Indonesian Journal on Health Science and Medicine
Vol 2 No 1 (2025): July
ISSN 3063-8186. Published by Universitas Muhammadiyah Sidoarjo
https://doi.org/10.21070/ijhsm.v2i1.162

Thyroid Hormones' Effect in the Sexual Organs of Humans and Laboratory Animals

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Abstract. General Background: Thyroid hormones (THs) are vital for the development and function of various physiological systems, including the reproductive system, in both humans and animals. Specific Background: Disruptions in TH levels, due to disease or environmental toxicants, have been implicated in fertility issues, pregnancy outcomes, and postnatal development. Knowledge Gap: However, comparative data on how thyroid dysfunction affects human versus rodent reproduction remain limited, particularly concerning mechanistic pathways and developmental endpoints. Aim: This study aimed to evaluate and compare the effects of thyroid hormone imbalances on the reproductive systems of humans and laboratory animals, focusing on both genomic and nongenomic mechanisms. Results: Findings show that both hypothyroidism and hyperthyroidism disrupt reproductive hormone balance, gametogenesis, and sexual development, though the severity and pathways differ between species. Animal testing protocols revealed species-specific responses in thyroid hormone metabolism, signaling, and reproductive outcomes. Novelty: The research integrates genomic-nongenomic TH pathways, evaluates reproductive endpoints in endocrine-disruptor assays, and compares species-specific thyroid function. Implications: These findings underscore the importance of refining animal models and screening protocols for better prediction of human reproductive risks, advocating for inclusion of thyroid-sensitive parameters in regulatory toxicity assessments.

Highlights:

1. Thyroid hormones play critical roles in reproductive system development in both humans and lab animals.
2. Hypo- and hyperthyroidism significantly affect fertility, menstrual cycles, and hormonal balance
3. Rodent models offer insights but may not fully replicate human thyroid physiology.

Keywords: Thyroid Hormones, Reproduction, Hormone Receptors, Thyroid Dysfunction, Rodent Models

Published : 20-06-2025

Indonesian Journal on Health Science and Medicine
Vol 2 No 1 (2025): July
ISSN 3063-8186. Published by Universitas Muhammadiyah Sidoarjo
https://doi.org/10.21070/ijhsm.v2i1.162

Introduction

Normal hormonal blood levels are necessary for tissue development and growth, as well as for maintaining organ and tissue functionality [1]. In humans and animals, variations in thyroid hormone levels may have detrimental effects on fertility, the outcome of pregnancy, and postnatal development. They also have a substantial influence on growth, hearing, mental clarity, and the development and functioning of the offspring's reproductive systems.An increased risk of unfavourable pregnancy results has been associated with both hyperthyroidism and hypothyroidism in humans. It has long been recognised that pregnancy and environmental factors, such as exposure to synthetic chemicals or drugs (such propylthiouracil (PTU)), hormones, or diet, might affect thyroid function.

For drugs that may interact with the endocrine system, the term "endocrine disruptor" is used. Originally, in vitro and in vivo research concentrated on their oestrogenic, anti-estrogenic, or anti-androgenic effects on people, experimental animals, and wildlife; but, more recently, studies have also focused on their effects on thyroid signalling [2]. In addition to controlling energy balance and many other metabolic processes, the thyroid hormones (THs), thyroxine (T4) and triiodothyronine (T3), are essential for the development and differentiation of various tissues and organs. The central nervous system's development during pregnancy is known to be significantly influenced by THs. This indicates that TH axis disruption may lead to serious damage, especially in the development of the mammalian brain, which can result in neurological abnormalities and mental retardation.Ovulation and menstrual irregularities may result from thyroid dysfunction, which affects women more often than males. Hypothyroidism manifests as menorrhagia, oligomenorrhea, infertility, or pregnancy loss, but hyperthyroidism often manifests as oligomenorrhea. But little is understood about the processes behind these reproductive disorders.

