T3 to rT3 and diiodothyronines (T2), respectively. T2 are in turn deiodinated to form monoiodothyronines. Deiodinase enzyme activity can be regulated by T3 and T4 levels and independently of the other deiodinases. Additional information on the deiodinases are found in Table 1 (Kelly, 2000; Kohrle, 2000).

Thyroid hormones are glucuronidated primarily by uridine diphosphatase glucuronosyl transferases (UDP-GTs) and excreted by the kidneys during ''Phase II metabolism.'' Three UDP-GT isoenzymes, which belong to the UGT1A gene subfamily, metabolize T3 and T4 in the rat. Types 1 and 2 glurcuronidate T4 and rT3, while type 3 glucuronidates T3. Glucuronidation is a major thyroid hormone metabolism pathway in laboratory animals and studies indicate that there are species- and gender-dependent variations in enzyme activity (Kelly, 2000). Glucuronidation normally is not a significant route of metabolism in humans, but may become important when T3 levels are increased (Findlay et al., 2000). UDP-GTs belong to the UGT1A family glucuronidate rT3 and T4 in humans (Findlay et al., 2000). UDP-GT activity can be modulated by numerous xenobiotics and the impact of long-term exposure to compounds that alter thyroid hormone glucuronidation pathways is currently unknown (Kelly, 2000).

Sulfation of T3 facilitates the metabolism of T3 by type I deiodinase enzymes; however, it is a poorly understood pathway of thyroid hormone metabolism. The sulfation pathway does not appear to contribute significantly to thyroid hormone metabolism in healthy humans, but the role of sulfation in thyroid hormone metabolism may increase when Type I deiodinase activity is decreased. Animal studies indicate that activation of the sulfation pathway inhibits T3 formation and increases degradation of T4 and rT3 to inactive metabolites (Kelly, 2000). However, T3-sulfate activity may be important in the human fetus. It is proposed that, in the absence of deiodination of T4, T3-sulfate serves as a source of fetal T3, where T3 is formed by tissue sulfatases and bacterial sulfatases in the intestine (Brucker-Davis, 1998).

Thyroid hormone half-life and TSH levels. The serum half-life of T4 and T3 in normal human adults is 5–9 days and 1 day, respectively. Comparatively, the serum half-life of T4 and T3 in rats is 0.5–1 and 0.25 days, respectively. The basis for the difference in half-lives is not completely understood, but it is proposed that the lack of high-affinity T4 binding proteins (e.g., TBG) in the adult rat plays a role. The lack of high-affinity T4 binding proteins in the rat is proposed to lead to a higher serum level of unbound T4, which is more susceptible to removal (e.g., metabolism, excretion; U.S. EPA, 1998). Higher production of rat T3, due to the short half-life, is postulated to be driven by high basal TSH levels. The higher production rate of TSH in rodents is proposed to play a role in differences in follicle morphology between rodents and humans. Studies by Dohler et al. (1979) also suggest that a number of other factors can contribute to and significantly alter the levels of and turnover of T3 and T4 in rats.

The basal level of TSH in rats is an area of some uncertainty. Several studies indicate that basal levels of TSH range from 1–4 ng/mL (Hiasa et al., 1987; McClain, 1989; Vansell and Klaassen, 2001). However, other citations indicate that basal rat TSH levels range between 50 and 200 ng/mL (U.S. EPA, 1998). It is proposed that these TSH levels are higher than those seen in humans.

In addition to species differences, sex differences in the thyroid hormone system exist in rats. TSH levels are approximately the same in men and women, but adult male rats have higher basal TSH levels than adult female rats. Additionally, the height of the thyroid follicles are approximately equivalent in both human sexes but are often greater in adult male rats than adult female rats (Capen, 1996).

ROLE OF THE THYROID HORMONES IN REPRODUCTION AND REPRODUCTIVE TRACT DEVELOPMENT

Normal function of the H-P-T axis is important in laboratory animal and human reproduction and development in both sexes. Thyroid hormones effects on reproductive function, fertility, and fetal development in

humans have largely been identified through adverse outcomes reported for individuals with thyroid dysfunction and through experimental manipulation of thyroid hormones in laboratory animals.

