Systemic Toxicology

Toxicology of the Endocrine System

Overview

Among the various organ systems of the body, the endocrine system is somewhat unique.

While most systems are associated with a specific physiological task, the endocrine system functions to regulate many of the activities associated with these other systems.

Disruption of normal endocrine function by exogenous chemicals can result in multiple, diverse, and dire consequences.

Overview

Toxicity to the endocrine system is most associated with altered development, growth, maturation, and reproduction.

Endocrine toxicity also can present as gastro-intestinal dysfunction, malaise, neurological and other disorders.

Therefore, endocrine toxicity often can be misconstrued as toxicity to some other endocrine-regulated system of the body.

Overview

The endocrine system, tragically entered the limelight because of the widespread use of the drug diethylstilbestrol (DES).

DES, a nonsteroidal synthetic oestrogen, was prescribed to pregnant woman from the 1940s to the 1960s as a prophylactic against miscarriage.

Following the discovery of the endocrine toxicity of this drug, many additional drugs and environmental chemicals have been shown to mimic the action of hormones or interfere with their hormonal function.

Overview

Endocrine toxicities often have been clearly shown, in laboratory studies, to result in endocrine-related toxicity.

In some instances, drug use or exposure to ambient environmental chemicals has been shown to result in endocrine toxicity.

The Endocrine System

The endocrine system can be broadly described as an assemblage of organs (glands) that produce chemical messengers (hormones) that regulate various bodily functions.

Functions regulated by the endocrine system are those involved in the maintenance of homeostasis and physiological progression.

Include: maintenance of the reproductive system, energy production, and metabolism.

The Endocrıne System

Endocrine signaling pathways from the central nervous system to the target organ typically occur along axes.

An axis is defined by the endocrine glands that produce signaling hormones along the cascade (i.e., hypothalamic–pituitary–gonadal axis), and sometimes, a terminal target organ of the signaling pathway (i.e., hypothalamic– pituitary–gonadal–hepatic axis).

The Endocrine System

Nuclear Receptors

Toxicologically the function of the terminal hormones of endocrine cascades (i.e., steroid, retinoid, thyroid hormones) appear to be most susceptible to disruption by chemicals.

Many foreign molecules share sufficient characteristics with these hormone molecules

Allow binding to the nuclear receptors of these hormones in either an agonistic or antagonistic fashion.

The Endocrıne System

The binding of the xenobiotic to the nuclear receptor results in aberrant receptor function with associated toxicological outcome.

Cell surface receptors to peptide hormones, on the other hand, can likely discriminate between peptide molecules and nonpeptide xenobiotics.

Minimizes the likelihood of interaction and associated disruption of function.

The Endocrıne System

The nuclear receptor superfamily consists of members of the steroid receptor family and the thyroid receptor family.

Members of these two receptor families are distinct in many structural and functional attributes.

