Selenium, the Thyroid, and the Endocrine System

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Recent identification of new selenocysteine-containing proteins has revealed relationships between the two trace elements selenium (Se) and iodine and the hormone network. Several selenoproteins participate in the protection of thyrocytes from damage by H_2O_2 produced for thyroid hormone biosynthesis. Iodothyronine deiodinases are selenoproteins contributing to systemic or local thyroid hormone homeostasis. The Se content in endocrine tissues (thyroid, adrenals, pituitary, testes, ovary) is higher than in many other organs. Nutritional Se depletion results in retention, whereas Se repletion is followed by a rapid accumulation of Se in endocrine tissues, reproductive organs, and the brain. Selenoproteins such as thioredoxin reductases constitute the link between the Se metabolism and the regulation of transcription by redox sensitive ligand-modulated nuclear hormone receptors. Hormones and growth factors regulate the expression of selenoproteins and, conversely, Se supply modulates hormone actions. Selenoproteins are involved in bone metabolism as well as functions of the endocrine pancreas and adrenal glands. Furthermore, spermatogenesis depends on adequate Se supply, whereas Se excess may impair ovarian function. Comparative analysis of the genomes of several life forms reveals that higher mammals contain a limited number of identical genes encoding newly detected selenocysteine-containing proteins. (*Endocrine Reviews* 26: 944–984, 2005)

I. Historical Aspects

SELENIUM (Se), DISCOVERED by Berzelius as early as 1817, is well known as an essential trace element (1). Excess supply of Se is equally well known for inducing

adverse effects. Administration of Se for prevention (2) and even therapy of cancer (3) still remains controversial. The characterization of the first mammalian enzyme containing the unusual amino acid selenocysteine (Sec) in its catalytic center, cellular glutathione peroxidase (GPx) (4, 5), initiated a new field of research. Comparative genomics (6) and cloning have revealed the complex mechanisms of the cotranslational decoding of the opal stop codon UGA as codon for the 21st proteinogenic amino acid Sec (7, 8). A relationship between Se and hormones was first suspected from observations on disturbed fertility of male animals with a Se deficiency (9) and of female animals affected by Se excess (10). A breakthrough for the connection between Se and hormones occurred with the simultaneous identification of type I 5'-deiodinase (D1) as Sec-containing enzyme by three groups (11–13). Additional studies elucidated the role of Se deficiency in the pathogenesis of endemic myxedematous cretinism (14, 15) and in regulating thyroid function (16, 17). In recent years, several new families of mammalian and 25 human individual Sec-containing proteins have been cloned and partially characterized with respect to their function (18–21) (Table 1). The essential role of selenoproteins in the endocrine network besides the thyroid axis is becoming evident: they are involved in peroxide degradation, cellular redox and transcription regulation, thyroid hormone deiodination, spermatogenesis, and several additional, still unknown biochemical pathways. Recently, the first mutations in selenoproteins [SECIS binding protein (SBP) 2 and SEPN1] have been linked to human diseases, *i.e.*, disturbances of thyroid hormone metabolism (22) and a rare form of congenital muscle dystrophy (23, 24).

II. Biosynthesis and Degradation of Eukaryotic Selenoproteins

The essential trace element Se is incorporated into proteins and a few modified tRNAs. Se may compete with sulfur in the biosynthesis of methionine, in which it is stochastically incorporated according to its nutritional availability. Therefore, increasing consumption of Se leads to higher Se content of proteins in the form of selenomethionine. No evidence exists for either a saturation of this process or a significantly altered function or metabolism of selenomethionine-containing proteins compared with their sulfur-methionine counterparts.

In contrast, the biosynthesis of the 21st amino acid, Sec, and its cotranslational incorporation into specific proteins are highly regulated (25). The codon UGA not only acts as an opal stop codon during translation, but also encodes the translational incorporation of Sec into proteins when the mRNA contains a distinct hairpin mRNA sequence downstream of the UGA codon in its 3'-untranslated region (3'-utr) (Fig. 1). This Sec insertion sequence (SECIS), or Sec translation element, prevents termination of the translation by competing for release factors that would otherwise lead to disassembly of the mRNA-ribosomal complex (7, 26). In eukaryotes, the SECIS structure recruits the SBP2 (27) and binds the Sec-specific elongation factor (EFSec) loaded with its tRNA^{Sec}. In prokaryotes, but not archeae, SelB exerts the

function of these two proteins (28–31). Several other candidate proteins binding to SECIS elements are currently being investigated (32, 33). The SBP2 specifically binds selenoprotein mRNAs, with no known preferences for individual SECIS structures. SBP2 probably prevents termination of protein translation at the UGA codon (34) but does not protect -tRNA (35). Mutations in SBP2 lead to impaired Se status and reduced expression of several selenoproteins, including plasma GPx (pGPx), selenoprotein P (SePP), and type II 5'-deiodinase (D2), resulting in abnormal thyroid hormone metabolism (22).