Reproductive Effects in Males

Humans. Normal thyroid hormone levels are important for maturation of the testes in prenatal, early postnatal, and prepubertal boys. Studies indicate that the major targets of T3-binding in the testis are the Sertoli cells. These cells, along with the gonocytes, comprise the seminiferous epithelium of the testis and are critical for normal sperm maturation (Jannini et al., 1995). In vitro studies suggest that T3 activation of TRα1 plays a role in testes differentiation and development (Jannini et al., 2000). T3 has been shown to increase glucose carrier units, insulin-like growth factor-1 (IGF-1), and inhibin; decrease aromatase activity and androgen binding protein; and inhibit the expression of Müllerian-inhibiting substance by Sertoli cells (Jannini, et al., 1995).

Laboratory animals. T3 affects testis maturation in the rat as described above for humans. TRα and TRβ are expressed in the testes of animals (Buzzard et al., 2000). It is proposed that TRα1 is the specific isoform of TR involved in testis function and development, and the main target of T3 is the Sertoli cell. Maximal Sertoli cell proliferation coincides with the maximal T3 binding capacity in the testis. Additionally, T3 plays a significant role in seminiferous epithelium differentiation (Jannini et al., 1995). Rodent studies also have demonstrated that T3 is important in the maturation of the Leydig cells in the interstitium of the testis. T3 is necessary to initiate the differentiation of mesenchymal cells into Leydig progenitor cells and works in concert with other hormones (e.g., leuteinizing hormone (LH), IGF-1) in the promotion of Leydig cell development (Mendis-Handagama and Ariyarante, 2001).

Data from deer, sheep, cattle, birds, and mink also suggest that T3 is a component of the neuroendocrine system regulating circannual (seasonal) cycles of reproductive activity in these species (Jannini et al., 1995). Although the mechanism is not known, it is postulated that T3 triggers cessation of reproduction at the end of the reproductive season since circulating T3 levels in deer rise at the time of seasonal transition to the nonbreeding state and thyroidectomy results in the absence of the seasonal regression of the testis.

Reproductive Effects in Females

Humans. The molecular mechanisms that affect female reproduction (including estrogen and androgen metabolism, sexual maturation, menstrual function, ovulation, fertility, and ability to deliver full-term infants) involve T3-induced modulation of hormone-induced transcription pathways and factors that affect hormonal status (Krassas, 2000). For example, T3 stimulates the production of sex hormone binding globulin (SHBG), a serum steroid-binding protein that can bind circulating testosterone, dihydrotestosterone, and estradiol. This stimulation provides a net increase in bound, circulating steroids (Krassas, 2000). Studies indicate that thyroid hormones have little to no effect on female reproductive tract development.

Numerous thyroid changes occur in the mother during pregnancy in response to the need to provide the fetus with thyroid hormones until the fetal H-P-T system is functional. For example, maternal thyroid gland is enlarged and iodide uptake is increased (Versloot et al., 1997). Additionally, estrogen levels in pregnant women stimulate expression of TBG in liver and induce roughly a doubling in serum concentrations. The observed TBG increase is concurrent with increases in total T3 and T4 serum concentrations (Karabinas and Tolis, 1998). This increase in TBG occurs during the first trimester and reaches a maximum at gestational weeks 20–24 (Karabinas and Tolis, 1998). Free thyroid hormone levels usually remain within the normal range in most women; however, free thyroid hormone levels may exceed the range during the first trimester due to the release of human chorionic gonadotropin from the placenta (hCG; see below).

Additional changes related to the thyroid system and thyroid hormone levels include decreased maternal serum iodide concentrations and increased T3-sulfate sources. In pregnant women, serum concentrations of iodide decrease due to increased renal clearance and transfer of iodide and iodothyronines to the fetus (Aboul-Khair et al., 1964). Placental transfer of iodide and monodeiodination of iodothyronines within the placenta provide iodide to the fetus especially as fetal thyroid hormone production increases in the second half of gestation. Increased loss of iodide and subsequent TSH stimulation of the thyroid gland causes maternal thyroid volume to increase 10–20% during pregnancy.