Tri-iodothyronine (T3) and thyroxine (T4) are the two main hormones generated by the thyroid gland. The primary secretory product of the thyroid gland, thyroxine, is deiodinated to produce peripherally active T3 [3]. In humans, the activity of thyroid hormone is receptor-mediated. Numerous

ISSN 3063-8186. Published by Universitas Muhammadiyah Sidoarjo
https://doi.org/10.21070/ijhsm.v2i1.162

physiological organs and tissue, including the heart, brain, placenta, lung, liver, skeletal muscle, kidney, and pancreas, have been shown to include nucleus binding sites for thyroid hormones.Thyroid hormones are implicated in the development and operation of the cardiovascular, neurological, immunological, and reproductive systems, according to research on both humans and animals. In particular, a large number of reviews and research have assessed how thyroid hormones affect the healthy growth and operation of the human reproductive system. Many research investigations have also examined the impact of thyroid hormones on the development of the reproductive tract in mice models. However, there is a dearth of information in the literature currently available on the comparative physiology of reproduction in humans and laboratory animals as well as the role of thyroid hormones in reproduction.The anterior pituitary gland secretes thyroid- stimulating hormone (TSH), which regulates the production and release of thyroid hormones in both experimental animals and humans. The hypothalamus generates thyrotrophin releasing hormone (TRH), which controls the production of TSH in the pituitary. The negative feedback loops of the hypothalamic-pituitary-thyroid (H-P-T) axis control the levels of thyroid hormone in the blood [4], [5]. The mechanism of cellular absorption of T3 is right now being studied [6]. T3 may enter cells by a carrier-mediated mechanism, according to one idea. According to in vitro studies, many laboratories animal as well as human tissues have specific T3 and T4 binding sites/carriers. An additional means of cellular transport is made possible by the specific and specialised interactions that occur between cell surface receptors and thyroid hormone protein binding proteins.

It is the thyroid gland that generates T4 and T3. The two main roles of thyroid hormones (THs) are as follows. The first plays a crucial part in development and growth. The transformation of tadpoles into frogs, in particular, is one of the most obvious instances of the significance of THs in growth and development in amphibians [7], [8], [9], [10]. The emergence of the human and other animals central nervous systems, the transition of salmon from freshwater-dwelling par to seawater-dwelling smolts, and the metamorphosis of flounders are other examples of the significance of THs in growth.Thyroid-stimulating hormone (TSH), a pituitary hormone, controls

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the manufacture and storage of TH, which mostly takes place in the thyroid gland. T4 makes up the majority of the thyroid's TH [11], [12]. Although T3 makes up a very minor fraction of thyroid-localized TH, tissue-specific deiodinases deiodinate T4 to produce the majority of T3. The following intricate mechanisms are involved in the synthesis, storage spaces. release, transportation, and metabolism of THs:

1) Thyroid gland uptake of iodide ions;
2) Iodide oxidation and tyrosine residue iodination in thyroglobulin;
3) Iodotyrosine residues combine to form iodothyronines;
4) Thyroglobulin proteolysis and blood release of T4 and T3;
5) Attaching to transport proteins in serum;
6) Target T3 production from T4 in tissue;
7) T4 and T3 breakdown in peripheral tissues; and
8) The liver's catabolism and biliary removal of THs [13], [14].

Methodology

Tests for substances that change the production, release, movement, and breakdown of thyroid hormones. Chemicals that promote the metabolism of thyroid hormones and those that block their production, release, and transport may both alter the levels of thyroid hormones in the blood. Particular tests may be performed to identify the process by which serum TH concentrations are reduced if a drug lowers them [15].

1. **Peroxidase assay:** The primary enzymes involved in the manufacture of THs are thyroid peroxidases (TPOs). Several synthetic chemical classes, including thionamides like propylthiouracil, aromatic amines like sulfathiazole, and polyhydric phenols like resorcinol, block thyroid peroxidase.
2. **Perchlorate discharge test:** In addition to competing with iodide for thyroid absorption, perchlorate may facilitate iodide outflow from follicular cells [16]. For many years, iodide organocation abnormalities in people and animals have been identified using a perchlorate discharge test. This assay involves exposing animals to a test chemical, followed by the administration of Na125I and perchlorate.