In addition to the eukaryotic homolog(s) of SelB, EFSec, Sec synthesis, and cotranslational insertion into the protein chain require: a specific Sec tRNA (Trsp), a Sec synthetase, and a selenophosphate synthetase (SPS2, SelD). The specific tRNA$^{Ser(Sec)}$, encoded by the *Trsp* gene, has been identified in most phyla (36, 37). Knockout of this gene in the mouse is lethal shortly after implantation, but heterozygous mutants are viable (38). Repletion of Se to Se-deficient rats restores normal steady-state levels and tissue distribution of the tRNA$^{Ser(Sec)}$ isoacceptor forms, and posttranscriptional modification of the tRNA$^{Ser(Sec)}$ influences its stability and function (8, 39). The transcription of the tRNA$^{Ser(Sec)}$ gene in the selenocysteyl mouse is regulated by a specific factor (Staf) under the control of several hormones (40).

The synthesis of Sec occurs in a complex reaction by pyridoxal phosphate cofactor-dependent selenophosphate incorporation into the serine of the serine-loaded tRNA$^{Ser(Sec)}$ via the enzyme Sec-tRNA synthase. The biosynthesis of selenophosphate is catalyzed by SelD. One form of this enzyme, encoded by the *SelD2* or *sps2* gene, is by itself a Sec-containing protein (41), although the role of the non-Sec form *SelD1* is still controversial (42, 43). Se supply controls the first step in the biosynthesis of Sec-containing proteins. The components required for cotranslational Sec incorporation into proteins are homologous to the systems so far defined in prokarya, archeae, and *Drosophila* (37, 44–48). Disruption of selenoprotein biosynthesis in *Drosophila* by inactivation of SelD affects cell proliferation and development (48). Mutants lacking the translation elongation factor SelB/EFSec are viable and fertile, even in the complete absence of selenoprotein biosynthesis (49). In contrast to the prokaryotic selenoprotein mRNA, in which the SECIS element lies immediately downstream of the UGA codon, in eukaryotes the SECIS element is located up to 6 kB downstream of the UGA codon in the 3'-utr. Translation of eukaryotic Sec-containing proteins, albeit at low efficiency, can be achieved in cell culture systems from cotransfected expression plasmids (50, 51). It is improved with tRNA$^{(Ser)Sec}$ and SelD2. In proteins, Sec exerts its prominent and specific functions due to its high redox potential and the low pK_a value (5.7) of its selenol (-SeH) group compared with that of most of the sulfhydryl (-SH) groups of cysteine residues ($pK_a \sim 8.5$). The -SeH group of Sec proteins is readily oxidized by H_2O_2 similar to some few acidic cysteine residues in selected proteins (52).

Sec degradation is catalyzed by pyridoxal-5'-phosphate-dependent Sec lyase, which is highly specific for Sec and does not metabolize cysteine (53). It forms alanine from Sec and recycles Se probably as elemental Se that may then be cotranslationally incorporated into tRNA$^{Ser(Sec)}$ by SelD2. Sec

