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FUNCTIONAL ACTIVITY OF THE THYROID GLAND IN STRESS CONDITIONS

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Absract

An analytical review was conducted of studies investigating the effects of acute and chronic stress on thyroid gland metabolism. Particular attention is given to the influence of stress and, specifically, glucocorticoids on thyroid status. The discussion encompasses stress-related alterations in iodine uptake, oxidation, and organification within thyrocytes, as well as changes in the peripheral metabolism of thyroid hormones, including their storage, transport, and tissue-specific deiodinase activity.The role of stress in the development of thyroid disorders is also examined, with emphasis on functional alterations of the thyroid gland associated with dysregulation of the hypothalamic–pituitary–adrenal axis. Emerging evidence suggests consistent patterns of thyroid dysfunction in conditions involving impaired pituitary–adrenal system activity.

Mechanisms underlying stress-induced thyroid impairment remain an important area for further investigation, particularly given the significant systemic consequences associated even with subclinical forms of thyroid insufficiency.

Keywords

stress, glucocorticoids, thyroid gland, thyroid hormones, iodine uptake and organification, deiodinases.

Introduction. In recent decades, a substantial body of research has focused on elucidating the effects of stress on thyroid gland function and the peripheral metabolism of thyroid hormones [1–4]. The growing scientific interest in this field appears to be associated with several interrelated factors. First, despite improvements in iodine prophylaxis programs, the incidence of thyroid disorders continues to increase in many regions worldwide [5, 6], stimulating further investigation into factors capable of modifying iodine metabolism within thyroid tissue [7]. Second, contemporary society is characterized by intensified psychological, social, environmental, and occupational stressors. Modern socio-economic development has effectively created an environment with persistently elevated stressogenic influences.

The biological consequences of chronic exposure to stressors may include both adaptive responses and maladaptive processes leading to structural and functional pathology. According to Hans Selye, the founder of stress theory, stress represents a nonspecific response of the organism to any demand placed upon it. The outcome of stress exposure involves the development of the general adaptation syndrome and the establishment of stress resistance; however, prolonged activation of stress systems may result in endocrine dysregulation.

Initial investigations conducted in the mid-20th century addressed the morphological effects of stress on the thyroid gland [8], glucocorticoid-mediated regulation of the hypothalamic–pituitary–thyroid axis at the hypothalamic and pituitary levels [9], and alterations in overall thyroid status [10]. Currently, particular attention is directed toward the role of glucocorticoids in regulating key stages of thyroid cellular metabolism, as well as toward identifying mechanisms underlying stress-induced thyroid dysfunction and potential preventive strategies.

Effects of Acute Stress on Thyroid Function

The impact of acute stress on thyroid activity depends primarily on the duration and intensity of the stressor and is typically characterized by a biphasic pattern of response [11].

Experimental models of acute psychogenic stress demonstrate that short-term immobilization (approximately two minutes) in rats is associated with an increase in circulating thyroxine (T4) and triiodothyronine (T3) concentrations [12]. However, prolonged immobilization lasting from 5 to 240 minutes results in a reduction of thyroid hormone levels [13], particularly T3 [14]. This decrease in T3 is accompanied by an elevation in reverse triiodothyronine (rT3), unchanged T4 concentrations, and suppression of thyroid-stimulating hormone (TSH) secretion [15].

Adrenalectomy and administration of metyrapone have been shown to prevent stress-induced alterations in iodothyronine metabolism observed during immobilization experiments, indicating a central role of glucocorticoids in mediating these changes. Moreover, administration of thyrotropin-releasing hormone (TRH) following immobilization increases circulating thyroid hormone levels , suggesting that stress-associated reductions in thyroid hormone concentrations are predominantly due to inhibitory regulation rather than depletion of synthetic capacity within the gland.

In certain experimental conditions, including 30-minute immobilization in mature and immature male rats at different circadian phases [1] and exposure to cold-water swimming , no significant changes in thyroid hormone concentrations were observed. Similarly, surgical stress did not significantly affect circulating thyroid hormone levels or alter T4 metabolism in hepatic, renal, or cerebral tissues .