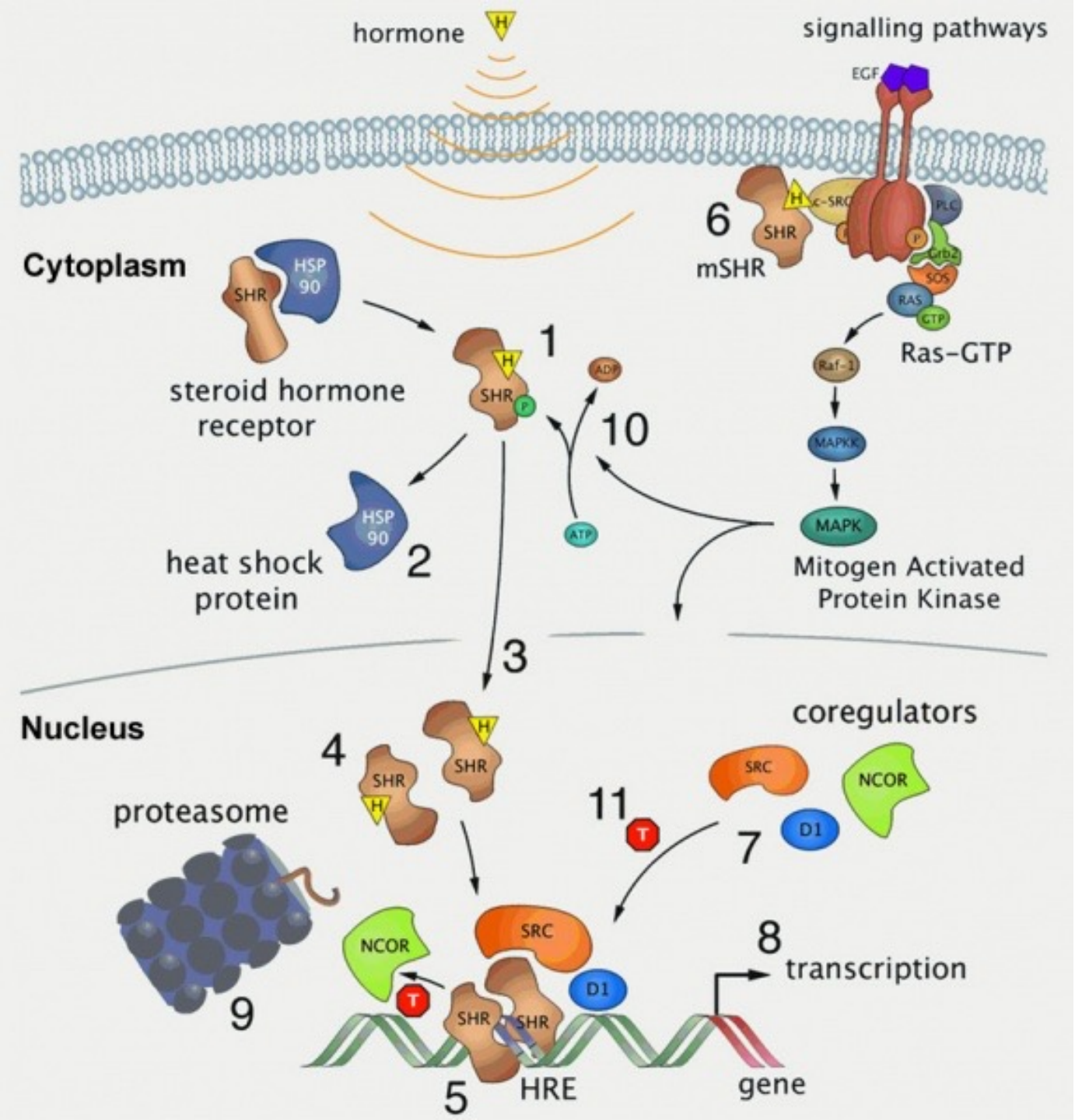
Steroid receptor family members – exist in the extranuclear matrix of the cell in association with various accessory proteins (hsp 90, hsp 70, hsp 56).

The Endocrıne System

Steroid Hormone Receptors (SHR) act as hormone dependent nuclear transcription factors.

Upon entering the cell by passive diffusion, the hormone (H) binds the receptor, which is subsequently released from heat shock proteins, and translocates to the nucleus.

There, the receptor dimerizes, binds specific sequences in the DNA, called Hormone Responsive Elements or HREs, and recruits a number of coregulators that facilitate gene transcription.



Steroid Hormone Signalling

Legend

1. hormone binding
2. chaperone interaction
3. nuclear translocation
4. receptor dimerization
5. DNA binding
6. putative membrane-bound receptors
7. coregulator recruitment
8. transcription
9. proteasomal degradation
10. modulation by cellular signalling pathways
11. antagonist resistance

This latter step can be modulated by receptor antagonists like tamoxifen (T), and cellular signalling pathways.

