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The Impact of Iron and Selenium Deficiencies on Iodine and Thyroid Metabolism: Biochemistry and Relevance to Public Health

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Several minerals and trace elements are essential for normal thyroid hormone metabolism, e.g., iodine, iron, selenium, and zinc. Coexisting deficiencies of these elements can impair thyroid function. Iron deficiency impairs thyroid hormone synthesis by reducing activity of heme-dependent thyroid peroxidase. Iron-deficiency anemia blunts and iron supplementation improves the efficacy of iodine supplementation. Combined selenium and iodine deficiency leads to myxedematous cretinism. The normal thyroid gland retains high selenium concentrations even under conditions of inadequate selenium supply and expresses many of the known selenocysteine-containing proteins. Among these selenoproteins are the glutathione peroxidase, deiodinase, and thioredoxine reductase families of enzymes. Adequate selenium nutrition supports efficient thyroid hormone synthesis and metabolism and protects the thyroid gland from damage by excessive iodide exposure. In regions of combined severe iodine and selenium deficiency, normalization of iodine supply is mandatory before initiation of selenium supplementation in order to prevent hypothyroidism. Selenium deficiency and disturbed thyroid hormone economy may develop under conditions of special dietary regimens such as long-term total parenteral nutrition, phenylketonuria diet, cystic fibrosis, or may be the result of imbalanced nutrition in children, elderly people, or sick patients.

Introduction

IODINE DEFICIENCY PRODUCES A SPECTRUM of disorders—endemic goiter, hypothyroidism, cretinism, and congenital anomalies—that are termed the iodine deficiency disorders (IDD) (1). Despite substantial global progress against IDD, it is estimated that 750 million people worldwide, or approximately 15% of the population, remain iodine deficient and goitrous (1). In iodine-deficient areas, multiple nutritional and environmental influences contribute to the prevalence and severity of IDD (2–4). Deficiencies of selenium (Se) and iron (Fe) can act in concert with iodine deficiency to impair thyroid metabolism and modify the response to prophylactic iodine (5–8). The effects of Fe and Se status on iodine and thyroid metabolism share certain parallels. Se deficiency reduces the activity of the Se-dependent deiodinase and peroxidase enzymes and thereby impairs thyroid metabolism in iodine-deficient populations (5,6). Similarly, Fe deficiency reduces heme-dependent thyroperoxidase activity, impairs thyroid metabolism, and influences the response to iodine in IDD (7,8). This review discusses the interactions of iodine, Se, and Fe deficiencies, from the point of view of both the biochemistry and relevance to prevention of thyroid disease in the context of IDD.

Iron and Iodine

Worldwide, more than 2 billion people—mainly young women and children—are Fe-deficient (9). In developing countries, 40%–45% of school-age children are anemic (9), approximately 50% because of Fe deficiency. Women of childbearing age and children are also highly vulnerable to iodine deficiency and are the main target groups of IDD control (1). These deficiencies often coexist; in regions of West and North Africa, 20%–30% of school-age children suffer from both goiter and iron-deficiency anemia (IDA) (27,10).

Extensive data from animal studies indicates that Fe deficiency, with or without anemia, impairs thyroid metabolism. Weanling rats fed Fe-deficient diets have significantly lower serum triiodothyronine (T_3) and thyroxine (T_4) (lower by 20%–60%) compared to rats fed adequate Fe (11–13). Rats with Fe deficiency and moderate IDA (mean hemoglobin [Hb], 85 g/L) have reduced conversion of T_4 to T_3 (14), and lower serum T_3 and T_4 concentrations compared to controls (15). Fe-deficient rats have significantly lower hepatic T_4-5′-deiodinase activity, with hepatic production of T_3 only 46% of controls (16). Weanling rats fed Fe-deficient diets have significantly blunted thyrotropin (TSH) responses to exogenous thyrotropin-releasing hormone (TRH), reduced turnover of

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serum T_3 (approximately 50% lower than controls), and lower hepatic thyroxine-5′-deiodinase activity (reduced by 41%) (17). [^{125}I]T_3 binding to hepatic nuclei is lower in Fe-deficient compared to control rats (18). A limitation of these studies has been the lack of pair-fed controls, making it difficult to distinguish the effects of reduced food intake associated with IDA from IDA *per se* as a cause of the lowered thyroid hormone levels.

Fe deficiency also impairs thyroid metabolism in human studies. Martinez-Torres et al. (19) reported 10% lower T_3 levels in human subjects with moderate-to-severe IDA (mean Hb, 75 g/L) and Fe deficiency without anemia when compared to Fe-replete subjects. Beard et al. (20) compared women with mild IDA (mean Hb, 110 g/L) and Fe-deficient women without anemia to Fe-sufficient controls, and found serum T_3 and T_4 were significantly decreased and TSH significantly increased in the Fe-deficient groups (20). Fe treatment of the Fe-deficient anemic women significantly increased serum T_3 concentrations (20).

Overall, these studies suggest that Fe deficiency:

- Blunts the thyrotropic response to exogenous TRH;
- Lowers serum T_3 and T_4 levels, but T_3 to a greater extent (decreased hepatic production of T_3 because of reduced hepatic thyroxine-5′-deiodinase activity);
- Lowers utilization of thyroid hormones (as evidenced by slower turnover of T_3 and reduced T_3 nuclear binding).