Administration of stress-equivalent doses of exogenous glucocorticoids produces a marked suppressive effect on circulating thyroid hormone concentrations . In pregnant sheep, dexamethasone reduces serum T4 and T3 levels while increasing rT3 concentrations; in fetuses, increased T3 and rT3 levels are observed without significant changes in T4 . In 18-day-old chick embryos, dexamethasone and corticosterone administration results in elevated T3 levels accompanied by reductions in T4 and rT3 .

2. The Influence of Repeated and Chronic Stress on Thyroid Function

The effects of repeatedly occurring and chronic stress on thyroid gland (TG) function largely correspond to the effects of acute stress and are characterized by bidirectional changes in blood T4 and T3 levels. Sixty days of unavoidable stress induced an increase in T3 concentration and a decrease in T4 in male rats . Under chronic stress, a decrease in both T3 and T4 concentrations was observed . Keeping animals under unavoidable stress conditions, in contrast to avoidable stress , as well as exposure to prolonged intensive stress , caused a decrease in T3 levels, as demonstrated by the authors using morphometric and biochemical methods of analysis.

Activation of thyroid function (increased T4 concentration) was noted after daily one-hour immobilization of cats for 7 days , mild chronic stress in Sprague–Dawley and Wistar rats (increased serum total T4 and T3 levels) , and prolonged transportation of male cattle (increased levels of total and free iodothyronines) .

Chronic stress during pregnancy in rats caused bidirectional changes in thyroid function: a decrease in the mother and an increase in thyroid status in the offspring . In the studies of Servatius R.J. et al. [30], it was shown that exogenous glucocorticoids (administration of 1 ml of solution containing 10 mg/L corticosterone) reduced T4 levels, whereas endogenous glucocorticoids (2-hour stress for 7 days) did not produce persistent changes in thyroid hormone levels in rats.

In a later study [13], it was established that 14 days of unavoidable stress in rats resulted in decreased serum T4 and T3 levels, no changes in TRH mRNA levels in the paraventricular nuclei of the hypothalamus, and increased mRNA levels of hypothalamic agouti-related protein (AGRP). A significant correlation between serum corticosterone levels and total T3 as well as AGRP mRNA levels suggests the involvement of this protein in stress-induced regulation of the hypothalamic–pituitary–thyroid axis.

3. Interrelationship of Hypothalamic and Pituitary Hormones of the Adrenal and Thyroid Systems

Administration of TRH was accompanied by a decrease in serum ACTH levels in stressed rats . Corticotropin-releasing hormone induces an increase in plasma TSH and T4 levels . In the study by Banos C. et al. , administration of ACTH at a dose of 2 mg to healthy volunteers reduced the TSH response to TRH. These data characterize antagonistic relationships between TSH and ACTH.

4. Influence of Glucocorticoids on TRH and TSH Levels

The synthesis of TSH is primarily determined by the balance between positive regulation by TRH and negative feedback by T3; in addition, somatostatin and dopamine exert inhibitory effects. Glucocorticoids reduce serum TSH levels in both animals and humans. Administration of a high dose of dexamethasone to humans resulted not only in suppression of TSH but also in a reduced TSH response to TRH administration . The suppressive effect of dexamethasone on TSH decreases in elderly individuals (68–75 years) .

A single administration of 500 mg hydrocortisone increases both TSH production and TRH stimulation ; only prolonged hypercortisolism (Cushing's disease) may lead to decreased TSH levels. The earlier restoration of circadian serum TSH rhythms compared with cortisol after betamethasone administration indicates that TSH levels are not under direct control of circulating cortisol .

In adrenalectomized (AE) rats, serum TSH levels decreased, but not pituitary TSH levels . Glucocorticoids caused a reduction in circulating TSH. Administration of dexamethasone to hypothyroid rats reduced serum TSH levels; dexamethasone enhanced the TSH reduction induced by T3 administration. However, no changes were observed in pituitary TSH content or in mRNA of the α- and β-subunits of TSH.