TABLE 1. Eukaryotic Sec-containing proteins

Enzyme/protein	Abbreviation	Reaction catalyzed	Tissue, cellular distribution	Human gene locus	Ref.
Glutathione peroxidases	GPx				
Cytosolic	cGPx (GPx-1)	$H_2O_2 + 2\ GSH \rightarrow 2\ H_2O + GSSG$	Many tissues and cells, cytosolic	3q11-q13.1	18, 576, 660
Plasma or extracellular	pGPx (GPx-3)	$H_2O_2 + 2\ GSH \rightarrow 2\ H_2O + GSSG$	Plasma, kidney, Gastrointestinal tract, thyroid; secreted	5q32	18, 576, 660
Gastrointestinal	GI-GPx (GPx-2)	$H_2O_2 + 2\ GSH \rightarrow 2\ H_2O + GSSG$	Gastrointestinal tract; cytosolic	14q24.1	18, 576, 660
Phospholipid-hydroperoxide	PHGPx (Gpx-4)	$ROOH + 2\ GSH \rightarrow ROH + 2\ GSSG + H_2O$	Many tissues and cells, testes; cytosolic and membranes, various splice forms	19p13.3	18, 575, 576, 660
Glutathione peroxidase	(GPx-6)	$H_2O_2 + 2\ GSH \rightarrow 2\ H_2O + GSSG$	Embryos and olfactory epithelium	6p22.1	20
Deiodinases					
Type I	5'D1	$rT_3 \rightarrow 3,3'\text{-}T_2$ $T_4 \rightarrow T_3$	Liver, kidney, thyroid; many tissues	1 p32-33	227, 232, 661
Type II	5'D2	$T_4 \rightarrow T_3$ $rT_3 \rightarrow 3,3'\text{-}T_2$	Brain, pituitary, placenta brown adipose tissue	14q24.2-3	227, 232, 661
Type III	5D3	$T_3 \rightarrow 3,3'\text{-}T_2$ $T_4 \rightarrow rT_3$	Brain, not in adult liver, not in pituitary and thyroid	14q32	227, 232, 356, 661
Thioredoxin reductases	TrxR	$Trx\text{-}S2 + NADPH + H^+ \rightarrow Trx\text{-}(SH)2 + NADP^+$			151, 157, 622
1	TrxR1		Liver, kidney, heart, bone, cytosolic	12q23-q24.1	104, 662
2	TrxR2		Mitochondrial, testes	3q21.2	663
3	TrxR3		Liver, kidney, heart, mitochondrial	22q11.21	115, 128, 662, 664
SelZF1,2		TrxR-like function, alternative splice form of TrxR3			63
Oxidized Trx (Trx-ox) and GSSG reductase	TGR	Trx and GSSG reductase, dual function		3p13-q13.33	155
Selenophosphate synthetase	SPS2, SelD2	Synthesis of selenophosphate	Testis, liver, many tissues		41
Unknown function					
Selenoprotein P	SePP	Inactivation of peroxinitrite, antioxidative defense, Se transport	Liver, many tissues, secreted	5q31	70, 78
Selenoprotein W	SelW		Many tissues, sex-specific expression	19q13.3	637
Prostate epithelial-specific selenoprotein	PES	300-kDa holoenzyme, 32 and 15-kDa subunits, Pi 4.5	Prostate		602
p15		H_2O_2 degradation, 32-kDa holoenzyme Pi 7.9; associated with UGTR in ER and involved in quality control of misfolded proteins	Thyroid, parathyroid, prostate, granulocytes, T cells	1p31	64, 67, 593, 665
p18			Liver, spleen, brain, kidney		666
Small selenoproteins		7 kDa, 5 kDa, 4 kDa, 3 kDa	Adrenals, brain, epididymis, pituitary, thyroid, prostate, *etc.*		667
SelH				11q12.1	20
SelI	Phosphotransferase			2p23.3	20
SelK				3p21.31	20
SelM				22q12.2	20
SelN, SEPN1		Mutations cause rigid spine syndrome (MIM602771)	Pancreas, ovary, prostate, spleen; ubiquitous	1p36.11	23, 63
SelO				22q13.33	20
SelR	Methionine sulfoxide reductase B	Redox-active		16p13.3	62
SelS		Responsive to low glucose and stress of the endoplasmic reticulum		15q26.3	20, 524
SelT		Redox-active	Ubiquitous	3q24	62
SelV			Seminiferous tubule	19q13.13	20
SelX			Pancreas, liver, kidney leukocytes; many tissues	16	63
SelY		Related to 5'D2	Inner organs		63

UGTR, UDP glucose glycoprotein glucosyltransferase; ER, endoplasmic reticulum; Pi, isoelectric point.
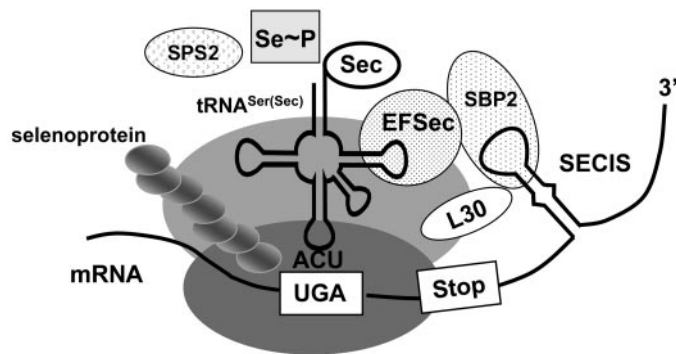
FIG. 1. Biosynthesis of selenoproteins and incorporation of Sec at UGA codons. Cotranslational incorporation of the 21st proteinogenic amino acid Sec into proteins occurs at the UGA codon, which recruits Sec-loaded tRNA$^{\text{Ser(Sec)}}$ (SelC) to the ribosome via an interaction of the Sec-specific translation factor EFSec with the SECIS binding protein 2 (SBP2). SBP2 recognizes the 3'-utr hairpin loop SECIS mRNA structure found in all mRNAs encoding Sec-containing proteins.

lyase is distantly related to the *Escherichia coli* enzyme NifS, which catalyzes the desulfurization of L-cysteine to provide sulfur for iron-sulfur clusters (42, 53). In contrast, selenomethionine is metabolized by the same enzymes handling methionine.