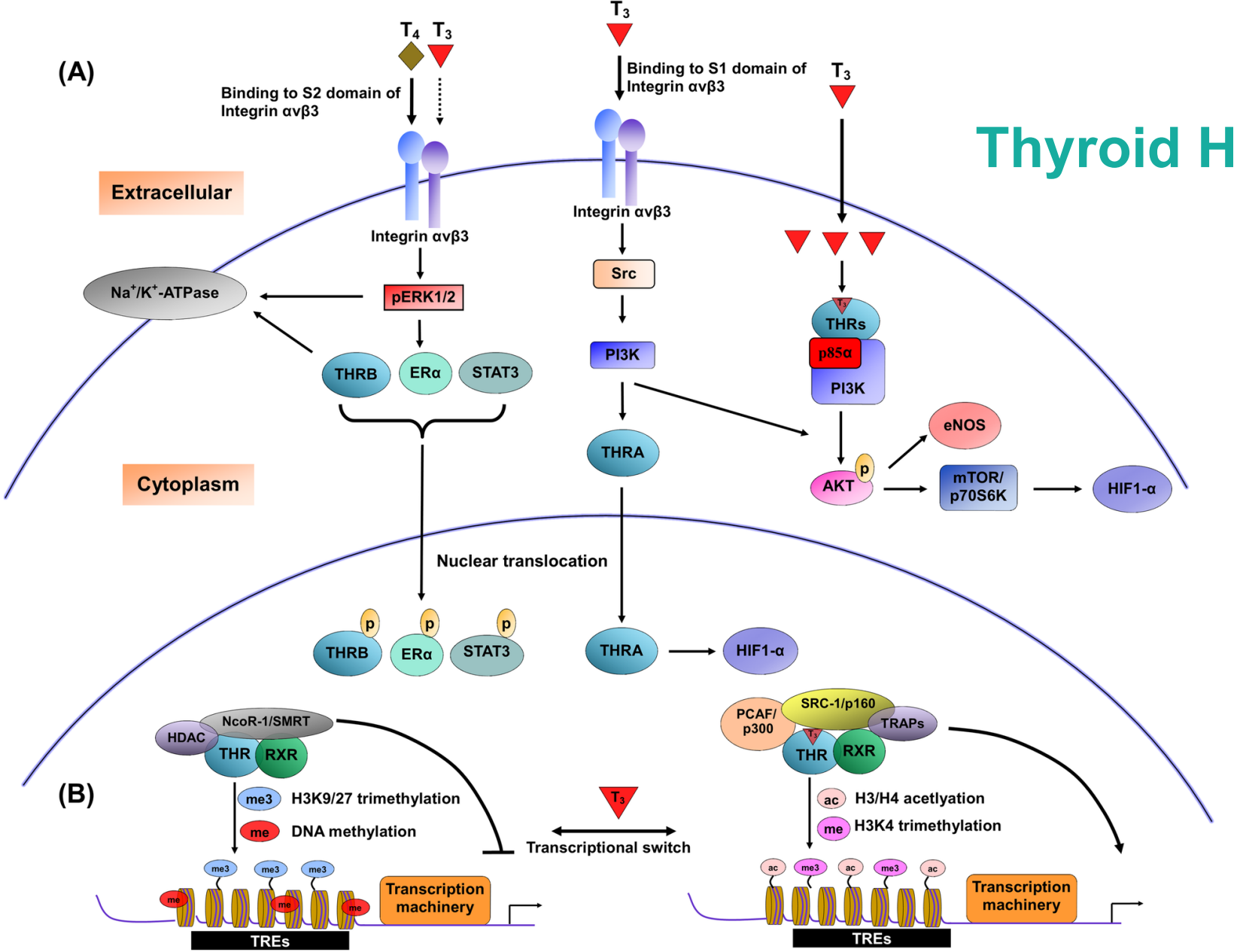
The Endocrine System

In contrast to the steroid receptor family, members of the thyroid receptor family typically do not associate with accessory proteins and are not localized to the extranucleus matrix.

Rather, these receptors exist in the basal state associated with chromatin in the cell nucleus.

When bound by hormone ligand, thyroid receptor family members dissociate from the chromatin and typically form heterodimeric combinations with the retinoid-X receptor (RXR).

Thyroid Hormone Signalling



In the nucleus, THRs form heterodimers with the retinoid X receptor (RXR) at thyroid hormone response elements (TREs), within the regulatory regions of downstream genes.

The Endocrıne System

Due to their lipophilic nature, steroid hormones are mobilized in the circulatory system by transfer proteins.

Sex hormone-binding globulin (SHBG) is one such transfer protein that binds testosterone, 17β -estradiol, and other sex steroids.

Roughly half of circulating testosterone and 17β -estradiol is bound to SHBG, also, receptors exist on the surface of some cells that are capable of binding unliganded SHBG.

The Endocrine System

Unliganded SHBG, which is bound to the cell surface receptor, can subsequently bind steroid hormone.

Binding of an appropriate hormone to the SHBG then stimulates a signal-transduction pathway within the cell.

Some steroid hormones function as SHBG: SHBG-receptor agonists, while others function as antagonists.

Endocrine Disruption

Xenobiotics can disrupt hormone activity through a variety of mechanisms, though the predominant mechanisms appear to involve:

a) binding to the hormone receptor, either as an agonist or antagonist

b) modulating endogenous steroid hormone levels.