More definitive data on the influence of glucocorticoids on the hypothalamic–pituitary–thyroid axis at the level of hypothalamic structures were obtained by Kakucska I. et al. . In adrenalectomized rats, an increase in corticotropin-releasing hormone mRNA and a parallel increase in pro-TRH mRNA (by 68.3%) were demonstrated in the paraventricular nuclei of the hypothalamus. In contrast, administration of corticosterone and dexamethasone caused a marked decrease in corticotropin-releasing hormone mRNA and pro-TRH mRNA by 43.2% and 73.2%, respectively. Minor changes in pro-TRH mRNA were observed in the lateral hypothalamus.

Stress is involved in the mechanism of reduced TRH/TSH secretion, possibly through glucocorticoids, cytokines, and opioids. A new regulatory mechanism has recently been proposed, involving pituitary-derived neuromedin B, gastrin-releasing peptide, and pituitary leptin, which act as local inhibitors of TSH release.

In in vitro studies, lipocortin-1 was identified as a mediator of glucocorticoid-induced suppression of TSH secretion by the anterior pituitary. Treatment of anterior pituitary cells with dexamethasone (0.1 µmol/L) significantly increased the amount of lipocortin-1 (LC-1) bound to the external surface of the cells and reduced intracellular LC-1 levels. Addition of the N-terminal fragment of LC-1 (amino acid residues 1–188) reduced TSH release induced by vasoactive intestinal polypeptide and forskolin but was insufficient when cells were stimulated with the calcium channel activator BAYK 8644 (10 µmol/L). The inhibitory effect of dexamethasone was reversed by the addition of monoclonal antibodies to LC-1.

The inhibitory action of dexamethasone has been used to monitor subclinical hypothyroidism in obese patients. Administration of TRH during dexamethasone treatment increases TSH levels only in patients with hypothyroidism but not in obese individuals with euthyroid status.

5. The Effect of Stress on Peripheral Metabolism of Thyroid Hormones (Activity of Deiodinases in Target Tissues)

The most important target tissues of thyroid hormones are the brain, liver, kidney, heart, muscle, and immune system. It is possible that glucocorticoids regulate tissue T3 levels.

During acute stress, the T3 content in the brains of male and female rats increases by 12–19%. Stress (deprivation of food and water for 2 days) increased T3 content in thymic lymphocytes of suckling rat pups and adult females, which normalized after 48 hours.

It is well known that T4, the main hormone produced by the thyroid gland, does not exhibit direct biological activity and can be considered a prohormone or a plasma reservoir of thyroid hormones, which apparently has important physiological significance. The main role in T4 activation is played by a family of selenocysteine-containing oxidoreductases known as iodothyronine deiodinases. Three types of these enzymes have been identified, and their activity largely determines the realization of thyroid hormone effects. Deiodinase localization and activity are tissue-specific.

Type I 5'-deiodinase (D1) is localized in the liver, kidneys, thyroid gland, lungs, eyes, and other tissues. Type II 5'-deiodinase (D2) is mainly found in the brain, pituitary, myocardium, skeletal muscles, and brown adipose tissue. Type III 5'-deiodinase (D3) is present in the liver, skin, brain, and placenta. D1 and D2 catalyze the conversion of T4 into T3, whereas D3 deiodinates the inner tyrosyl ring at positions 3 and 5, inactivating T3 and T4 and playing an important role in regulating thyroid hormone bioavailability during embryonic development.

The effects of glucocorticoids on different tissue deiodinases are differentiated and depend on tissue type and age; their role in regulating deiodinases during embryogenesis has been established. Administration of dexamethasone to sheep in late pregnancy induced increased fetal hepatic D1 activity and decreased renal D3 activity.