III. Recently Discovered Eukaryotic Selenoproteins

A. Selenoenzymes and new selenoproteins with unknown functions

The first discovered mammalian selenoprotein was the cytosolic GPx (cGPx) (4, 5). Four other Se-dependent peroxidases have been characterized in the last few years (Table 1 and Fig. 2). A fifth, highly homologous non-seleno-GPx (GPx-5), which does not contain Sec and is controlled by androgens, has been described in epididymis and testes of rodents and monkeys (54–56), in bovine keratinocytes, and in eyes and human skin (57, 58). Apparently, the mRNA of this GPx-5 is not translated into a functional protein in human epididymis (59). A sixth GPx form, highly abundant in the testes, which has no homolog in the mouse, has recently been identified in the systematic *in silico* screen for selenoproteins in the human genome (20).

The selenoprotein nature of the enzyme D1 had been established by two groups (11, 12) using biochemical and *in vivo* metabolic labeling approaches. Cloning of D1 subsequently identified a functional UGA and the SECIS structure in its mRNA (60). D1 was the first member of a second group of selenoproteins, the iodothyronine deiodinases (Fig. 3). The cloning of the D1 gene revealed the structural elements required for translation and identification of the SECIS structure (13, 60). Recently, another Se-containing enzyme family of three members, the mammalian thioredoxin (Trx) reductases (TrxRs) (Fig. 4), was identified. Their prokaryotic orthologs do not contain Se (61).

Several other Sec-containing proteins (Table 1) whose biological functions are unknown (PES, p15, SelH, SelI, SelK, SelM, SelN, SelO, SelR, SelS, SelT, SelV, SelX, and SelZ) or not yet fully established (SelP, SelW) have been characterized or cloned during the last 5 yr (20, 62–65). Most of these proteins
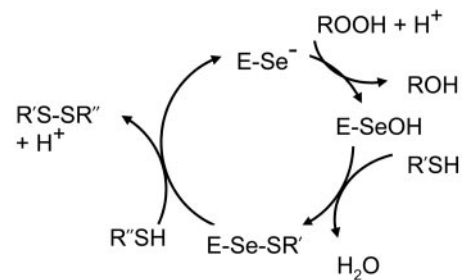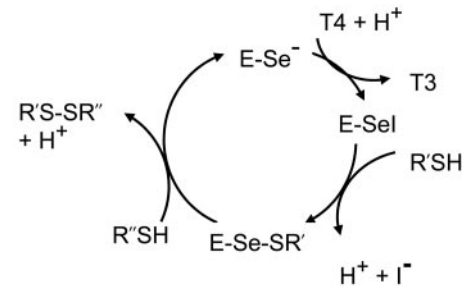
FIG. 2. Mechanism of reaction of GPx (A) and deiodinase (B). The selenoproteins GPx and D1 catalyze peroxide (ROOH) degradation respectively T_4 deiodination in a two-substrate ping-pong mechanism of reaction. Peroxide reduction by the GPx forms an oxidized selenenyl residue (E-SeOH) in the active site of the enzyme GPx, which is regenerated by reduced (di-)thiols (RSH) (A). Deiodination of the thyroid hormone T_4 generates the oxidized E-SeI intermediate that is reduced by (di-)thiols (RSH) while iodide is released (B).

appear to be involved in redox reactions, such as the methionine sulfoxide reductase B (SelR) (66). They metabolize unusual substrates or contribute to the reduction of reactive oxygen species (ROS) such as peroxides or peroxinitrite. Sep15, highly expressed in human thyroid, prostate, and testes, seems to be closely associated with the endoplasmic reticulum resident enzyme UDP-glucose-glycoprotein-glucosyltransferase. It may participate in quality control of misfolded, newly synthetized proteins (67). In addition, Sep15 is involved in growth inhibition and apoptosis (68). The SEPN1 gene has been discovered by *in silico* cloning based on the SECIS motive (63). It is the first link of a selenoprotein to a rare human congenital disease, the rigid spine syndrome, a form of muscular dystrophy (23, 69).