Fetal Thyroid System Development

Thyroid system development in the human fetus can be divided into three phases. Phase I, which includes initial development of the hypothalamus, the pituitary gland, and the thyroid gland, occurs between embryonic day 10 and gestational week 11. Follicular maturation and accumulation of iodide occurs by gestational week 11 (Fisher and Klein, 1981; Gillam and Kopp, 2001). TR are detectable in the brain by the 10th week of human gestation and the presence of thyroglobulin in the fetal thyroid and T4 in the brain is observed by the 11th week of human gestation (Gillam and Kopp, 2001). During Phase II (gestational weeks 10–35), maturation of the thyroid system is evident from a progressive increase in fetal serum TBG, TSH secretion, TR in the brain, and T3 levels (Fisher and Klein, 1981; Klein et al., 1982; Gillam and Kopp, 2001). Phase III takes place in the last trimester and postnatally. Maturation of H-P-T interaction and control characterizes this period of development. By the 4th postnatal week, maturation of the H-P-T system appears to be complete.

Development of the rat thyroid gland during pregnancy, which is approximately 3 weeks long, occurs in approximately the same phases and order as in humans. TR are detectable by gestation day (GD) 14 and thyroglobulin is first detected by GD 15 (Perez-Castillo et al., 1985; Kawaoi, 1987; Rodriguez et al., 1992;). Iodine uptake, TPO expression, TSH secretion, and thyroid hormone synthesis are first noted by GD 17 (Kawoi, 1987; Rodriguez et al., 1992). Unlike humans, rats are born during Phase II of maturation of the thyroid system. Therefore, maturation of H-P-T interaction and control

(Phase III) occurs postnatally in the rat and is complete by 4 weeks of age.

Despite similarities between species in the order of thyroid development, there are some significant differences. The fact that thyroid system maturation appears to occur at about 4 weeks in both species, differences in the life-span of humans (about 70 years) and rats (about 2 years) show that thyroid maturation occurs much earlier in overall development of humans. Additionally, rat fetal development is solely dependent upon maternal thyroid hormones until approximately GD 18 (of an approximately 21-day gestational period; Phase II); human fetal development is at least partially dependent upon maternal T3 until approximately 34 weeks gestation (of an approximately 266-day gestational period; Phase III; Fisher and Klein, 1981).

Laboratory animals. T3 levels affect estrous cycle regulation, behavior, pregnancy maintenance, fetal growth, and lactation in laboratory animals. Mating behavior (lordosis) stimulated in ovarectomized rodents by estradiol administration is inhibited by T3, suggesting that T3 may exert an inhibitory influence on estrogen-mediated reproductive behavior (Vasudevan et al., 2002). In addition, the thyroid gland is necessary for the transition to the anestrous state in some seasonally breeding animals. For example, in ewes T3 needs to be present at the end of the breeding season to initiate anestrous. T3, however, does not play a role in maintaining anestrous and the timing of the subsequent breeding season (Vasudevan et al., 2002). As in humans, pregnancy alters thyroid status rodents. Normal pregnancy results in a decrease in the total T4 and T3 present in animals that has been correlated to the decrease in free T4 levels seen in humans (Calvo et al., 1990). Also similar to humans, the thyroid gland enlarges during pregnancy. However, unlike humans, uptake of iodide decreases in pregnant rats and no changes were found in urinary excretion of iodide during the last days of gestation (Feldman, 1958; Versloot et al., 1997).

Role of the placenta. Studies show that the deiodinases present in the human placenta rapidly metabolize maternal T4 to T3 for use by the fetus with a significant amount of T4 still transferred to the fetus (Chan and Kilby, 2000). The placenta is freely permeable to iodide and TRH, but not to TSH. It is proposed that the maternal TRH provided to the fetus may have a role in regulating fetal thyroid function before complete maturation of the H-P-T system. Data indicate that TR isoforms are present in the placenta and expression of receptor proteins increases with fetal age (Chan and Kilby, 2000; Leonard and Koehrle, 2000).

Near the end of the first trimester in humans, the maternal serum concentration of hCG produced by the placenta is sufficient to partially stimulate the maternal H-P-T axis activity by binding to the TSH receptor. Activation of the TSH receptor by hCG leads to stimulation of T4 production, decreases in serum levels of TSH, and increases in free levels of T4, an effect that is exacerbated if more than one fetus is being carried. In approximately 2% of these cases, the degree of TSH depression and T4 stimulation may lead to gestational transient thyrotoxicosis (GTT) in the mother (Glinoer, 1997, 1998). In the majority of pregnancies, this effect is transient and the normalization of free T4 levels correlates with decreased hCG levels. Most clinical cases of GTT are very mild, presenting with symptoms of hyperthyroidism (e.g., weight loss, increased anxiety) and an increase in episodes of morning sickness.