In 20-day-old rat fetuses, dexamethasone did not affect circulating thyroid hormone levels despite decreased deiodinase activity in the liver and kidney and increased activity in the brain; apparently, at this stage, thyroid secretion rather than peripheral deiodination determines thyroid status. However, in 5-day-old rat pups, dexamethasone increased circulating T3 and T4 as well as D3 activity in the liver and kidney but not in the brain; in 12-day-old pups, the effects of dexamethasone persisted only for hepatic and renal D3.

The effects of stress on deiodinase activity in various tissues have not been fully established. Glucocorticoids most significantly affect D2 activity in the brain. Even mild short-term stress induced a marked increase in type II 5'-iodothyronine deiodinase activity in the brain, accompanied by a 300% increase in T3 concentration. These effects were not observed in the liver, and no changes in type I 5'-iodothyronine deiodinase activity were detected in either the brain or liver. The effects of dexamethasone are characterized by upregulation of D2 activity.

Administration of steroidogenesis inhibitors aminoglutethimide and metyrapone inhibited D2 activity in rat adrenal glands both under physiological rest and stress conditions, suggesting that a normal corticosterone level is required for the deiodinase response to stress exposure.

Glucocorticoid regulation appears to be most differentiated for D2. Recent in vitro studies using rat and mouse pituitary cells have demonstrated increased D2 activity and mRNA expression after glucocorticoid addition , whereas the effect was opposite in mouse mammary epithelial HC11 cells. In At-20 pituitary tumor cells, D2 was identified, and both its activity and mRNA expression were stimulated by glucocorticoids and CRH.

Reduced circulating thyroid hormone levels and TRH mRNA during fasting or caloric restriction are accompanied by increased D2 activity and D2 mRNA expression. Investigation of D2 activation mechanisms during fasting revealed that decreased leptin levels play a permissive role in glucocorticoid-induced regulation of D2.

Data regarding the influence of glucocorticoids on D1 activity in various tissues are inconsistent. Cold stress in rats for 24 hours and 28 days, as well as cold stress combined with immobilization, reduced hepatic 5'-deiodinase-1 activity. Immobilization of rats for 6–8 hours was associated with decreased D1 activity in the liver and kidneys, due to reduced enzyme activity rather than decreased substrate availability, since serum T4 levels remained unchanged [15].

In adult rats, glucocorticoids induce a decrease in hepatic D1 activity. However, in vitro studies in rat hepatocyte cultures showed the opposite effect: glucocorticoids increased D1 activity and D1 mRNA expression. In NRK 52E kidney cells, dexamethasone increased D1 activity and mRNA expression, whereas in pituitary tumor cell cultures no effect of glucocorticoids on D1 or its mRNA was observed.

In fish (Nile tilapia), dexamethasone disrupts peripheral deiodinase activity by reducing D1 and D2 activity in the liver, and its prolonged administration leads to increased availability of circulating T3.

A decrease in plasma T3 and an increase in rT3 during stress may be associated with glucocorticoid stimulation of D3. Glucocorticoids reduce D3 expression in rat brown adipose tissue cells. In studies of human cell lines, estradiol increased D3 activity in ECC-1 cells, whereas dexamethasone inhibited D3 in WRL-68 cells only in the presence of fetal bovine serum in the culture medium.

Dexamethasone dose-dependently inhibits the stimulatory effect of T3 on intercellular adhesion molecule ICAM-1 protein expression in human ECV 304 cells.

The presented data indicate that glucocorticoids modulate thyroid hormone effects by influencing the activity of various deiodinases in target tissues. They most significantly induce D2 activity in the brain, markedly increasing T3 levels in brain tissue, while in the liver and kidneys stress exerts an inhibitory effect on D1 activity. The mechanisms of glucocorticoid regulation of T4 deiodination in different tissue cells require further investigation.

6. Influence of Glucocorticoids and Stress on Deposition and Transport of Thyroid Hormones in Blood

Glucocorticoid hormones regulate the concentration of serum thyroxine-binding globulin (TBG); a single administration of supraphysiological doses of glucocorticoids reduces TBG levels in the blood. ACTH-induced hypersecretion of endogenous glucocorticoids in healthy women resulted in decreased serum TBG levels for four days.