SePP, a glycosylated human plasma protein containing up to 70% of plasma Se, is an unusual selenoprotein that contains up to 10 Sec residues per molecule in most mammals, 12 in bovine species, and up to 17 in zebrafish. Recent research implies both a low efficiency peroxidase function and the binding of heavy metals such as mercury or cadmium (70, 71). SePP, which has strong affinity for heparin, avidly binds to the endothelial surface and might protect the endothelium from oxidative damage (18, 72, 73). Secreted SePP mainly is of hepatic origin, but several tissues express its mRNA. If translated at adequate Se supply, SePP might function in extracellular compartments or at cellular surfaces as a component of cellular antioxidative defense systems and actively
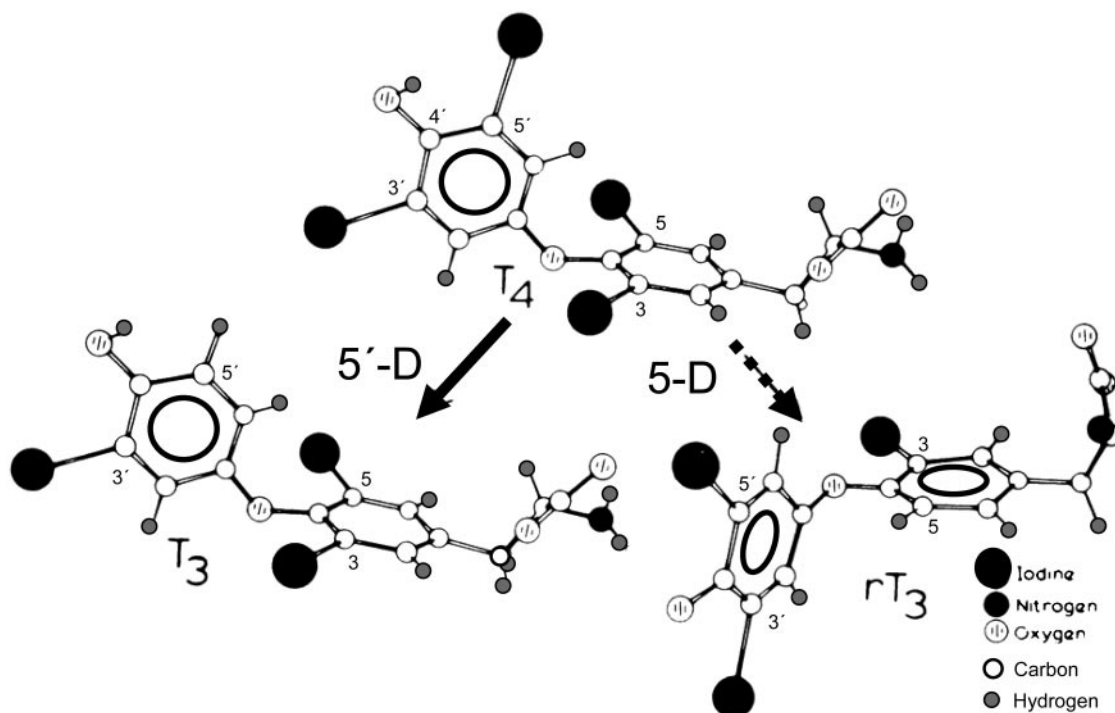
FIG. 3. Deiodination of thyroid hormones by 5′- and 5-deiodinases. The prohormone L-T_4 is deiodinated in the 5′-position of the phenolic ring to yield the active hormone T_3 by the two selenoproteins D1 and D2. Deiodination in 5-position of the tyrosyl ring produces rT_3, which is devoid of thyromimetic action.

scavenge peroxinitrite (18, 74–77). The successful generation of two viable mouse knockout models for SePP (78, 79) provides strong evidence for the initial hypothesis that SePP serves as a Se transport and delivery protein for other tissues. In these models nutritive Se accumulates in the liver, the main site of SePP synthesis, whereas other tissues including brain show markedly lower Se content and activities of selenoproteins. This may induce ataxia and impaired growth (78) due to disturbance of the GH axis (see *Section III.B*). Increased selenite in drinking water can rescue the mouse

FIG. 4. The Trx-TrxR system. The Trx-TrxR enzyme system links the NADPH generation by the pentose phosphate cycle to the reduction of several redox-active endogenous or xenobiotic substrates and represents a key component of the cellular redox regulation and control.

phenotype (33, 80). Other cytoplasmic and plasma Se-binding proteins are known (*e.g.*, SP56) (81).

According to metabolic labeling experiments with 75-selenite in severely Se-depleted rats, 2-D gel electrophoretic autoradiographic patterns reveal more than 25 individual selenoproteins (82). These might represent transcripts with different start sites and promoters and translation products of alternative splice forms of the 25 human or 24 mouse selenoprotein-encoding genes. Several new genes encoding putative selenoproteins are currently being characterized (Table 1) (6, 20, 62, 63, 83, 84). The proteins were identified by the *in silico* approach based on comparative genomics and characteristic sequence and structure motifs of selenoprotein-encoding genes.