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3. **The challenge test for thyrotropin-releasing hormone (TRH):** In this experiment, the hyrotropin-releasing hormone (TRH) challenge test is examined. In this test, the normal functioning of the hypothalamus pituitary-thyroid axis is evaluated. This test measures TSH levels before to and throughout the TRH difficulty, to put it briefly [17]. The TRH challenge should cause serum TSH levels boost. The response is diminished when hypothyroidism of central origin develops, and it is hyperreactive when hypothyroidism develops at the thyroid level. Applications of this test have been developed in both clinical and experimental situations.
4. **Serum protein-binding assays:** Transthyretin (TTR), thyroid-binding globulin (TBG), and albumin are the serum-binding proteins for THs in mammalian systems. Particular to THs are TTR and TBG, and T4 is more receptive to these serum-binding protein than T3 [18], [19], [20]. TG is present in humans and primates but absent in rodents. TBG seems to be the cause of humans' much longer half-lives of T4 and T3 than those in different animals, particularly rodents.
5. **Deiodinase assays:** About 80% of the thyroid glands T4 is deiodinate by target tissues in mammals, resulting in either T3, the most active form of the THs, or reverse T3 (rT3), an inert iodothyronine. Many enzymes are involved in the deiodination of T4, T3, and its metabolites [21], and tissue-specific protein expression plays a role.

A. Metabolism and Excretion of Thyroid Hormones

There are three different enzymatic pathways that may regulate thyroid hormone function: deiodination, glucuronidation, and sulfation. The production and metabolism of T3 and T4 in peripheral tissues are often associated with deiodination, which has a substantial impact on thyroid hormone metabolism. Moreover, iodine substituents at the fifth position on thyroid hormones may be removed by type I deiodinases, turning T4 into rT3 [22]. Type I deiodinase is responsible for producing around 85% of the T3 in the blood across many organs. When type III deiodinases extract iodine from the five locations on thyroid hormones, T4 and T3 are transformed into

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rT3 and diiodothyronines (T2), respectively. Afterward, T2 is deiodinated to produce Mon iodothyronines [23].

B. Nongenomic Effects of THs

By stimulating the cytoplasmic cytoskeleton, mitochondria, or integrin-related receptors on the cell membranes, THs also have nongenomic effects on the female reproductive system. These effects target extra-nuclear signalling that is regulated by hormone-mediated rapid cellular response. This is accomplished independently of the intra-nuclear THRs via which T3 produces its genomic effects. Though there have been relatively few publications on the mitochondria and cytoskeleton in reproductive system cells to far, the majority of nongenomic research has focused on the interaction between THs and integrin receptors [24].(Figure 1)