It is not yet clear how Fe deficiency exerts its effects on thyroid metabolism. Using an *in vitro* incubation method, Kaplan and Utiger (21) found that outer ring deiodinase activity is not affected by either ferric or ferrous Fe. Thyroid metabolism could be impaired by Fe deficiency through anemia and lowered oxygen transport, similar to the thyroid impairment of hypoxia (22,23). Another mechanism may involve thyroid peroxidase (TPO). The initial steps of thyroid hormone synthesis—iodide incorporation into tyrosine residues of thyroglobulin and covalent linking of the residues to generate the diphenylether structure—are catalyzed by heme-dependent TPO. The activity of other Fe-containing enzymes can be impaired by Fe deficiency. Studies have shown that cytochrome oxidase, myeloperoxidase, and succinate-ubiquinone oxidoreductases are all sensitive to depletion during Fe deficiency (24,25). Similarly, Fe deficiency could lower TPO activity and interfere with thyroid hormone synthesis (4). We have recently shown that TPO activity is significantly reduced in IDA (7). Male weanling Sprague Dawley rats ($n = 84$) were assigned to seven groups. Three groups (ID-3, ID-7, ID-11) were fed a Fe-deficient diet containing 3, 7, and 11 ppm Fe, respectively. Three groups were pair-fed and one control group was fed *ad libitum*, both with Fe-sufficient diets (35 ppm Fe). After 4 weeks, Hb, T_3, and T_4 were significantly lower in the Fe-deficient groups than in the control group ($p < 0.001$). TPO activity (by both guaiacol and iodine assays) was markedly reduced by Fe deficiency ($p < 0.005$). Compared to *ad libitum* fed controls, TPO activity in GU/total thyroid in the ID-3, ID-7, and ID-11 groups was decreased by 56%, 45%, and 33%, respectively (Fig. 1). These data indicate that Fe deficiency sharply reduces TPO activity, and suggest that decreased TPO activity contributes to the adverse effects of IDA on thyroid metabolism (7).

To investigate the relevance of these findings to public health and IDD control, we conducted a series of clinical trials in North and West Africa, in areas of endemic goiter with a high prevalence of IDA. The aims of these studies were: (1) to determine if goitrous children also suffering from IDA have a normal response to oral iodine supplementation; (2) to determine if Fe supplementation in goitrous children with IDA would improve their response to oral iodized oil and iodized salt; and (3) to determine whether the addition of Fe to iodized salt would improve the efficacy of the iodine in iodine deficient children with a high prevalence of IDA.

The first series of studies were done in primary schools in an area of endemic goiter in the mountains of western Côte d'Ivoire. In 1997, the median urinary iodine concentration and the goiter rate by palpation in school-aged children in this region were 28 μg/L and 45%, respectively (8), indicating moderate-severe IDD (1). Goitrous, school-aged children ($n = 104$) were divided into two groups: group 1 consisted of goitrous, nonanemic children; group 2 consisted of goitrous children with IDA (8). Baseline measurements included ultrasonographic thyroid gland volume (Tvol), TSH, T_4, and urinary iodine (UI). Each child in groups 1 and 2 then received an oral dose of 0.4 mL iodized poppyseed oil (Lipiodol®, Guerbet, France) containing 200 mg of iodine. At 1, 5, 10, 15, and 30 weeks postintervention, measurements of iodine and thyroid status were repeated. At 15 and 30 weeks, Tvol was significantly reduced in group 1 compared to group 2 ($p < 0.001$). A sharp difference in goiter prevalence was apparent at 15 and 30 weeks, when goiter rates were 62% and 64% in group 2 but only 31% and 12% in group 1 (Fig. 2). Median TSH values at 5, 10, 15, 30, and 50 weeks were reduced significantly ($p < 0.01$) compared to baseline in group 1. At 15 and 30 weeks, median TSH values were significantly lower in group 1 compared to group 2 ($p < 0.01$). Mean serum T_4 increased significantly from baseline in group 1 at 30 weeks ($p < 0.01$), and at 15 and 30 weeks, T_4 values in group 1 were significantly greater than in group 2 ($p < 0.01$).

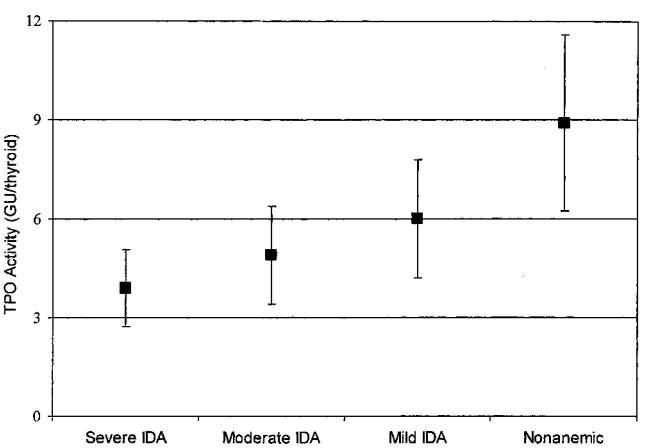

FIG. 1. Mean thyroid peroxidase activity by the guaiacol assay per total thyroid in iron-deficient anemic (IDA) rats and control, nonanemic rats. Mean (standard deviation [SD]) hemoglobin in severe IDA = 40.3(5.2) g/L; moderate IDA = 58.4(5.9) g/L; mild IDA = 72.4(6.1) g/L; control = 136.3(10.9) g/L. Data from Hess et al. (7).