THYROID DYSFUNCTION

There are three categories of thyroid dysfunction that have been characterized in adult humans: subclinical hypothyroidism, overt hypothyroidism, and hyperthyroidism. Subclinical hypothyroidism is defined as a slightly elevated TSH concentration and normal serum free T3 and T4 concentrations associated with few or no symptoms (Ross, 2000). The prevalence of such mild hypothyroidism increases with age for both sexes. Although there can be various causes of this condition, many subclinical hypothyroidism patients are positive for TPO antibodies, which may lead to overt hypothyroidism.

Overt hypothyroidism or underactive thyroid gland is the most common clinical disorder of thyroid function (Braverman and Utiger, 2000). It is best defined as high serum TSH concentration and a low free T4 serum concentration. Insufficient iodine levels or low iodine intake are a major cause of overt hypothyroidism. However, in areas where iodine intake is adequate, the most common cause of hypothyroidism is Hashimoto's thyroiditis, an autoimmune disease caused by autoantibodies to TPO. Other autoimmune diseases and radiation also are causes of hypothyroidism. Overall, women are more susceptible to autoimmune disease than men, suggesting they may be more susceptible to the development of hypothyroidism.

Hyperthyroidism (or thyrotoxicosis) is characterized by an increase in serum T3 and T4 and a decrease in serum TSH. The most common cause of hyperthyroidism is Graves' disease (production of antibodies to TSH receptor). In two studies, the peak age-specific incidence of Grave's disease was between 20 and 49 but incidence has been reported to increase with age, with the peak occurring at 60–69 years in a Swedish study (Berglund et al., 1990).

The following sections discuss the effects of thyroid dysfunction on reproduction and reproductive tract development in humans and laboratory animals.

Role of Thyroid Hormone Dysfunction on Male Reproduction and Reproductive Tract Development

Humans. Adult hypothyroidism is associated with effects on gonadotropin secretion and bioactivity, sex steroid metabolism, and testicular function, resulting in normal or decreased serum levels of SHBG, low total serum testosterone levels, and normal levels of estradiol. A hypergonadotropic state was observed in severe hypothyroid (myxedematous) men, but normal and decreased levels were also seen. In hypergonadotropic men, the biological/immunological LH ratio also was increased (Jannini et al., 1995). It was proposed that hypothyroidism can decrease ejaculation volume and sperm progressive forward motility (Jannini et al., 1995).

As seen with adult hypothyroidism, adult hyper thyroidism also effects gonadotropin secretion and

bioactivity and testicular function. Adult hyperthyroidism is associated with increased SHBG, LH, and FSH responses to gonadotropin-releasing hormone (GnRH). Male hyperthyroidism also is associated with breast development (gynecomastia; up to 85% incidence), which may be due to an increased estrogen/androgen ratio, increased conversion of androgen to estrogen, increased serum levels of SHBG, and increased total testosterone and/or progesterone levels (Jannini et al., 1995). Furthermore, hyperthyroid males may have a lower than normal sperm count, with normal motility, and a decreased libido.

Studies of the effects of T3 on adult male fertility have led to conflicting results, possibly due to small study sizes. In studies of hyperthyroid male adults with Grave's disease, disruption of the hypothalamic-pituitary (H-P) gonadal axis resulted in significantly decreased sperm motility and normal sperm density and morphology (Hudson and Edwards, 1992); the free testosterone to free estradiol ratio was below normal values. In another study using adult males with Grave's disease, sperm count was decreased, but not sperm motility (Abalovich et al., 1999). Krassas et al. (2002), in a prospective study on 23 hyperthyroid adult males, showed sperm motility was significantly decreased and decreased libido was reported in approximately one-half the study subjects.

Perinatal and/or prepubertal alterations in the thyroid system are associated with altered development of the male reproductive system. In normal children, increases in LH serum levels are greater than FSH serum levels (Jannini et al., 1995). Comparatively, boys with hypothyroidism exhibit increases in FSH serum levels that are greater than LH serum levels. Precocious sexual development, which is characterized by enlargement of the testes without virilization, has been associated with prepubertal thyroid failure (Jannini et al., 1995). Histopathological studies of the testis in males with juvenile-onset hypothyroidism show fibrosis and hyalinization, fibroblastic proliferation, and peritubular interstitial fibrosis, with sparse numbers of Leydig cells in the interstitial space.