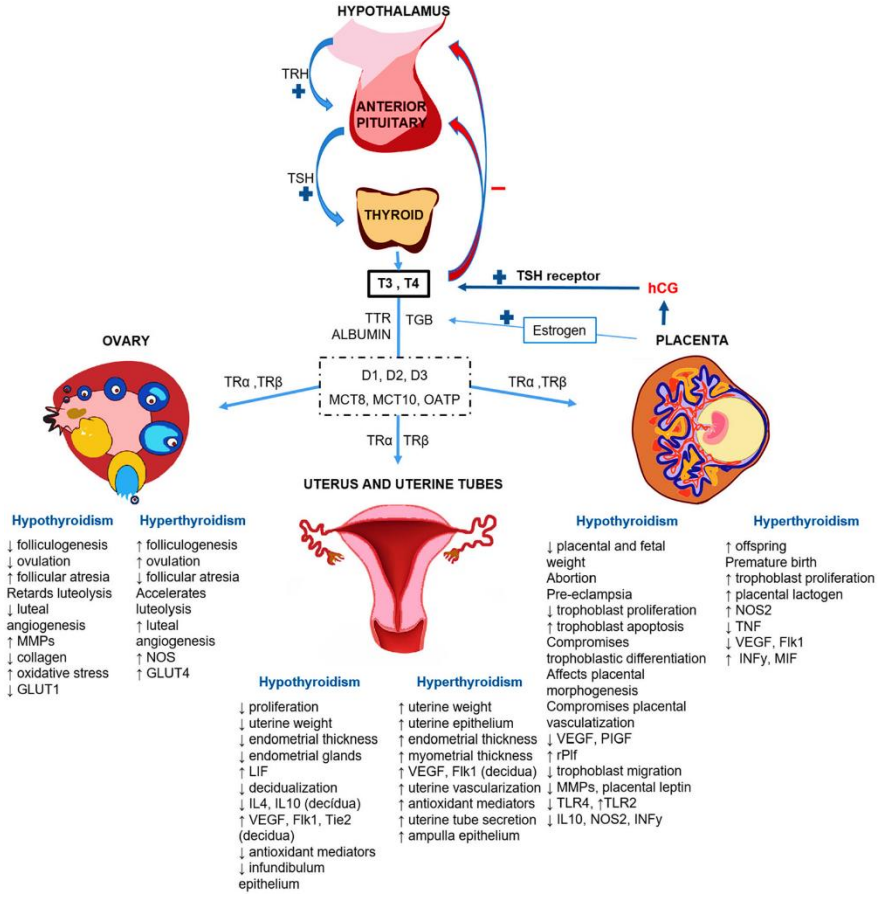

Fig. 1 Reproductive hormones and TH's nongenomic effects on the Female Reproductive System. [14]

Although it has both S1- and S2-binding domains, integrin αvβ3 does not have a basic preference for THRs. Not to be confused with the peptide or protein

ISSN 3063-8186. Published by Universitas Muhammadiyah Sidoarjo
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hormones related to reproduction attached to membrane G-protein-coupled receptors (GPCRs) Figure 1. When T3 is specifically recognized by the S1 domain of integrin αvβ3 in human glioblastoma U-87 MG cells, Src kinase initiates the phosphatidylinositol-3-hydroxykinase (PI3K) signaling pathway, which leads to the downstream cytoplasmic THR shuttling to the nucleus and the activation of hypoxia-inducible factor 1-alpha (HIF-1α) [16, 18]. In **Figure 2.** The S2 domain regulates the extracellular-signal-regulated kinase 1/2 (ERK 1/2) system. Following the beginning of ERK1/2 signaling, mitogen-activated protein kinase (MAPK) is activated. The nucleus absorption of THRβ1 from the cytoplasm and the growth of tumour cells are the results of this pathway, which also causes the phosphorylation of STAT-1α, STAT3, p53, and ERs [25], [26]. Integrin and peptide and protein receptors for hormones may produce crosstalk by stimulating the same signaling pathway, although using separate ways to achieve their effects. The signaling pathways shown in Figure 1 are initiated by THs and some reproductive hormones.

I. THYROID HORMONE DYSFUNCTION'S IMPACT ON MALE REPRODUCTION AND THE DEVELOPMENT OF THE REPRODUCTIVE TRACT

Humans: Testicular function, sex steroid metabolism, and gonadotropin bioactivity and production are all impacted by adult hypothyroidism. Blood levels of SHBG, total serum testosterone, and oestradiol are thus either normal or reduced. Although hypergonadotropic conditions were seen in men with myxedema, or chronic hypothyroidism [27], normal and reduced levels were also observed. In hypergonadotropic men, the biological/immunological LH ratio also improved.Increased levels of SHBG, LH, and FSH in response to gonadotropin-releasing hormone (GnRH) are linked to adult hyperthyroidism. Male hyperthyroidism is linked to breast growth (gynaecomastia; up to 85% incidence) for a variety of reasons, such as increased levels of total testosterone and/or progesterone, a higher ratio of oestrogen to androgen, a higher conversion of androgen to oestrogen, and an elevated blood level of SHBG [28].Changes in the thyroid system during pregnancy and/or the prepubescent period are linked to changes in the male reproductive system's development. Serum levels of LH rise more than those of FSH in healthy

ISSN 3063-8186. Published by Universitas Muhammadiyah Sidoarjo
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children. On the other hand, FSH serum levels rise more than LH serum levels in males with hypothyroidism [29], [30]. Prepubescent thyroid insufficiency has been linked to premature sexual development, which is characterised by testicular growth without virilisation.