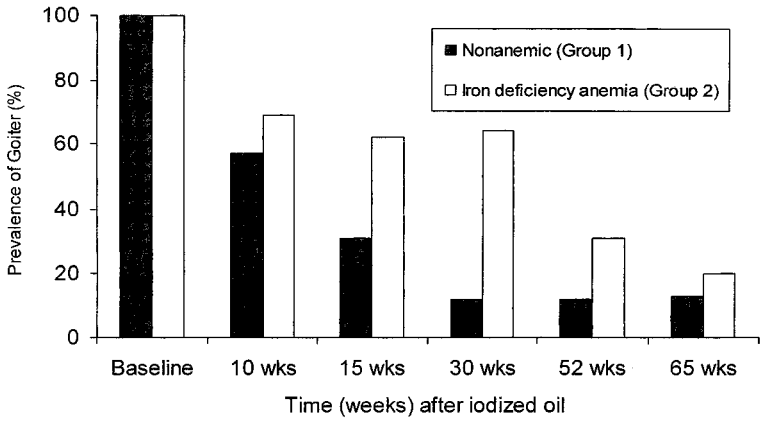

FIG. 2. Number of children in group 1 (iodine-deficient, nonanemic children) and group 2 (iodine-deficient, anemic children) with goiter by thyroid ultrasound. Subjects were followed for 65 weeks after receiving 200 mg of oral iodine, with group 2 receiving oral iron supplementation from weeks 30–42. Data from Zimmermann et al. (8,26).

In this study, both anatomic (thyroid size) and biochemical (TSH, T_4) measures indicated that treatment with iodized oil significantly improved thyroid function in the nonanemic children compared to the children with IDA (8).

Using the same subjects as in study 1, beginning at 30 weeks after oral iodine, the anemic children in group 2 received 60 mg oral Fe as Fe sulfate 4 times per week for 12 weeks (26). Fe supplementation in group 2 resulted in an increase in mean Hb (standard deviation [SD]) from 97(8) g/L at 30 weeks to 122(8) g/L at 50 weeks. Change in Tvol from baseline in group 2, which had plateaued at weeks 10 through 30, was significantly reduced by Fe supplementation ($p < 0.01$). Goiter prevalence in the anemic group (Fig. 2), which had remained at 62%–64% from weeks 10 through 30, was reduced after Fe supplementation to 31% and 20% at 50 and 65 weeks (Fig. 2) (26).

In a second study, goitrous, Fe-deficient children ($n = 169$) were invited to join a double-blind intervention study and were randomly assigned to two groups (27). Iodized salt had recently been introduced into the area and was widely available. Mean salt iodine content (SD) in random household samples was 25.2 (18) ppm. At baseline, the median UI was 162 μg/L. Despite adequate UI and salt iodine levels, the prevalence of goiter by ultrasound was 58.6%. One group of children received oral Fe sulfate (60 mg elemental Fe) 4 tables per week for 16 weeks; the second group received placebo. At 1, 6, 12, and 20 weeks, measurements of Fe and iodine status were repeated. over 20 weeks, mean Hb (SD) improved from 110(10) to 124(9) in the Fe group ($p < 0.05$). Table 1 shows the changes in Tvol and goiter prevalence in the Fe-treated and placebo groups. At 12 and 20 weeks, Tvol was significantly reduced in the Fe-treated group compared to placebo ($p < 0.01$ between groups). At 20 weeks the mean %ΔTvol in the Fe-treated and placebo groups was -22.8 (10.7)% and -12.7 (10.1)%, respectively. At 20 weeks the goiter rate was significantly lower ($p < 0.02$) in the Fe-treated compared to the placebo group. Median TSH and mean serum T_4 remained within the normal range in both groups throughout the study (27).

The final study was done in an area of endemic goiter in northern Morocco. The study aim was to determine if cofortification of iodized salt with Fe would improve efficacy of the iodine in goitrous children with a high prevalence of anemia (28). In a 9-month, randomized, double-blind trial, 6–15-year-old children ($n = 377$) were given iodized salt (25 μg iodine per gram of salt) or dual fortified salt (DFS) with iodine (25 μg iodine per gram of salt) and Fe (1 mg Fe per gram of salt, as ferrous sulfate encapsulated with partially hydrogenated vegetable oil). In the DFS group, Hb and Fe status improved significantly compared to the iodized salt group ($p < 0.05$). At 40 weeks, the mean decrease in thyroid volume measured by ultrasound in the DFS group (-38%) was twice that of the iodized salt group (-18%) ($p < 0.01$). Compared to the iodized salt group, serum T_4 was significantly increased ($p < 0.05$) and the prevalence of hypothyroidism and goiter decreased ($p < 0.01$) in the DFS group (Fig. 3). In this study, addition of encapsulated Fe to iodized salt improved the efficacy of iodine in goitrous children with a high prevalence of anemia (28).