Laboratory animals. Altered T3 activity produces unique effects in different laboratory animal species. Studies in male monkeys showed that administration of T4 increased SHBG concentration, increased peripheral aromatization of androstenedione, did not alter cortisol globulin binding, and increased testosterone levels (Bourget et al., 1987).

In mature male rats, administration of T4 (producing a hyperthyroid state) led to decreased total lipids, cholesterol, and phospholipids in the testes; increased amounts of testicular testosterone; and increased testicular pyruvate kinase activity (Longcope, 2000a). In another study, administration of T4 to intact adult male rats (producing a hyperthyroid state) led to a decrease in LH and FSH levels and an increase in testosterone levels (Schneider et al., 1979). Interestingly, decreases in LH and FSH levels also were observed in male rats that were thyroparathyroidectomized (producing a hypothyroid state) and levels returned to control levels after administration of T4 (Bruni et al., 1975).

In rats, hypothyroidism induced or occurring soon after birth is associated with a marked delay in sexual maturation and development. Hypothyroidism beginning in the perinatal phase and continuing through the prepubertal period leads to an arrest of sexual maturity and absent libido and ejaculate (Longcope, 2000a). Transient hypothyroidism is associated with increased transcription of genes associated with rat Sertoli cell division (Bunick et al., 1994). As these rats age, testis size, Sertoli cell number, and sperm production are increased (Cooke, 1991; Longcope, 2000b). Therefore, perinatal and neonatal hypothyroidism appears to retard Sertoli cell differentiation, increases the period of Sertoli cell proliferation, and increases spermatogenic efficiency (Kirby et al., 1992).

Administration of slightly higher than physiological levels of T4 to male mice appears to induce sexual maturation. Furthermore, T3 administration decreases proliferation and stimulates differentiation and glucose uptake in Sertoli cells from immature rats. Paradoxically, higher doses of thyroid hormones result in decreased weights of testes and seminal vesicles in mice and rabbits (Longcope, 2000a).

Role of Thyroid Hormone Dysfunction on Female Reproduction and Reproductive Tract Development

Humans. Hypothyroidism is associated with decreased rates of metabolic clearance of steroids and increases in peripheral steroid aromatization in adult women. The binding activity of SHBG is decreased in hypothyroid women. This decreased SHBG activity increases the unbound fractions of testosterone and estradiol present in the plasma and leads to increased levels of these steroids that are available and functional. Hypothyroidism also is associated with oligomenorrhea, amenorrhea, polymenorrhea, and menorrhagia (Krassas, 2000).

Severe hypothyroidism is associated with diminished libido and failure of ovulation, but ovulation and conception can occur in the presence of mild hypothyroidism. These pregnancies are often associated with spontaneous abortions in the first-trimester, stillbirths, or premature births. Thyroiditis, due to autoimmune disease, is especially common in the postpartum period (Krassas, 2000). These patients may experience hypothyroidism, hyperthyroidism, or hyperthyroidism followed by hypothyroidism within this time period. While most postpartum thyroiditis patients regain normal thyroid function, many women develop permanent hypothyroidism. Studies also have observed that pregnant women with autoimmune thyroid disease, who were diagnosed with subclinical hypothyroidism, were observed to have a greater risk of miscarriage early in the pregnancy (Glinoer et al., 1994).

Studies indicate that hyperthyroidism also alters the steroid system significantly. Hyperthyroidism is associated with increased mean plasma levels of estrogen, androstenedione, and testosterone; increased synthesis of androstenedione and testosterone; decreased clearance of 17-β-estradiol; and increased metabolism of androstenedione to estrone and testosterone to estradiol (Krassas, 2000). Mean LH levels in both phases of the menstrual cycle were higher in women with hyperthyroidism than in euthyroid women. Similar to men, hyperthyroidism is associated with increased levels of SHBG. Epidemiological studies of hyperthyroid women show increased incidences of oligomenorrhea or amenorrhea (Krassas, 2000).