Prolonged immobilization stress (8 hours) caused a reduction in TBG concentration by more than 50%, although T4 concentration remained unchanged [15]. After adrenalectomy (AE) in rats, the ability of serum to bind T4 increased threefold. Using polymerase chain reaction methods, it was established that hepatic TBG mRNA levels in rats increased more than fivefold after AE and decreased below intact control levels following administration of replacement doses of corticosterone. Apparently, glucocorticoids tonically regulate serum TBG levels at the transcriptional level.

7. Influence of Glucocorticoids on Iodide Uptake by the Thyroid Gland

Iodine uptake is a key function of thyroid cells and is under the control of thyroid-stimulating hormone (TSH); TSH stimulates ^{131}I uptake both in vivo and in vitro, as well as the expression of the sodium-iodide symporter (NIS) in cultured human thyrocytes. The sodium-iodide symporter (NIS) is localized on the apical membrane of thyrocytes, and its activity is coupled with Na^+/K^+-ATPase activity. TSH affects transcription of the NIS gene through Pax-8 and, apparently, through factors activated by intercellular interactions during folliculogenesis.

High doses of iodine directly inhibit iodide uptake by affecting regulation of NIS protein and mRNA expression. Immobilization stress, as well as ACTH administration to hypophysectomized rats, increased thyroid ^{131}I uptake in vitro. Cultivation of FRTL-5 thyrocytes under hypoxic conditions was accompanied by increased iodide uptake , while heat stress (15 minutes at 45°C) abolished this effect.

In cultured sheep thyroid follicles, it was established that a combination of TSH and cortisol (10 nmol/L) optimally stimulates iodide uptake without additive or synergistic effects; the same effect was reproduced by a combination of dexamethasone and TSH . In addition, physiological concentrations of insulin and insulin-like growth factors (IGF-I and IGF-II) potentiated the stimulatory effect of TSH.

Further studies demonstrated a dual-level direct effect of hydrocortisone on thyroid cell metabolism. Hydrocortisone at physiological concentrations (1–1000 nmol/L) dose-dependently stimulated TSH- and 8-bromo-cAMP-induced iodide uptake by increasing cAMP production and activating cAMP-dependent metabolic pathways in primary cultures of porcine thyrocytes. The stimulatory effect of hydrocortisone combined with TSH was inhibited by the glucocorticoid antagonist RU486, suggesting that the specific action of hydrocortisone is mediated through glucocorticoid receptors in thyrocytes.

The stimulatory effect of glucocorticoids on ^{131}I uptake has been proposed as a therapeutic approach in breast cancer and prostate cancer . After incubation of NP-1 cells with dexamethasone (10^{-8}–10^{-6} M), iodide uptake increased 1.5-fold, while NIS mRNA expression and protein concentration increased 1.7-fold. Cell death in NP-1 cells increased from 55% to 95%, indicating enhanced cytotoxicity of ^{131}I. In the same studies, using cloning and cell proliferation assays without radioisotopes, dexamethasone treatment reduced proliferation of prostate cancer cells.

Thus, stress exposure may be considered a factor promoting increased iodide accumulation in the thyroid gland—at least in the case of acute stress. However, further research is required to provide definitive conclusions, given the multi-level effects of glucocorticoid hormones on thyroid homeostasis.

8. Effects of Glucocorticoids on Oxidation and Organification of Iodide by Thyroid Cells

Studies investigating the effects of stress or glucocorticoids on iodide oxidation by thyroid peroxidase (TPO), iodination of thyroglobulin, and subsequent secretion of thyroid hormones are scarce in the literature. An inhibitory effect of tenfold administration of corticosterone (25, 50, 100 μg per 100 g body weight) on thyroid peroxidase activity in young female turtles has been demonstrated [40], although the mechanism of this inhibitory effect has not been investigated.