Taken together, these data demonstrate that IDA blunts the efficacy of iodine prophylaxis while Fe supplementation improves the efficacy of oral iodized oil and iodized salt in goitrous children with IDA. This suggests that a high prevalence of IDA among children in areas of endemic goiter may reduce the effectiveness of iodized salt programs. IDA may have a greater impact on IDD than previously described goitrogens because of its high prevalence in vulnerable groups. The data also argue strongly for the dual fortification of salt with iodine and Fe, not only to reduce the prevalence of Fe deficiency but also to increase the efficacy of the iodine in populations that are both Fe deficient and goitrous.

Selenium, Iodine, and the Thyroid

The essential trace element Se is involved in thyroid hormone synthesis, metabolism, and action (29). In several regions of the world people are exposed to inadequate Se supply because Se contents of surface soils have been depleted by erosion and glacial washout similar to iodine. Therefore, plant and animal food chains contain inadequate amounts of both of these elements. Several diseases have been attributed to deficiencies of these two essential trace elements:

TABLE 1. CHANGES IN THYROID VOLUME AND GOITER PREVALENCE[a] IN SCHOOLCHILDREN TREATED WITH IRON OR PLACEBO AT 6, 12, AND 20 WK AFTER BASELINE

Thyroid volume	*Iron-treated* (n = *85*)	*Placebo* (n = *81*)
Baseline (mL)	5.6 (3.5–16.4)	5.8 (3.4–24.7)
6 weeks (mL)	5.6 (2.9–15.4)	5.8 (2.9–22.5)
Change from baseline (%)	−0.9 ± 13.4	3.4 ± 13.5
No. subjects with goiter	58 [68]	64 [78]
12 weeks (mL)	4.9 (2.5–16.0)[b]	5.2 (2.4–22.7)
Change from baseline (%)	−13.2 ± 11.6	−7.9 ± 11.1
No. subjects with goiter	46 [54]	51 [63]
20 weeks (mL)	4.3 (2.1–12.9)[c,d]	5.1 (2.1–21.4)[e]
Change from baseline (%)	−22.8 ± 10.7[c,d]	−12.7 ± 10.1
No. subjects with goiter	37 [43][f]	50 [62]

As mean ± standard deviation (SD) or medians (range). Percentages in brackets.
[a]Prevalence of goiter significantly lower in the iron group: $p < 0.02$ comparing time and group model relative to time only model (logistic regression).
[b]$p < 0.05$ vs. baseline of iron group.
[c]$p < 0.01$ vs. placebo at 20 wks.
[d]$p < 0.01$ vs. baseline of iron group.
[e]$p < 0.05$ vs. baseline of placebo group.
[f]$p < 0.02$ vs. placebo at 20 weeks.
To reduce the effects of variability among individuals, change from baseline (%) was calculated for each child before deriving means.
Data from Hess et al. (27).

myxedematous cretinism in some parts of central Zaire (30), Kashin-Beck disease in Tibet (31), or Keshan disease (32,33) in some regions of China. Keshan disease is caused by a Coxsackie B virus infection under conditions of Se deficiency (34) without concomitant iodine deficiency. The different pathologies already indicate that additional factors such as malnutrition, consumption of goitrogens contained in staple foods such as cassava or millet (Sudan, Africa), fungal contaminants of grains (Tibet, Siberia), or bacterial or viral infections are required to trigger these (endemic) diseases associated with Se deficiency.

A connection between Se and iodine in thyroid hormone synthesis had been suggested by Dumont' group, who observed an increased coupling efficiency for thyroid hormone synthesis, radioiodide uptake, and organification in thyroid glands of Se-deficient rats (35,36). Their data were compatible with the hypothesis that inadequate Se supply, leading to a decreased glutathione peroxidase (GPx) activity in the thyroid, increases hydrogen peroxide steady-state levels and thus thyroid peroxidase activity and efficiency of thyroid hormone synthesis (35). Studies in animal models and field experiments in Zaire and Tibet established the requirement for adequate Se supply in normal thyroid hormone biosynthesis. Relations between Se status and thyroid hormone metabolism were reported by Beckett et al. (37) who found decreased hepatic and renal type I (5′DI) and decreased brain type II 5′-deiodinase (5′DII) activity in Se-deficient rats and suggested a role of Se in deiodination reactions. The unequivocal identification of 5′DI as selenocysteine-containing enzyme was simultaneously achieved in 1990 by two groups (38,39). Using affinity labeling procedures for the 27 kd substrate-binding subunit of 5′DI isolated from 75-Se metaboli-

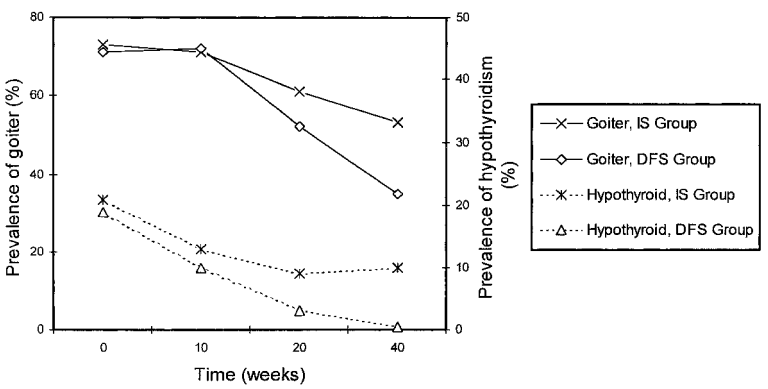

FIG. 3. By logistic regression, the prevalence of goiter and hypothyroidism was significantly reduced in children receiving dual fortified salt containing iron and iodine (DFS) ($n = 183$), compared to a control group receiving iodized salt (IS) ($n = 184$). For both, the group difference increased with time ($p < 0.01$, comparing time and group model relative to time only model). Data from Zimmermann et al. (28).