B. Preferential selenium supply of the vital endocrine organs during deficiency and repletion

A general observation during Se depletion was the retention or redistribution of Se to the brain, the endocrine organs, and the reproductive organs, whereas liver, muscle, skin, and other large tissues rapidly lose their Se (85). In these tissues, Se is rapidly mobilized from cellular cGPx stores, whereas expression of other selenoproteins such as phospholipid hydroperoxide GPx (PHGPx) and GI-GPx, the deiodinases (especially type II and type III), and TrxRs is hardly affected or may even be increased (type I 5′D). Uptake of Se compounds into cells is assumed to occur via anion transporters (86–91). Selenite is assumed to be transported by the sulfate transporter (92, 93). In the hierarchy of biosynthesis of selenoproteins during Se repletion, some mRNAs are preferentially

translated into selenoproteins. This preference may be directed by the two forms of SECIS elements (29, 94, 95). Full expression of SePP 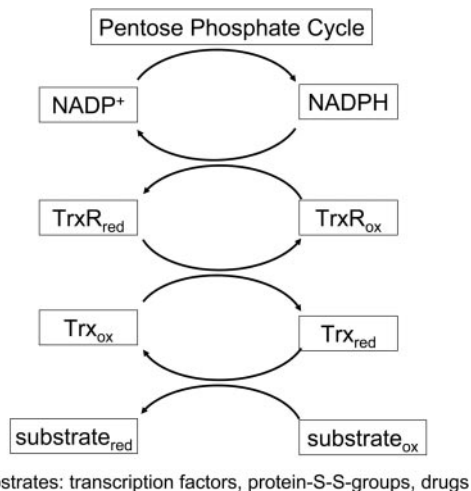requires a greater Se intake than does full expression of pGPx. This suggests that SePP is a better indicator of Se nutritional status than is GPx (96). In general, those proteins residing high in the hierarchy of Se retention during Se depletion also appear to lead in the priority for repletion (97–102).

IV. Hormonal Regulation of the Thioredoxin/Thioredoxin Reductase System

A. Expression and secretion of thioredoxin and thioredoxin reductase

Eukaryotic TrxR isoenzymes have been identified (61, 103–117). Trx, a potent low molecular weight reductant (118–120), is involved in many intracellular and extracellular redox reactions. It also has been proposed as a CD4$^+$ T cell-secreted, B cell-promoting growth factor with possible involvement in regulation of IL-2/Tac receptor function (121–123). It also may be a chemoattractant for neutrophils, monocytes, and T cells (124), possibly influencing autoimmune processes and inflammatory reactions as well. Cytokine- or stress-dependent secretion of TrxR in normal and transformed cells (125) suggests a potential role for the extracellular TrxR-Trx system in antioxidant defense and prevention of immune attack (126).

B. Biochemistry and structure of thioredoxin reductase

Mammalian TrxRs are flavin adenine dinucleotide-containing flavoproteins using nicotinamide adenine dinucleotide phosphate (NADPH) + H$^+$ as their cofactor system, and therefore the pentose phosphates cycle as reducing pathway. Their active site contains a reduced pair of cysteine residues in the N-terminal region. They differ from glutathione reductases by a conserved C-terminal GCUG sequence (U stands for Sec) that is essential for enzyme activity. Lack of Sec incorporation and premature termination of the polypeptide chain at the C residue in the absence of adequate Se supply produces an inactive protein (110, 111). A similar C-terminal structure has also been identified in one of the TrxR proteins of *Caenorhabditis elegans*, but not in a second TrxR enzyme more similar to the prokaryotic TrxR without the Sec residue (127). This essential penultimate Sec residue in mammalian TrxR may act as a cellular redox sensor for regulation of gene expression (128) or in apoptosis (129). TrxRs are members of the pyridine nucleotide-disulfide oxidoreductase family, which includes glutathione reductase, lipoamide dehydrogenase, and mercuric ion reductase.

The discovery of several TrxR genes and their splice variants (at least three isoenzymes: TrxR1, -2, and -3) (61, 117) suggests a specific compartmentalized and fine-tuned regulation of redox-sensitive proteins and signaling cascades (130).

C. Thioredoxin reductase and thioredoxin are involved in signal transduction and regulation of gene expression

1. Redox-regulated transcription factors. Several of the redox reactions modulated via the Se Trx/TrxR system are medi-

ated through the cellular redox/DNA repair protein redox factor 1 (Ref-1). This stimulates DNA-binding activity of several classes of redox-regulated transcription factors, such as activator protein 1 (AP-1), nuclear factor κB (NFκB), Myb, Ets, and the redox-sensitive nuclear receptor family (131–135). Several signals have been found to translocate TrxR into the nuclear compartment where preformed Ref-1 and TrxR1 exist. Interaction with transcription factors AP-1 and p53 may result. The signals include: activation of protein kinase C (PKC), stimulation by *cis*-diaminedichloroplatinum II, oxidative stress, cytokines, lipopolysaccharide, or UV irradiation (133, 136–139) (Fig. 5).

Direct effects of Se compounds and TrxR- or Trx-dependent modulation of redox-sensitive signaling pathways have been shown for NFκB (140), AP-1 (jun and fos) (141), Sp1 (142), glucocorticoids (143), estradiol (134, 135, 144), retinoids (145), and other nuclear receptor systems, Janus-activated kinases, MAPK, protein-tyrosine phosphatases (128), thyroid transcription factor-1 (TTF-1), and p53 (136, 143). The Sec residue of TrxR and other selenoproteins could act as a sensor for cellular ROS (128), which themselves regulate the phosphorylation cascades.