Endocrine Disruption

Hormone Receptor Agonists

Xenobiotics can act as receptor agonists and stimulate receptor-dependent physiological processes in the absence of the endogenous receptor ligand (hormone).

Among the steroid hormone receptors, the estrogen receptor appears most susceptible (promiscuous) to the agonistic action of xenobiotics.

Estrogen receptor agonists are diverse in molecular structure.

Endocrine Disruption

Hormone Receptor Antagonists

Receptor antagonists are defined as chemicals that bind to a hormone receptor but do not activate the receptor.

Rather, these chemicals inhibit receptor activity by preventing the endogenous hormone from binding to and activating the receptor.

Some xenobiotic may act as either agonist/antagonist

Endocrine Disruption

For example, the drug tamoxifen functions as an estrogen receptor antagonists in reproductive tissue but functions as an agonist with respect to the preservation of bone mineral density and reducing serum cholesterol concentrations

Tamoxifen can function as a prophylactic against the growth of estrogen-responsive breast cancers and osteoporosis via two different mechanisms.

Endocrine Disruption

Environmental estrogen receptor antagonists include some phytochemicals (i.e., flavonoids) and polychlorinated biphenyl (PCBs; i.e., 3,3,4,4-tetrachlorobiphenyl).

Estrogen receptor antagonism typically leads to de-feminization (loss of female traits).

Endocrine Disruption

Androgen Receptor

Chemicals that bind to the androgen receptor in an antagonistic fashion include the pharmaceuticals spironolacton and cimetidine.

Some environmental chemicals act as androgen receptor antagonists include the metabolites of the agricultural fungicide, some DDT metabolites and some hydroxylated PCBs.

The consequence of androgen receptor antagonism is typically considered demasculinization (loss of male traits).

DDT has been banned in the United States (and many countries) since 1972 after it became clear that it was linked to birth defects, diminished fertility and miscarriages.

Endocrine Disruption

Glucocorticoid Receptor:

Some drugs (i.e., mifepristone) elicit antagonistic activity toward the glucocorticoid receptor.

This is associated with adverse side effects of some drugs and has been capitalized upon therapeutically for the modulation of the glucocorticoid receptor.

Glucocorticoid receptor antagonists can adversely affect growth, development, and other glucocorticoid-regulated processes.

Endocrine Disruption

Organizational versus Activational Effects of Endocrine Toxicants

Effects of receptor agonists or antagonists on endocrine related processes are often described as being either organizational or activational.

Organizational – typically results from neonatal or prenatal exposure during which time hormones are directing various irreversible aspects of development.

Endocrine Disruption

The disrupting effect of the toxicant also is irreversible.

These organizational effects may be evident only later in life during maturation or reproduction.

E.g., neonatal exposure to DES resulting in proliferation of epithelial cells of the reproductive tract at reproductive maturity

Endocrine Disruption

Activational effect – occurs in the same time frame as the exposure and is the consequence of the toxicant disrupting the immediate role of a hormone in some physiological process.

Effects are reversible following cessation of exposure to the toxicant.

E.g., Exposure of adult males to an antiandrogen can result in a decrease in prostate size, and restoration of gland size up cessation of exposure.

Endocrine Disruption

Inhibitors of Hormone Synthesis

Endocrine toxicants can elicit anti-hormone activity by lowering levels of endogenous hormone in the body.

With steroid hormones, chemicals typically elicit this effect by inhibiting enzymes necessary for synthesis of the hormone.

For example, the cytochrome P450 enzyme CYP19 is responsible for the aromatization of testosterone to form 17β-estradiol.

Endocrine Disruption

CYP19 inhibitors can lower endogenous 17β-estradiol levels resulting in de-feminization.

Cytochrome P450s enzymes also are critical to various hydroxylation reactions that contribute to the synthesis of androgens and other steroid hormones and inhibition of these enzymes can result in a variety of anti-steroid hormone effects.

Consequences of the lowered steroid hormone levels are typically comparable to those effects elicited by antagonists of the hormone's receptor.

Endocrine Disruption

Inducers of Hormone Clearance

Steroid and thyroid hormones are inactivated and cleared from the body by the same biotransformation processes that are involved in chemical detoxification.