cally labeled, enzymatically active liver membrane preparations, comparisons between Se-adequate and Se-deficient rats, and peptide mapping of the labeled 5′DI subunit, a one-to one ratio of affinity label incorporation and Se content of the 5′DI active site was found indicating the presence of selenocysteine in the active site of 5′DI. Subsequent expression cloning of 5′DI identified a UGA triplet encoding selenocysteine in the 5′DI gene (40,41).

Selenocysteine-Containing Proteins of the Thyroid

Since 1990 several new selenoproteins have been functionally characterized, cloned, and inactivated in knockout mouse models to identify their function. Table 2 illustrates that central metabolic pathways and regulation of gene expression are under control of selenocysteine-containing proteins. The biosynthesis and cotranslational incorporation of selenocysteine into eukaryotic proteins contain this 21st proteinogenic aminio acid, encoded by the opal stop codon UGA in the context of a SECIS secondary structure in the 3′-untranslated region of corresponding mRNAs, have recently been characterized (42,43). Genetic defects in the biosynthesis of the selenocysteine-tRNA (44) or aberrant expression of these selenocysteine-containing proteins lead to developmental defects or altered metabolic functions (45,46) because these proteins are not only involved in degradation of hydroperoxides, cellular redox control, thyroid hormone metabolism, but also control gene transcription via the thioredoxin (Trx) system. Many of these selenoproteins are expressed in the thyroid gland, which has a high Se content among human organs (47), and are involved in pituitary function and feedback regulation (48).

Expression and Regulation of Selenoproteins in the Thyroid

Among the selenocysteine-containing proteins the deiodinases and the glutathione peroxidase (GPx) family play a major role in the thyroid hormone axis. Two 5′-deiodinases (5′DI and 5′DII) catalyze the activation of the prohormone T_4 to the thyromimetically active thyroid hormone 3,3′,5-triiodothyronine (T_3) and 5′DI is also involved in the degradation of reverse T_3 (3,3′,5′-triiodothyronine) to 3,3-T_2. The third selenocysteine-containing deiodinase (5-D) removes iodide in 5-position and inactivates T_4 to rT_3 and T_3 to 3,3′-T_2. So far no expression of 5-D has been found in thyroid tissue. High 5′DI activities were found in thyroid tissue of rodents, guinea pigs, and humans whereas most other mammals have rather low 5′DI expression in their thyroids (49,50). 5′ DII that is not expressed in adult rat thyroid has been described in human thyroid glands (51), but its cellular location remains controversial (52). Also, GPx and thioredoxin reductase(s) (TrxR) are expressed in thyroid tissue (Fig. 4). The cellular (cGPx), phospholipid-hydroperoxide (PHGPx), and plasma glutathione perioxidase (pGPx) are found in thyrocytes, the latter being secreted toward the apical space. Calcium inophors (A23187) or phorbol esters (PMA) inhibit pGPx release (53,54), block stimulation of 5′DI expression by TSH, but induce TrxR expression (55,54). TSH stimulation of 5′DI is most pronounced under Se deficiency (56), but no stimulation of pGPx or TrxR occurs by the TSH cyclic adenosine monophosphate-(cAMP) signaling cascade.

Currently the molecular mechanism of the compensatory increase in cGPx activity of thyrocytes exposed to enhanced oxidative stress during iodine deficiency accompanied by increased TSH stimulation is unknown (57–60). When activation of protein kinase A pathways is predominant enhanced T_3 production via stimulation of 5′DI and 5′DII is observed. The promoter of human 5′DII contains a functional cAMP-responsive element, mediating this TSH effect (61–64). Together, these observations indicate that thyroid stimulation by TSH and growth factors leads to enhanced H_2O_2 production and elevated efficiency of thyroid hormone synthesis under adequate supply with iodide and Se. When activation of protein kinase C-pathways prevails, enhanced H_2O_2-production and thyroglobulin (Tg)-iodination and coupling might result.

Selenoprotein p15, expressed at rather high levels in thyroid tissue (65), seems to be involved in quality control of correct glycosylation during biosynthesis of secreted glycosylated thyroid proteins. Selenoprotein p15 is associated with UDP-glucose:glycoprotein glucosyltransferase, a major chaperone for glycoproteins (66). SAGE gene profiling revealed that selenoprotein p15 is overexpressed in papillary thyroid carcinoma (67). Selenoprotein W is also expressed in the thyroid (68).