Research in this area appears particularly relevant, considering the key role of thyroid peroxidase in thyroid hormone biosynthesis. Electron microscopic examination of thyrocytes revealed accumulation of colloid droplets in the cytoplasm of follicles, which allowed the authors to postulate that prednisone may reduce basal thyroid hormone secretion by inhibiting lysosomal hydrolysis of colloid in follicular cells .

9. Role of Glucocorticoids in the Regulation of Thyroid Hormone Receptors

It is well established that T3 exerts most of its effects by binding to nuclear thyroid hormone receptors. A synergistic interaction between T3 and glucocorticoid hormones has been demonstrated in growth hormone synthesis in rat pituitary cells and in T3-induced metamorphosis in amphibians.

Glucocorticoid hormones enhance the metabolic action of T3. Dexamethasone increases the specific binding capacity of thyroid receptors in rat liver. Administration of dexamethasone to adrenalectomized rats increases the concentration of thyroid receptor β1 protein and its mRNA . Molecular studies using COS-7 cell transfection methods have shown that dexamethasone enhances the transcriptional activity of the thyroid receptor β1 promoter .

10. Thyroid Function in Adrenal Dysfunction

Considering the multilevel effects of glucocorticoids on thyroid status and peripheral metabolism of thyroid hormones, it is important to investigate thyroid functional activity under conditions of adrenal dysfunction.

Adrenalectomy (AE) in rats increases TSH stimulation of the thyroid gland and enhances its secretory activity [88]. In patients with adrenal insufficiency, withdrawal of glucocorticoid replacement therapy led to increased T3 concentration and decreased reverse T3 (rT3), while T4 and TSH levels remained unchanged .

Clinical studies describe cases of thyroid dysfunction in patients with hypercortisolism before and after adrenalectomy, as well as in adrenal insufficiency. The state of the hypothalamic–pituitary–adrenal axis largely determines thyroid status in humans.

In hypercortisolism associated with Cushing’s syndrome, patients exhibit reduced serum thyroid hormone and TSH concentrations; moreover, nodular goiter was detected in 56.2–66.6% of patients, significantly higher than in the control group. Prolonged hypercortisolism in Cushing’s syndrome leads to inhibition of both basal and TRH-stimulated TSH secretion .

In these patients, the pituitary response to TRH administration is weakened, and a negative correlation between plasma TSH and cortisol levels (but not T3) has been observed; after treatment, TRH responsiveness returns to normal.

A single case has been described in which Graves’ disease with severe thyrotoxicosis developed 140 days after successful surgery in a patient with Cushing’s syndrome. The authors suggest that suppression of hypercortisolism may activate previously latent autoimmune processes in the thyroid gland.

In another case, a woman with Cushing’s syndrome developed Graves’ disease with hyperthyroidism nine months after unilateral adrenalectomy . In some patients, adrenalectomy performed due to hypercortisolism resulted in transient thyroid dysfunction presenting as hypo- or hyperthyroidism [94].

After adrenal removal in a patient with Cushing’s syndrome, during reduction of prednisone replacement therapy to 5 mg/day, “silent thyroiditis” was detected, characterized by low TSH, elevated thyroid hormone levels, extremely low iodine uptake, and increased titers of antibodies to microsomal fraction and thyroglobulin .

Recent studies have shown that postoperative glucocorticoid deficiency after adrenalectomy in Cushing’s syndrome may lead to secondary hypothyroidism and hypercalcemia .

Murakami T. et al., in 103 patients with ACTH deficiency, identified signs of hypothyroidism—reduced free T3 and T4 concentrations, elevated TSH levels, and characteristic clinical manifestations of thyroid insufficiency (cold intolerance, muscle rigidity, loss of interest in life). After hydrocortisone therapy, disturbances of the pituitary–thyroid axis were resolved in more than 70% of cases, suggesting that glucocorticoid deficiency may be one of the causes of thyroid dysfunction.