Laboratory animals: Different laboratory animal species have distinct effects when T3 activity is altered. T4 injection raised peripheral aromatisation of androstenedione, elevated SHBG concentration, did not change cortisol globulin binding, and raised testosterone levels in male monkeys, according to studies. When supplied to adult male rats, T4 (which causes hyperthyroidism) increased testicular testosterone, testicular pyruvate kinase activity, and reduced total lipids, cholesterol, and phospholipids in the testes [31]. In another study, T4 administration caused intact adult male rats to develop hyperthyroidism, which increased testosterone levels while lowering FSH and LH levels. Surprisingly, male rats after thyroidectomy also had decreases in LH and FSH levels, which subsequently returned to normal following T4 administration.

II. The impact of thyroid hormone dysfunction on the development of the reproductive tract and female reproduction

Humans: Peripheral steroid aromatisation is increased and steroid metabolic clearance is decreased in adult females with hypothyroidism [32]. Women with hypothyroidism have less SHBG binding activity. This decreased SHBG activity boosts the unbound parts of both testosterone and oestradiol in the plasma and results in higher amounts of accessible and functioning testosterone and oestradiol. Hypothyroidism is also associated with menorrhagia, polymenorrhea, amenorrhoea, and oliogomenorrhea.

Laboratory animals: Rats with hyperthyroidism had changed oestrous cycles and enhanced hCG responses (large cystic ovaries but few corpora lutea). Hypothyroidism does not lead to infertility, even if it disrupts the process of gestation, usually in the early stages of pregnancy. These investigations demonstrate increased embryo resorption, smaller litter sizes, and a higher rate of stillbirths [33]. The uterine response to oestrogen is likewise diminished in hypothyroid rats.

Results and Discussion

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ISSN 3063-8186. Published by Universitas Muhammadiyah Sidoarjo
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III. LABORATORY ANIMALS AND HUMANS: COMMONALITIES AND DIFFERENCES IN THYROID FUNCTION

Thyroid function is essential for the development and maintenance of several systems in the mammalian body, such as the neurological, cardiovascular, and reproductive systems. The physiological and biological effects of thyroid hormones on these structures have been the subject of many investigations so far [34]. Since the thyroid systems of mammals are mostly undamaged, these animals probably rely on them for growth and survival. The function and impact of the thyroid gland and T3 on human and lab animal reproduction are well documented in the literature. The comparative physiology of the thyroid system's functioning across species, however, has not received much attention [35], [36]. Understanding and assessing the variations and similarities across species is essential for ensuring proper and comprehensive research design, reviewing data from laboratory animals, and extrapolating to possible risks to human health.

3.1 Evaluation of Thyroid Development and Function in Humans and Rodents

The opening workshop session addressed a summary of the similarities and differences between the thyroid systems of humans and animals. Two rat models of thyroid dysfunction in humans are shown in Table1.

Table 1 Human and rat thyroid systems are compared.

Parameter	Human	Rat	Mouse
Half-life of T_4	5-8 days	0.5-1 days	0.5-0.75 days
Half-life of T_3	1 day	0.25 day	0.45 day
Thyroxine-binding globulin with high affinity	Present	Absent	Absent

ISSN 3063-8186. Published by Universitas Muhammadiyah Sidoarjo
https://doi.org/10.21070/ijhsm.v2i1.162

Primary differences in serum TSH	Globulin that binds thyroxine	Albumin	Albumin
Serum TSH levels vary by sex.	No difference	Adult males> adult females 20 µg/kg body	Adults' males> adult females'
The quantity of T4 needed when the thyroid gland is not functioning	2.2 µg/kg body weight/ day	Thyroid hormone	Information Not Found
The foetal pituitary-thyroid development	The secretion of TSH and T3 rises between weeks 18 and 20 of pregnancy. Late in the first and early second trimesters, it starts to operate. By the fourth postnatal week,	By the seventeenth day of pregnancy, synthesis and TSH-secreting cells are seen. Becomes operational in the latter stages of pregnancy, and by the fourth postnatal week, maturation	Information Not Found

ISSN 3063-8186. Published by Universitas Muhammadiyah Sidoarjo
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	maturity seems to be complete.	seems to be finished.	