2. Modulation of intracellular signaling cascades by TrxR/Trx. Involvement of the TrxR/Trx system in transcription regulation and proliferation has been demonstrated for several cell types. In A431 cells, epidermal growth factor (EGF) leads to H$_2$O$_2$ and ROS production, similar to direct H$_2$O$_2$ stimulation, with oxidation of the Sec residue of TrxR and oxidative inhibition of phosphotyrosine phosphatase 1B and tyrosine phosphorylation of proteins. Trx reduces phosphotyrosine phosphatase 1B and regenerates the system. Prolonged incubation with EGF or H$_2$O$_2$ induces neosynthesis of TrxR with its regulatory consequences (128). Trx1 is also induced by many variants of "stress," such as UV radiation, x-rays, viral infection, oxidative stress, and several cytostatic (*cis*-platinum II) compounds or redox-active
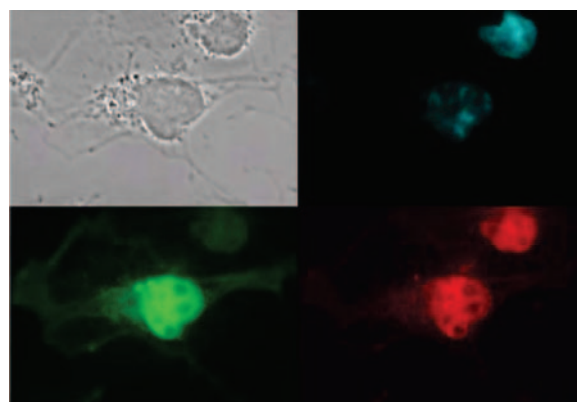
FIG. 5. Subcellular localization of Trx 1 and TrxR 1 in COS-7 cells. Two cells are shown with daylight microscopy (*upper left*) and DAPI nuclear staining (*upper right*). A green fluorescent protein-Trx 1 fusion protein was transiently transfected into COS-7 cells and showed faint cytosolic and strong nuclear staining under routine cell culture conditions (*lower left*, the second cell is not transfected). Antibody-based staining of TrxR 1 in these two cells using a red fluorescence-labeled secondary antibody showed a very similar pattern of cytosolic and nuclear staining in both cells. (The primary antibody was given by K. Becker, Giessen; the experiments were performed by K. Paunescu and F. Jakob).

agents (136). Selenite inhibits UVB-induced cell death (146) and cell death enzymes, and these effects are reversed by dithiothreitol (DTT) or β-mercaptoethanol compounds.

3. TrxR/Trx-modulated effects on proliferation and tissue specific gene expression. Trx enhances, whereas oxidants inhibit, the effect of various transcription factors and nuclear receptors: the estrogen receptor α and glucocorticoid receptor (135, 147). Dominant negative Trx mutants or antisense Trx plasmids inhibit breast tumor cell growth and revert the transformed phenotype (148, 149). Trx also augments redox-sensitive DNA binding activity of the tumor suppressor protein p53, (also activated by Ref-1), and thus stimulates p21 production. A transdominant inhibitory mutant of Trx suppressed the effects of Trx on Ref-1, p53, and p21 activation (136).

Alterations of intracellular glutathione levels have been shown to differentially affect gene expression in the differentiated thyroid cell line FRTL-5 (150). Depletion of intracellular glutathione by treatment of cells with the inhibitor of γ-glutamylcysteine-synthetase butylsulfoxime specifically impairs the transactivation potencies of the thyroid-enriched transcription factors Pax-8 and more so of TTF-1 on the promoters of thyroglobulin (Tg) and to a lesser extent thyroperoxidase (TPO) genes. Se may influence thyroid gene expression directly via selenoprotein or indirectly through modulation of the cellular redox status.

4. Additional substrates of the TrxR/Trx system. Apart from its action on cellular redox components as an antioxidative system, TrxR appears to be involved in reduction of Trx peroxidase and peroxiredoxins, enzymes that degrade H_2O_2 to water (151–153). Furthermore, TrxR and Trx supply reducing equivalents for cellular redox-regulated enzymes such as ribonucleotide reductase, a factor in DNA biosynthesis. Other TrxR substrates include several drugs, dehydroascorbic acid and ascorbyl free radical, vitamin K_3, lipoic acid and lipid hydroperoxides, and NK-lysine, a cytotoxic peptide produced by natural killer cells (154, 155). This broad specificity is unusual but might be due to the C-terminal penultimate exposed Sec residue of TrxR (156, 157).