Studies on the effects of hypothyroidism on postnatal development of the reproductive system in females have produced conflicting results. Hypothyroidism in infancy can lead to a delay in sexual maturity. Additionally, hypothyroidism in early puberty can delay onset of puberty followed by anovulatory cycles. On the other hand, in some cases, hypothyroidism has been associated with precocious puberty and galactorrhea, which is proposed to be due to overlapping actions of TSH, prolactin, FSH, and LH. Fetal hypothyroidism does not appear to affect female reproductive tract development (Krassas, 2000).

Results of studies on the effects of hyperthyroidism on postnatal development of the reproductive system in females also are inconsistent. Some studies indicate that hyperthyroidism occurring before puberty delays the onset of menses, while other studies show no significant effect on menarche. As with hypothyroidism, fetal hyperthyroidism does not appear to affect reproductive tract development in girls (Krassas, 2000).

Laboratory animals. Hypothyroidism in adult rodents is associated with altered estrous cycles and leads to enhanced responses to hCG (with development of large cystic ovaries but few corpora lutea) in rats. Hypothyroidism does not result in sterility, but does interfere with gestation, usually during the first half of pregnancy. Increased resorption of embryos, reduced litter sizes, and increased stillbirths are noted in these studies. A decrease in uterine response to estrogen also is noted in hypothyroid rats (Longcope, 2000a).

Hyperthyroidism in adult female rats, induced by administration of T4, is associated with long periods of diestrus with few mature follicles or corpora lutea. In rats, administration of excess T4 has been associated with an increase or no change in pituitary LH and a decrease in serum LH. Furthermore, studies have shown that a marked excess of thyroid hormones causes abortion and neonatal death (Longcope, 2000b).

Fetal hypothyroidism in the rat is associated with the development of small ovaries that are deficient in lipid and cholesterol. Hypothyroidism in sexually immature rats is associated with delayed vaginal opening and sexual maturation, smaller ovaries and follicles compared to untreated control animals, and under-developed uteri and vaginas. In contrast, fetal hypothyroidism in sheep does not affect female reproductive tract development (Longcope, 2000b).

Studies on the effects of hyperthyroidism on female reproductive tract development have produced differing results in mice and rats. Small doses of thyroid hormone given to young female mice resulted in earlier vaginal opening and onset of the estrous cycle than in controls (Longcope, 2000a). In contrast, large doses of T4 given to neonatal rats delayed both vaginal opening and onset of the estrous cycle. Methodological limitations in the rat studies (induction of hypothyroidism after a brief period of hyperthyroidism) limit the usefulness of these study results (Schneider et al., 1979).

SUMMARY

Similarities and Differences in Thyroid Function Between Laboratory Animals and Humans

The thyroid system plays a critical role in the development and maintenance of several systems within the mammalian body including, but not limited to, the cardiovascular, nervous, and reproductive systems. To date, many studies have focused on understanding and evaluating the physiological and biological roles thyroid hormones have on these systems. The presence of a highly conserved thyroid system in mammals indicates this system plays an integral role in animal development and survival.

There is a significant literature database focused on assessing the role and effects of the thyroid gland and T3 on reproduction in humans and in laboratory animals. However, there is limited analysis and information on the comparative physiology of the thyroid system's role among species. Understanding and evaluating the differences and similarities among species is necessary to ensure appropriate and complete study design and interpretation of results from laboratory animals, and extrapolation to potential human health risks. Therefore, the present article focuses on evaluating these similarities and differences.

Overall, studies indicate that the anatomy of the thyroid gland and the synthesis of thyroid hormones are similar in laboratory animals and humans. Regulatory mechanisms that modulate thyroid hormone synthesis and release (H-P-T axis) also appear to be conserved in humans and rodents. The presence of such a conserved system and the fact that the amino acid sequences of the thyroid hormone binding proteins show a high degree of sequence homology (between 70 and 90%) provide further evidence that the thyroid system is important in humans and animals.

There are, however, significant differences between human and rodent thyroid hormone pharmacokinetics, associated with differences in thyroid gland morphology. The shorter half-life of T3 and T4 in rats is associated with increased production in the rat, when compared to the human (U.S. EPA, 1998) Although the reasons for this difference are not understood completely, it is proposed that very low levels of high-affinity T4 binding in the rat play a role. The higher turnover of T3 and T4 in the rat leads to higher basal TSH levels in rats when compared to humans. The higher rate of thyroid hormone metabolism in rats, when compared to humans, also is associated with differences in follicle morphology. Such differences also may have implications for thyroid hormone effects in reproductive tract development and reproduction. For example, rats are more prone to thyroid hyperplasia and tumors than humans (even under conditions of thyroid dysfunction in humans). When such effects are observed in rodent toxicity studies, very careful consideration should be given to this fact before assuming that similar exposures in humans would lead to similar effects. However, it should be kept in mind that exposure to a chemical that induces hyperplasia or tumors in rodents might lead to a different adverse thyroid effect in humans.