- **Thyroid hormone production and function:** Human and animal thyroid hormone production and function are similar and controlled by physiological feedback mechanisms [37], [38], [39]. Thyroid hormones control how cells use oxygen and how they metabolise fats, carbohydrates, and proteins. However, there are some significant species-specific variations in metabolism and movement.
- **Thyroid system development:** Although the stages of thyroid development at birth vary, the thyroid systems of humans and rats grow similarly. The thyroid system is less developed in rats at birth. By four weeks of age, the hypothalamic-pituitary-thyroid axis is fully functional, having started at birth. The hypothalamic-pituitary-thyroid axis in humans develops throughout pregnancy, from the fourth to fifth weeks to the thirty and thirty-five weeks, and by the time the rat is born, the thyroid system is fully matured and functioning.
- **Pregnancy:** The kidney's ability to remove iodine is enhanced during pregnancy. Consequently, if the diet is incomplete or just somewhat adequate in iodine, low blood iodine levels may develop during pregnancy [40]. Serum TSH measurements may identify subclinical hypothyroidism. Although there are no clinical symptoms of hypothyroidism and T3 and T4 levels are within normal limits, this syndrome is characterised by slightly elevated TSH serum levels. TSH blood levels are correlated with thyroid gland size, which rises by 10–20% during pregnancy. Thyroid gland histology and TSH serum levels are more sensitive indicators of thyroid health than T3 and T4 serum levels.
- **Thyroid dysfunction:** Adult male laboratory animals and people with hyper- and hypothyroidism exhibit abnormalities in the reproductive system, including alterations in follicle stimulating hormone and leuteinizing hormone (LH) levels, steroid levels and ratios, the number of sperm, and libido [41]. Adult male rats and humans are affected by hypothyroidism in distinct ways.
- **Animal models of thyroid disease:** The possibility of forecasting health risks to humanity using animal models was investigated. Considering the physiology of the thyroid system and the negative effects that differ between

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humans and animals with altered thyroid systems, some of the current models may not be particularly accurate in predicting the effects on human health. Because the thyroid systems of rats and humans vary, rat models of thyroid cancer do not correspond to human hazards . Thyroid hypertrophy caused by chemicals, for instance, may result in thyroid cancer in rats, but it can also cause noncancerous goitre in humans. Thyroid cancer has only been shown to be caused by ionising radiation in humans [42].

- **In vitro assays:** People for the Ethical Treatment of Animals' in vitro screening tests. Unpublished data) have been generated to find compounds that could have in vivo hormonal activity. In order to validate these assays, it is necessary to not only validate the technique but also to comprehend the extent to which these assays accurately anticipate real-world consequences. These assays have not yet been approved for use as a chemical screening tool and are now used in research to address certain mechanistic problems [43].

In both humans and rats, the thyroid gland produces T4 10–30 times more often than T3, the primary physiologically active form. The thyroid gland produces about 10% of the T3 in peripheral tissues. T4 is changed into the remaining quantity of T3 by deiodinase activity. In humans and rats, extrathyroidal deiodinase activity is responsible for about 80% and 60% of T3 production, respectively. Tpe III inactivates T3 and T4 to 3,3´-diiodothyronine (T2) and 3,3´,5´-triiodothyronine (reverse T3, or rT3), respectively, whereas type I and type II deiodinases convert T4 to T3. The brain, pituitary, thyroid, liver, and kidney are the tissues in adult humans and rats with the highest amounts of T3.