Selenium and Iodine Depletion in Animal Experiments

Complex changes of transcription, stabilization of mRNA, expression, and function of selenocysteine-containing enzymes have been observed in thyrocytes during individual or combined Se and iodine depletion and repletion in animal models. General agreement has been reached in the concept that the thyroid, similar to other endocrine and reproductive organs including the brain, has a remarkable ability to retain or even accumulate Se during states of Se deficiency. Se repletion to deficient rats rapidly restores the expression and function of thyroid 5′DI, cGPx, and PHGPx (69) with kinetics and amplitudes differing from those of other tissues such as liver, kidney, or the brain (70,71). 5′DI activity and mRNA is maintained or even elevated in Se deficient thyroids in spite of a decreased Se content of the gland (72). In second-generation Se–deficient rat pups more complex changes are observed (58). Alterations in transcript levels during Se deficiency might be caused by altered mRNA stability and non-sense–mediated decay (71).

During manipulations of Se and iodine status major alterations of other components of the thyroid hormone axis feedback regulation network occur such as expression and function of pituitary 5′DI and 5′DII (73,74). In the rat brain, Se deficiency decreases T_3 concentrations in the hippocampus, hypothalamus, and striatum, but T_4 levels are unaltered with exception of an increase in cerebral cortex (75). Se deficiency during development of rats leads to tissue-specific and development-related alterations of Se content, deiodinase isoenzyme activities, and thyroid hormone levels (76). In most tissues deiodinase activities are preserved as long as tissue Se levels are maintained around at least 20% of control (76). This could be achieved over several generations and indicates that deiodinases rank high in the hierarchy of Se supply. Se deficiency also shunts iodothyronines into sulfation reactions (77) leading to in increased half-lifes of thyroid hormones.

Table 2. Eukaryotic Selenocysteine-Containing Proteins

Enzyme/protein	*Abbreviation*	*Reaction catalyzed*	*Expressed in thyroid gland*
Glutathione peroxidases	GPx		
Cytosolic	cGPx	$H_2O_2 + 2\ GSH \rightarrow 2\ H_2O + GSSG$	+
Plasma or extracellular	pGPx	$H_2O_2 + 2\ GSH \rightarrow 2\ H_2O + GSSG$	+
Gastrointestinal	GI-GPx	$H_2O_2 + 2\ GSH \rightarrow 2\ H_2O + GSSG$	−
Phospholipid-hydroperoxide	PH-GPx	$ROOH + 2\ GSH \rightarrow ROH + 2\ GSSG + H_2O$	+
Deiodinases			
Type I	5′DI	$T_4 \rightarrow T_3$, $rT_3 \rightarrow 3,3'\text{-}T_2$	+
Type II	5′DII	$T_4 \rightarrow T_3$	+ (human not rat)
Type III	5DIII	$T_4 \rightarrow rT_3$	−
Thioredoxin reductases	TrxR	$Trx\text{-}S2 + NADPH + H^+ \rightarrow Trx\text{-}(SH)2 + NADP^+$	
$\alpha/1$	TrxR1		+
2	TrxR2		
$\beta/3$	TrxR3		
SelZF1,2		TrxR-like function, alternative splice form of TrxR3?	
Trx and GSSG reductase	TGR	Trx and GSSG reductase, dual function	
Selenophosphate synthetase	sps2, selD2	Synthesis of selenophosphate	
Unknown function			
Selenoprotein P	SeP	Inactivation of peroxinitrite?, antioxidative defense	+
Selenoprotein W	SeW	?	+
Prostate epithelial-specific selenoprotein	PES	300-kd holoenzyme, 32 and 15-kd subunits, pI 4.5	
p15		H_2O_2 degradation, 32-kd holoenzyme pI 7.9; associated with UGTR in ER and involved in quality control of misfolded proteins	
Small selenoproteins		7 kd, 5 kd, 4 kd, 3 kd	
Se1N, SEPN1		Mutations cause rigid spine syndrome (MIM602771)	
Sel R, identical to SelX?		methionine sulfoxide reductase	
SelT		?, redox-active?	
SelX		?	
SelY		?, related to 5′DII?	
SelZ		?	

GSH, glutathione; H_2O_2, hydrogen peroxide; T_4, thyroxine; T_3, triiodothyronine; T_2, diiothyronine.

Selenium Deficiency and Iodine Load

Combined Se and iodine deficiency are etiologic factors involved in the pathogenesis of myxedematous cretinism in Zaire (5,78) as indicated by the initial observation that Se supplementation in cretinous children led to impairment of hypothyroidism and myxedematous coma in one case (79,80). In contrast, Se supplementation subsequent to restoring adequate iodine supply did not cause these detrimental effects. Alterations in serum hormone levels (decrease of T_4, maintenance respectively increase in T_3 and TSH) suggested that Se supplementation activated the deiodinase enzymes and increased turnover of thyroid hormones with the subsequent loss of iodide because of the impaired or damaged thyroid structure and function (79).

Studies in rodent models revealed necrosis and infiltration by mononuclear inflammatory cells in the affected Se-deficient thyroid glands after administration of high doses of iodide. No such destructive processes were observed when high iodide doses were given to Se adequate rats (81). Fibrotic processes involved the formation of transforming growth factor-β (TGF-β) by invading macrophages as indicated by suppression of these destructive processes after previous administration of TGF-β–neutralizing antibodies (82,83). Se deficiency impairs regenerative compensatory proliferation of epithelial cells after high iodide load while that of fibroblasts is increased (82–84). However, these observations of aggravation of iodine-induced inflammation and necrosis were not confirmed in a different study with comparable experimental setup, but using a different rat strain (85).