Elevated TSH levels were observed in patients with Addison’s disease; administration of glucocorticoids produced dose-dependent inhibition of TRH-induced stimulation of thyrotropin production, suggesting that glucocorticoids regulate pituitary sensitivity to TRH .

11. Stress-Induced Thyroid Pathology and Investigation of Pathogenetic Mechanisms

At the present stage of research, there are no definitive data regarding the role of stress in inducing pathological changes in the thyroid gland (TG), despite the established close interrelationship between the adrenal and thyroid axes. Isolated cases of autoimmune thyroid pathology developing after surgical treatment of hypercortisolism (Cushing's syndrome) have been described.

According to Polish researchers, secondary adrenal insufficiency may be a cause of autoimmune thyroid diseases in humans. Among 176 patients with idiopathic isolated secondary adrenal insufficiency, 73% were found to have concomitant autoimmune thyroiditis (AIT). At the same time, stress may contribute to the onset and progression of autoimmune diseases, although the mechanisms are not fully understood.

Severe stress exposure may trigger Graves' disease, and an association between stress and Hashimoto's thyroiditis has also been reported [105]. Since stress has a pronounced effect on the immune system, immunomodulation is considered a factor capable of inducing autoimmune thyroiditis in genetically predisposed individuals .

Recently, it has been established that stress hormones acting on antigen-presenting immune cells may influence the differentiation of bipolar T-helper cells from Th1 to Th2 phenotype, resulting in suppression of cellular immunity and enhancement of humoral immunity. The phenotypic expression of autoimmune thyroid diseases largely depends on the Th1/Th2 immune balance.

Indirect evidence supports the hypothesis that stress may influence the clinical expression of autoimmune thyroid diseases in susceptible individuals, promoting the development of Graves' disease through a shift in Th1/Th2 balance from Th1 toward Th2. Conversely, recovery from stress or the immunosuppressive effect of pregnancy may induce a “reverse shift” from Th2 to Th1, leading to autoimmune (sporadic) thyroiditis .

12. Influence of Iodine Deficiency on the Function of the Hypothalamic–Pituitary–Adrenal System

It has been shown for the first time that in rats with chronic iodine deficiency, the normal circadian rhythm of corticosterone secretion is absent, and the stress-induced increase in corticosterone levels is attenuated. This reduced amplitude persisted for one month after restoration of iodine status. Thus, iodine deficiency decreases the activity of the hypothalamic–pituitary–adrenal (HPA) axis.

Hyperthyroidism causes more than a threefold decrease in blood cortisol levels in fish and reduces mRNA levels of corticotropin-releasing hormone-binding protein in the pituitary , although ACTH and CRH receptor levels remained unchanged.

Conclusion

A close, multilevel interrelationship between the hypothalamic–pituitary–adrenal and hypothalamic–pituitary–thyroid axes has been clearly established (Figure). The effects of stress depend on its duration, being characterized by activation of the pituitary–thyroid system during the acute phase and suppression during prolonged and chronic stress.

Stress induces a decrease in T3 concentration and an increase in rT3 production through activation of deiodinase D3. Glucocorticoids stimulate TSH-mediated activation of iodide uptake, inhibit thyroid peroxidase activity in the thyroid gland, and consequently inhibit iodide organification. Glucocorticoids increase the concentration of thyroid receptor β1 protein and mRNA and inhibit the biosynthesis of thyroxine-binding globulin in hepatocytes.

The data presented in the review are summarized in the schematic diagram shown in the figure. The role of stress in the development of thyroid pathology has not been definitively established; however, several studies discuss the contribution of stress and glucocorticoid deficiency to the development of autoimmune thyroiditis through suppression of cellular immunity and enhancement of humoral immunity.

Mechanisms of stress-induced thyroid dysfunction remain an important subject for further research, given the serious systemic consequences even of subclinical thyroid insufficiency.

Whether anti-stress agents capable of modulating the amplitude of the stress response to constant daily exposure to stressors are currently necessary remains an open question.

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