The type and amount of cellular deiodinase activity may vary among species, diets, hormonal states, developmental stages, and tissue types (Table 2). Type III deiodinase, for instance, is produced in large quantities by the fetus rat but in relatively small levels by the adult rat. The enzyme type I deiodinase is found in the cell membrane, and fasting reduces its activity while elevated thyroid hormone increases it [44]. Type II deiodinase is found on the endoplasmic reticulum of cells and may degrade quickly as thyroid hormone levels rise. (Table 2

Table 2 Deiodinases' characteristics in humans and lab animals.

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Property	Activity of Deiodinase Type I (5 and 5)	Type II Deiodinase (5' deiodinase activity)	Type III Deiodinase (5' deiodinase activity)
Limiting K_m	0.5 µM	1-2 nM	5-20 µM
Reaction catalysed	T4 to rT3 or T3	T4 to T3	T4 to rT3
Inhibitors	Propranolol, halogenated aromates, iopanoate, and thiouracils	rT3, iopanoate, flavonoids, and increased T4 levels	Iopanoate, flavonoids
Tissue distribution	Thyroid, kidney, liver, skeletal muscle, placenta, euthyroid pituitary, and central nervous system	Thyroid, pituitary, brown adipose tissue, and placenta in the central nervous system	Rat fetal tissue is found in large quantities in almost every tissue except the pituitary, thyroid, kidney, and liver.
Hyperthyroidism	Increase	Decrease	Increase
Hyperthyroidism	Decrease	Increase	Decrease

Sodium iodide symporter transcripts have been found in the thyroid, stomach, ovaries, salivary glands, mammary glands, lacrimal glands, and mice and rats, according to gene expression investigations. Nonetheless, symporter gene expression varies significantly across species. Human symporters are expressed in the heart, thymus, and adrenal gland, however neither mice nor rats exhibit this expression. Most species, including humans and rats, have the thyroid gland's sodium iodide symporter gene expression primarily modulated by TSH .

Thyroid hormones influence hormonal state and reproduction in female humans and rodents by modifying hormone-induced transcription

ISSN 3063-8186. Published by Universitas Muhammadiyah Sidoarjo
https://doi.org/10.21070/ijhsm.v2i1.162

pathways and other variables [45]. Furthermore, changes in thyroid function during pregnancy seem to be comparable in humans and rats. It's interesting to note that in humans and rats, thyroid hormones seem to be important for the development of the male reproductive system but not the female.

IV. SELECTED THYROID-ACTIVE CHEMICALS' REPRODUCTIVE IMPACT ON HUMANS AND RODENTS

This session's presentations and discussions compared the effects of four thyroid-active medications in humans and rats. Pregnant women are usually administered MTZ and PTU, two medications used to treat hyperthyroidism. Both human and veterinary medicine make extensive use of SMZ as an antibacterial agent. Thyroid hormone production is inhibited by these substances because they block thyroid peroxidase in the thyroid gland and PTU inhibits monoiodinase. The anticonvulsant medication PB enhances thyroid hormone metabolism and excretion while inducing hepatic enzymes.

Although the precise way that PTU and MTZ affect testis development is unknown, one theory that was put out at the conference was that they do so by stimulating cyclin-dependent kinase (CDK) inhibitors. P27KIP1 mutant mice showed increased proliferation of Sertoli cells, which is comparable to that found in hypothyroid animals. T3 is thought to influence Sertoli cell maturation via controlling p27KIP1 expression, which in turn influences cell cycle regulation. According to immunohistochemical research, p27 expression is low in cells that proliferate quickly, such as newborn Sertoli cells or Sertoli cell tumours, as well as in animals with hypothyroidism.

SMZ decreases thyroid peroxidase activity, same like PTU and MTZ do. Studies on rodents have shown that very high dosages of SMZ have detrimental effects on reproduction, which are linked to elevated serum TSH. At levels that have a major impact on the thyroid gland, SMZ seems to be a mild toxin of the male reproductive system in rodents. High dosages of structurally related compounds, such as sulfonamides and sulfasalazine, have also been shown to have reproductive effects in rats, but these effects are not linked to changes in thyroid function.