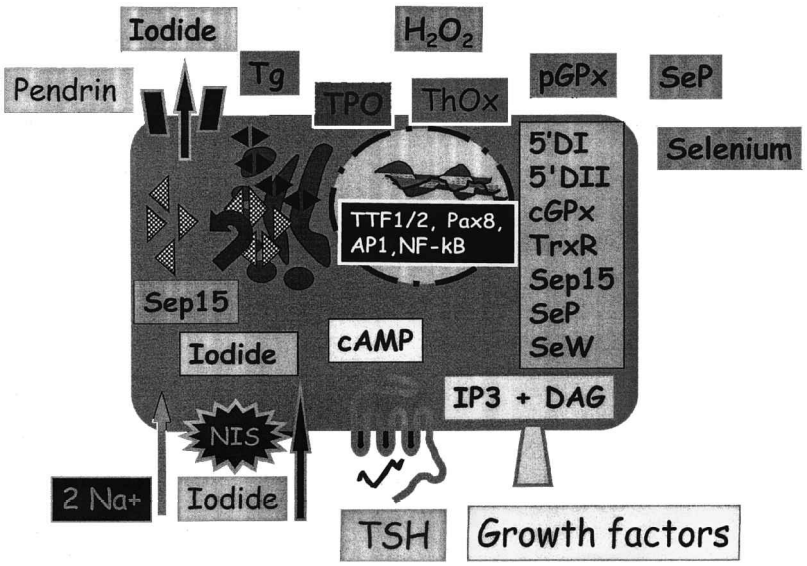

FIG. 4. Schematic presentation of selenoproteins expressed and secreted by thyrocytes and metabolic pathways relevant for thyroid-specific function. Tg, thyroglobulin; TPO, thyroperoxidase; ThOx, thyrooxidase; NIS, sodium-iodide symporter; TSH, thyrotropin; cGPx, cytosolic glutathione peroxidase; pGPx, plasma glutathione peroxidase; SeP, selenoprotein P; 5′DI, type I 5′-deiodinase, 5′DII, type II 5′-deiodinase; TrxR, thioredoxin reductase; p15, selenoprotein 15.

Additional factors such as dietary consumption of goitrogens, e.g., thiocyanate or goitrin contained in or released from staple foods of these regions may contribute to the Se and iodide interaction (86), and last, determine which disease variant is manifesting, myxedematous cretinism as in some regions in Zaire, Kashin-Beck disease found in Tibet and northeast Asia, or Keshan disease in some Se-deficient regional belts over China.

In a longitudinal intervention trial in goitrous, nonanemic children living in an iodine- and Se-deficient area in western Cote d'Ivoire, oral iodized oil was administered and thyroid size and thyroid hormone metabolism was analyzed. Positive thyroid response to iodine supplementation (decreased thyroid volume and serum TSH) at 50 weeks was significantly impaired depending on the extent of Se deficiency (26), but no adverse effects of administration of iodized oil were observed.

Relations between Se and iodine status and thyroid hormone levels were examined in goitrous children in southeast Poland in comparison to a control group in another region. Blood Se and plasma GPx activity were lower in the goitrous group than in controls but differences of free T_4 and TSH levels were only identified in girls belonging to the low and high Se quartiles without evidence for altered iodine status (87).

Provided iodine supply reaches minimal critical levels or low intake as in many parts of Europe additional Se supplementation is not harmful as described in Zaire where Se-enhanced degradation of thyroid hormones by deiodination occurred in treated children (79): Roti et al. (88) reported that low dose Se administration does not cause thyroid insufficiency in subjects with mild iodine deficiency. Of interest are also several observations in cell culture, animal models but also in an epidemiological survey, that at high or excessive Se supply the (hepatic and renal) 5′DI activity decreases (89–91) probably provoked by cytotoxic effects resembling the constellation of the low-T_3 syndrome. Activities of other selenoproteins such as GPx are not decreased under these conditions. Therefore decreased 5′DI activity and decreased serum T_3 levels might be indicative of Se intoxication, however, this hormone constellation is not specific and unsuitable for diagnostic purposes of intoxication.

Selenium, Iodine, and Kashin-Beck Disease

Se deficiency has been linked to Kashin-Beck disease, an osteoarthyropathy encountered in northeast Asia and Tibet. A comprehensive survey in Tibet revealed not only severe Se but also iodine deficiency in affected children who also showed signs of malnutrition (31). Whereas iodine supplementation improved the clinical condition, thyroid hormone parameters and partially restored growth, an additional Se supply did not improve the osteoarthropathy. Development of Kashin-Beck disease appears to be caused by a multifactorial process where malnutrition and fungal contaminants of consumed grain might lead to irreversible destruction of chondrocytes and/or bone-forming cells. However, it is surprising that in Tibet no myxedematous cretinism is found despite combined Se and iodine deficiency. In animal studies reduced growth and impaired bone metabolism was observed during Se deficiency that reduces intestinal calcium absorption and also affects the growth hormone insulin-like growth factor-I (IGF-I) axis (92,93) (R. Moreno-Reyes, unpublished data). Retarded growth patterns have already been described in animal models of long-term Se deficiency, but formerly no links to chondrogenesis and osteogenesis have been made (94).