Other distinctions between humans and laboratory animals are the mechanisms of thyroid hormone metabolism. Both species rely on hepatic deiodinases to convert the prohormone T4 to the active hormone, T3. In humans, deiodinases also play a major role in deactivating T3. In contrast, removal of T3 from the circulation by glucuronidation and sulfation pathways is greater in rats than in humans. Therefore, in order to predict human health outcomes, a comparison of the

Table 2
Selected Parameters of Thyroid System in Humans and Rats (Adapted From U.S. EPA, 1998)

Parameter	Human	Rat
Half-life of T4	5–9 days	0.5–1 day
Half-life of T3	1 day	0.25 day
Thyroxine-binding globulin levels	High	Very low
Amount of T4 required in absence of functional thyroid gland	2.2 μg/kg bw/day	20 μg/kg bw/day
T4 production (rate/kg bw)	1 ×	10 ×
Sex difference in serum TSH levels	No difference	Adult males have higher levels than adult females
Follicular cell morphology	Low cuboidal Follicular height is equal in males and females.	Cuboidal Follicular height in males is greater than in females

Table 3
Comparison of Thyroid System Development in Human and Rats

Parameter	Human (birth at gestational week 39)	Rat (birth at gestational day 21)
Thyroid gland development	TR detectable by 10th week of gestation Thyroglobulin detectable by 11th week of gestation Iodide uptake by 11th week of gestation TSH secretion detected between 18 and 20 weeks gestation T4 detectable and follicular maturation by 11th week of gestation T3 secretion increases between 18 and 20 weeks gestation	TR detectable by GD 14 Thyroglobulin detectable by GD 15 Iodide uptake detected by GD 17 TSH secreting cells appear by GD 17 TPO and thyroid hormone synthesis detected by GD 17
Maturation of pituitary-thyroid axis	Becomes functional late in the 1st and early 2nd trimester H-P-T maturation (complete functional interaction) occurs in last trimester and postnatally Maturation appears complete by 4th postnatal week	Becomes functional in late gestation and postnatally H-P-T maturation (complete function interaction) occurs postnatally Maturation appears complete by 4th postnatal week

magnitude of thyroid dysfunction that results in adverse effects in various organs/tissues and between humans and rodents is warranted.

In addition to species differences, there are sex differences in the thyroid hormone systems. Adult male rats have higher basal TSH levels than adult female rats, whereas TSH levels are approximately the same in men and women. Studies also indicate the height of the thyroid follicles are often greater in adult male rats than adult female rats but are approximately equivalent in both human sexes (Capen, 1996). Table 2 shows selected parameters in humans and rats.

Furthermore, there are differences in changes in TBG levels among rats, mice, and humans. As mentioned previously, TBG levels increase in humans and rats during pregnancy, while TBG levels decrease in mice during pregnancy (Savu et al., 1989).

This analysis shows there are significant differences in the basic morphology and biological activity of the thyroid systems in human and laboratory animals (more specifically, rodents) to be considered when evaluating animal studies and extrapolating these results to human health effects. Due to differences in thyroid hormone synthesis, basal TSH levels, metabolism, differences in alterations to binding proteins during pregnancy, and endpoint sensitivity, findings in rodents that thyroid hormone, TSH, or TRH levels are altered due to exposures to an environmental agent may not correlate to an adverse effect in humans.

Differences in Thyroid Development

The pattern of thyroid development in rodents appears to be similar to the pattern in humans. In rodents and humans, TR receptors are the first component of the thyroid system detected. Thyroglobulin and iodine uptake are then observed. Finally, TSH secretion is sufficient to be quantified. Further details of the time points when these components are observed can be found in Table 3.

Despite similarities in the order of fetal thyroid system development, the noted differences should be considered when extrapolating laboratory animal effects to humans. For example, the rat thyroid system is significantly less mature than humans at birth and likely leads to differences in responses to neonatal exposures in rats and humans. This difference, as well as other potential species differences, does not necessarily indicate that

effects in animals are irrelevant to humans. However, care and further studies should be undertaken to assure that the effects seen in animals are related to the relevant developmental stages in humans.