V. HUMAN RELEVANCE AND PROTOCOL FACTORS

ISSN 3063-8186. Published by Universitas Muhammadiyah Sidoarjo
https://doi.org/10.21070/ijhsm.v2i1.162

It has been disputed whether the current rat toxicity testing models are suitable for evaluating the risks to human thyroid health. According to the most recent testing standards, T3, T4, and TSH levels may be measured in sub chronic and chronic toxicity investigations if an impact is predicted. Weights and histology of thyroid glands are often reported. According to the recommendations for screening for developmental and reproductive damage, thyroid status testing is excluded. However, determining thyroid weight during necropsy is one of many ways to diagnose reproductive damage. It is still debatable whether study methodology and endpoints are best for evaluating the effects on the thyroid system. For rats, the existing procedures do not sufficiently address the concerns of dosage, timing, duration, and life stage exposure.The most common experimental animal used to detect chemical dangers is the rat. Rats are better able to sustain a normal pregnancy throughout testing and are less likely to have spontaneous abnormalities than mice and rabbits. Additionally, the adult rat is a suitable size for collecting many blood samples for TSH, total T3, and total T3 measurements. Thyroid hormone level blood tests (spot tests) needing.Changes in thyroid function at certain stages of newborn development may have significant impacts on the organism's growth. The timing and length of exposures at times of greatest susceptibility for the developmental end points under study, as well as the identification and selection of suitable end objectives for the life stage under study, are all necessary for a thorough protocol design. Serum chemistry alone is not a reliable way to evaluate the impact of thyroid hormones. For instance, determining the sensitivity of blood thyroid hormone levels in humans and rats to events mediated by thyroid hormones in the central nervous system and other thyroid-sensitive endpoints requires meticulous examination and laboratory confirmation.The design of a thorough screening program should have endpoints that drive the course of further toxicity testing. Thus, it is necessary to distinguish moderate thyroid effects from other harmful effects and to have the flexibility to include endpoint screening for thyroid effects into existing testing methods. The two-generation reproductive toxicity research design was suggested to include end points to evaluate the thyroid health of the mother and children. Screening for thyroid-related effects in

ISSN 3063-8186. Published by Universitas Muhammadiyah Sidoarjo
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the offspring is part of this research methodology. Affected puppies, for instance, can be underweight at birth or weigh little as they grow. To find out whether the foetal thyroid gland is impacted, it might be checked if pups are not thriving. Discussions were held about both new and standard endpoints for measuring thyroid-related effects during pregnancy. Since acoustic startle reaction has a strong cross-species connection between rodents and humans, it may be used to evaluate postnatal neurotoxicity in rat pups. In neonatal mammals, thyroid hormones regulate body temperature. Other end points that might be evaluated include the pups' reactions to shivering and/or temperature regulation. Existing reproductive toxicity methods might be supplemented with the aforementioned assays.

VI. SUMMARY

An overview and discussion of the significance of thyroid-related effects on development and reproduction in mice for predicting similar outcomes in humans were given. For this workshop, a background thyroid paper was prepared that went into great detail on this complex subject. Rats and humans shared and differentiated in multiple significant ways (Table 1). It was considered necessary to compare the severity of thyroid malfunction, which negatively impacts several organs and tissues, in people and rats in order to forecast human health consequences. It was examined if the current rat toxicity testing models might be used to evaluate the risks to human thyroid health. The requirements for developmental and reproductive toxicity testing do not currently include thyroid status testing. However, for some reproductive regimens, a thyroid gland weight assessment is advised. Currently, standards for developmental and reproductive toxicity testing do not include thyroid status testing. However, certain reproductive techniques suggest determining thyroid gland weight. Blood T3, T4, and TSH levels may be assessed if an influence is suspected, and thyroid gland weight and histology may be examined during necropsy for subchronic and chronic toxicity examinations. Present biochemical testing methods do not adequately screen for thyroid problems that may affect fertility and child development. Therefore, it was recommended at this workshop that thyroid function be assessed as part of testing methods for reproductive and

ISSN 3063-8186. Published by Universitas Muhammadiyah Sidoarjo
https://doi.org/10.21070/ijhsm.v2i1.162

developmental toxicity.

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