Predominant among the hormone biotransformation processes are hydroxylation, glucuronic acid conjugation, and sulfate conjugation.

The thyroid hormones T_3 and T_4 are inactivated and cleared following sulfate and glucuronic acid conjugation, respectively.

Endocrine Disruption

The glucuronosyl transferase enzymes that are responsible for the elimination of T_4 are induced following exposure to phenobarbital type inducers.

Thus exposure to chemicals such as some dioxins and PCBs can result in enhanced clearance of thyroid hormone resulting in low circulating thyroid hormone levels.

The resulting hypothyroid state can result in a variety of pathological conditions.

Endocrine Disruption

Hypothyroidism in adults results in various activational abnormalities including impaired cardiovascular, pulmonary, intestinal, and renal function.

Chronic fatigue, and difficulty in concentration are also associated with thypothyroidism in adults.

Enhanced clearance of sex steroids can contribute to endocrine disruption if the toxicity also results in impaired hormone synthesis.

Endocrine Disruption

Hormone Displacement from Binding Proteins

Steroid and thyroid hormones are typically distributed throughout the body while bound to serum-binding proteins such SHBG, corticosteroid-binding globulin, thyroxine-binding globulin (transthyretin), and albumin.

Some xenobiotics can compete with hormones for binding to the blood proteins.

As a result the circulating hormone reservoir can be depleted and free hormone becomes limited.

Incidents of Endocrine Toxicity

Organizational Toxicity

Offspring exposed to DES during fetal development experienced a variety of problems upon attainment of sexual maturity.

DES daughters experience a significantly increased risk of clear cell adenocarcinoma of the vagina and cervix.

DES daughters have increased risk of a variety of reproductive disorders including structural abnormalities of the reproductive tract, infertility, ectopic pregnancy, miscarriage, and pre-term delivery.

Incidents of Endocrine Toxicity

Less is known of the risks faced by males exposed to DES during fetal development.

Epidemiological studies of DES sons have suggested increased risk of various testicular abnormalities including epididymal cysts, testicular varicoceles, and undescended testis.

Hyperplasia and metaplasia of the prostatic ducts in DES sons also have been reported.

Incidents of Endocrine Toxicity

Activational Toxicity

- Administration of estrogenic pharmaceuticals to children or adults can result in a variety of abnormalities associated largely with secondary sex characteristics that are reversible upon cessation of drug treatment.

- Gynecomastia, the development of breast tissue in males, is often the consequence of perturbations in the normal androgen/estrogen ratio.

Incidents of Endocrine Toxicity

Prolonged administration of drugs with estrogenic or antiandrogenic activity can cause gynecomastia.

Also, activational toxicity from estrogenic drugs has been reported to cause pseudoprecocious puberty in children

This includes, pubic or facial hair, morphological changes in sex organs, breast development, etc. in preadolescent individuals.

Incidents of Endocrine Toxicity

Hypothyroidism

Toxicity resulting in hypothyroidism is manifested at several organ systems, and individual effects may be misdiagnosed as organ-specific toxicity.

Hypothyroidism can result from various causes other than chemical toxicity including diseases of the hypothalamic–pituitary–thyroidal axis, iodine deficiency, and heritable defects in thyroid hormone production.

Incidents of Endocrine Toxicity

Chemical agents that have historically been recognized for their ability to cause hypothyroidism include lithium, and para-aminosalicylic acid.

Disruptions in thyroid hormone levels can occur through chemical-induced increases in the metabolic inactivation and elimination of the hormone.

Chemicals that are capable of increasing the metabolic clearance of thyroid hormone include the polycyclic halogenated hydrocarbons (PHH) (i.e., dioxins, furans, PCBs and PBBs).

Epilogue

The endocrine system possesses many targets at which toxicants can elicit either reversible or permanent effects on an individual.

Effects of chemicals on endocrine-regulated processes such as development, maturation, growth, and reproduction have been well documented various studies.

Less is known of the potential effects of endocrine toxicants on more generalized endocrine-regulated processes.

Epilogue

However, it is important to recognize that chemicals have the potential ability to interfere with other hormone cascades, including those involving mineral corticoids, glucocorticoids, retinoids, and perhaps some peptide hormones.

Research is needed to increase our understanding of the susceptibility of endocrine signaling pathways involving these hormones to chemical toxicity and, ultimately, to our establishing chemical exposure limits that include these considerations.

The End