Furthermore, differences in the life stage when the thyroid system fully matures is another factor that should be fully evaluated when attempting to relate adverse effects in laboratory animals to those that might occur in humans. As noted above, the thyroid system matures earlier, relative to birth, in humans than it does in rodents. Therefore, compensatory mechanisms that may be in place in human neonates may not be available to rodents at an equivalent life stage.

Similarities and Differences in the Role of Thyroid Hormones on Reproduction and Development

Thyroid hormones play a central role in the development of several laboratory animal and human systems. Overall, studies indicate that the role of thyroid hormones in development of reproductive structure and function is similar in humans and rodents of both sexes. Additionally, alterations in thyroid status in humans and rats during pregnancy also appear to be similar. T3 appears to play a significant role in male reproductive tract development in rodents and humans. Comparatively, T3 plays a significant role in female reproductive tract development in rats, but not in humans. Despite the general similarities in the role of T3 on reproduction and reproductive tract development, the exact roles of these hormones (e.g., mechanisms of action and interactions with other hormones) have not been fully evaluated and thus are not addressed in this study.

Furthermore, physiological differences in various stages of development may produce significant differences in the role of T3 in development of the reproductive tract. For example, maximal Sertoli cell proliferation occurs from late gestation through postnatal day 12 in rodents. In humans, it occurs from mid-gestation through 1 year of age and from about 10 years of age through puberty (Sharpe et al., 2003). Such differences are likely to translate into species differences in the outcomes of exposures to thyroid toxicants.

Thyroid Hormone Dysfunction

Hyper- and hypothyroidism-induced alterations in the endocrine system are seen in adult male laboratory animals and humans. However, the specific changes and the directions of the changes depend on the species and the thyroid dysfunction observed. Hypothyroidism produces differing effects in juvenile male laboratory animals and humans. Prepubertal hypothyroidism is associated with precocious sexual development in humans and arrest of sexual maturity in rats.

Hypothyroidism in adult female humans and rats is associated with altered estrous cycles and interference with gestation, usually during the first trimester (humans) or first-half (rodents) of pregnancy. Increased stillbirths and abortions are noted in humans and increased resorptions, reduced litter sizes, and increased still births are noted in rodents. This suggests that thyroid function is necessary to maintain pregnancy in rats and humans. Hyperthyroidism in adult female humans and rats is associated with altered levels of LH. Alteration in sex steroid metabolism and increased incidences of oliogomenorrhea and amenorrhea also are noted in humans.

Fetal hypothyroidism in female rats alters reproductive tract development, but a similar effect is not seen in the female humans. Hypothyroidism in the pre-pubertal period is associated with delayed sexual maturity in female rats and humans. However, there have been some observations of ''precocious puberty'' associated with hypothyroidism in female humans.

Studies of hyperthyroidism in prepubertal female humans and rats have produced conflicting results. Some studies indicate hyperthyroidism in humans and rats leads to early onset of menses and puberty, while other studies indicate that it either delays (rats) or does not affect the onset of menses (humans).

CONCLUSIONS

The thyroid system is highly conserved in laboratory rodents and humans. Thyroid dysfunctions are associated with numerous morphological, physiological, and behavioral disorders, including reproductive and developmental disorders in humans and laboratory animals.

Despite many similarities in the thyroid systems of humans and laboratory animals, there are significant differences that should be taken into account when designing, conducting, and interpreting animal studies. The material reviewed reveals differences among species and sexes that could significantly impact the interpretation of rodent thyroid toxicity data in terms of predicting effects in humans. Species differences that need to be considered include metabolic turnover rates, basal TSH levels, sodium-iodide symporter sensitivities, windows of susceptibility, the role of the thyroid system on reproductive tract development and function, and the magnitudes of thyroid system changes that result in adverse health effects. In addition, a greater understanding is needed of the molecular mechanisms of cellular T3 uptake, intracellular transport, interactions with other hormonal systems, and the mechanisms by which changes in T3 lead to adverse effects.

Additional data in these areas, from both humans and rodents, will provide a better understanding of thyroid system similarities and differences and will reduce uncertainties in predicting the adverse health effects of thyroid toxicants on humans.

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