Selenium Content of the Thyroid

High Se content and Se retention or accumulation in the thyroid gland has been known for several years (47). The mean content is in the range of 1–3 ppm (0.2–2 μg/g wet weight or 1–25 nmol/g wet weight) with rather high variations between individuals. Thyroid Se content is as high or higher than in kidney, where Se is deposited as insoluble Cd- or Hg-selenide during life (96–99). No significant correlations were found between Se content of liver, kidney, and thyroid of the same individual (96,97). Alterations of thyroid Se content have been observed in glands from subjects with hyperthyroidism, adenoma or carcinoma (98,100–102). Of interest is that prediagnostically low serum Se may be an indicator of later manifesting thyroid cancer (103). We found no significant correlation between Se content and activity of the two selenoenzymes GPx and 5′DI in the same tissue aliquots of patients operated on for various thyroid disorders, indicating regulation of these selenoproteins by factors other than Se supply (105,106). TSH-dependent variation of Se content in thyroid glands of various pathology has been described (107).

Vitamin A supply and zinc status also affect thyroid function. In zinc deficient rats decreased 5′DI activity, lower T_3 and free T_4 serum concentrations and marked alterations of follicle cellular architecture including signs of apoptosis were found (102,108).

Se and the Thyroid Hormone Axis in Special Life Conditions: Pregnancy, Newborns, Elderly People, Risk Groups with Benign and Malignant Disease

In the most comprehensive cancer prevention study using long-term Se supplementation to patients with non-melanoma skin cancer no reduction in the incidence of the (rare) thyroid cancer has been observed (109). However, unexpectedly high rates of thyroid cancer were found in patients on long-term hemodialysis, who frequently have an impaired Se status and low plasma GPx levels (110,111).

Impaired thyroid hormone metabolism and economy has been observed in children and patients with phenylketonuria (PKU) maintained on protein-free or protein-pure diets, long-term total parenteral nutrition, cystic fibrosis, or short bowel syndrome. The latter groups might experience disturbed Se resorption that mainly occurs in the proximal intestinal tract (112). The serum T_3/T_4 ratio might be a valid indicator of decreased T_4 activation to the active hormone T_3 under conditions of Se deficiency that can be monitored by pGPx levels as biomarker. Whether a such relation also exists in premature or low birth weight infants where inappropriate TSH and thyroid hormone levels are frequently observed remains controversial (113). Se supplementation, therefore, appears not indicated in premature babies provided adequate nutrition is achieved. It is known that Se intake and plasma Se levels decline in infants fed Se-poor (milk) formula before meat-derived food additives are fed as "Beikost" compared to breastfed babies (114).

However, during pregnancy and the postpartum period the maternal plasma Se (and iodine) status is decreasing because of considerable transfer of both trace elements to the growing fetus via the placenta (1–4 μg of Se per day) and via breast milk (3–6 μg of Se per day) to the feeding baby in addition to enhanced maternal urinary losses (115,116). Therefore, adequate supplementation of both trace elements to the pregnant and lactating mother is indicated in areas of limited or inadequate supply of Se and/or iodine (117). Se supplementation in children with congenital hypothyroidism on T_4-treatment did not affect serum thyroid hormone concentrations or the impaired T_3/T_4 ratio but decreased Tg levels and normalized the TSH difference observed between matched euthyroid controls and children with congenital hypothyroidism, indicating improvement of the central thyroid hormone feedback and decreased thyroid stimulation (118).

Alterations of thyroid hormone levels and set points are also observed in elderly and old people. Old healthy Italian subjects had higher TSH and lower free T_3/free T_4 ratios associated with lower Se and zinc values compared to adult and elderly people (119,120). Whether this reflects altered (hepatic) T_3 production similar to constellation in Se-deficient patients or patients with low-T_3 syndrome is not clear. Altered nutritional habits or food preferences and unbalanced composition together with subclinical diseases might influence these parameters. Se supplementation improves the decreased T_3/T_4 serum ratio and increases serum Se parameters and biomarkers (121).

Se and Nonthyroidal Illness or Euthyroid Sick Syndrome

With the discovery of the selenoprotein nature of deiodinases, initially, a relation between low serum Se levels observed during severe diseases and impaired hepatic production of T_3 by 5′DI had been assumed. However, the limited impairment of deiodinases by Se deficiency *in vivo* and several prospective placebo-controlled interventional studies revealed that low circulating T_3 levels in starvation, severe illness, after surgical interventions, trauma or during sepsis are not directly linked to Se deficiency or Se-dependent alteration of hepatic 5′DI activity. Treatment of septic shock patients with selenite improved their clinical condition and prognosis but recoveries of thyroid hormone levels to normal constellations was more related to improved clinical condition and not concomitant to elevations of Se levels (122,123). Impaired hepatic T_3 production under conditions of severe illness might be caused by tissue-specific cytokine action on 5′-deiodinases in connection with decreased thyroid hormone production and secretion caused by interruption of the negative feedback regulation at the central and pituitary level and direct inhibitory cytokine effects on the thyroid (124–127).

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