V. Selenium, Cell Defense, and Thyroid Pathology

A. Selenium and thyroid pathology in humans: endemic cretinism

1. Introduction. Within populations with severe endemic iodine deficiencies, higher percentages of mental retardation

occur. This complication of iodine deficiency is called an endemic cretinism (158). Its consequences are much more damaging than the main characteristic of such endemias: endemic goiter. Because cretinism may be an extreme manifestation among the prevalent general mental retardations, its pathogenesis is of considerable social and medical interest. Two characteristic forms of cretinism can be distinguished: myxedematous cretins and neurological cretins (Table 2). The former show, aside from their mental retardation, signs of severe hypothyroidism, developmental retardation (*i.e.*, dwarfism), myxedema, and—unlike the normal population of the area—they present no goiter. Neurological cretins are almost normally developed, do not exhibit signs of hypothyroidism, have goiters as the rest of the population, but have various neurological deficits. These sometimes include deaf-mutism. Pure forms of myxedematous cretinism predominate in Central Africa, but there are neurological cretins and myxedematous cretins with neurological defects. In other endemic regions like New Guinea or in South America, only neurological cretinism is detected. Both forms, along with intermediates, coexist in India (159, 160). The concept that the two syndromes are linked to a common cause, *i.e.*, iodine deficiency, is now well accepted (161–164). Neurological cretinism stems from deficient thyroid hormone in early fetal development (165–167). Myxedematous cretinism is associated with thyroid insufficiency during late pregnancy and early infancy (159, 168, 169). The distinct geographical distribution of the two forms of cretinism, as well as their different phenotypes, suggests that other factors are involved. Among these are: 1) autoimmune disorders and TSH inhibitory antibodies (170, 171); 2) nutritional habits like cassava consumption and the thiocyanate overload that ensues, impeding iodide trapping (172); 3) trace element deficiencies like zinc, copper, manganese, iron, and Se (173–175) through their involvement in enzymes implicated in cell defenses; 4) vitamin A and E deficiencies also involved in cell defenses against free radical attacks (176); and 5) enzyme deficiencies like superoxide dismutase deficiency or glucose-6-phosphate-dehydrogenase, possibly leading to decreased efficacy in glutathione reduction (176).

The role of hereditary factors has not been elucidated in detail. For the Central Africa endemia, only thiocyanate and Se have been seen to significantly interact with thyroid hormone metabolism (14). They also may contribute to thyroid destruction (161–164, 177).

TABLE 2. Features of myxedematous and neurological endemic cretinism

Myxedematous cretinism	Neurological cretinism	Sporadic congenital hypothyroidism
Severe hypothyroidism (myxedema, dry skin)	Euthyroid	(Severe) hypothyroidism
No goiter, thyroid involution	Goiter	Goiter or athyroid dysgenesis
Dwarfism, retarded bone and sexual development	"Normal" growth	Retarded bone and sexual development
	Spastic diplegia, squint	
	Deaf-mutism, neurological deficits	Hearing deficits, inner ear defects
Mental retardation	Mental retardation	Mental retardation
Partially reversible	Irreversible	(Partially) reversible
Combined iodine and Se deficiency and isothiocyanate ingestion	Iodine deficiency	Various causes from developmental to gene defects

2. Myxedematous cretinism resulting from thyroid destruction in early life. Myxedematous cretins are hypothyroid as shown by their clinical (skin texture, sensitivity to the cold, slowness, slow reflexes), biological (low thyroid hormone levels), and radiological characteristics (bone development retardation) (178). Signs of developmental (height) and mental retardation are proportional to the degree of hypothyroidism, which suggests a causal relationship (162–164). All these characteristics are similar to those of sporadic congenital hypothyroidism.

Primary thyroid insufficiency causes hypothyroidism as shown by the high serum TSH levels and the absence of thyroid response to additional TSH administration. The insufficiency itself results from thyroid atrophy, presumably from thyroid damage, and as demonstrated by the absence of goiter, a low radioiodine uptake, a reduced thyroid activity under radioiodide scanning, and a rapid radioiodine turnover (161, 162, 164, 179). A unique autopsied thyroid of a Congolese cretin showed severe fibrosis with a few overactive follicles constrained in a fibrotic network (Fig. 6). Thyroid destruction is a slow process (169, 180). It affects the population well beyond the pathology of myxedematous cretinism (181).

In myxedematous cretins, the damage may start *in utero*, and most of the damage will occur around birth and during the first years of life (169) when brain development depends on the presence of thyroid hormone. This onset of hypothyroidism in severe cretinism, according to bone age, dates from before or shortly after birth (178).

3. Thyroid fibrosis as a common feature of endemic cretinism and goiter. The description of a thyroid destruction process in an area of endemic goiter, *i.e.*, thyroid hyperplasia, may appear paradoxical. However, the same pathological process can be proposed to explain the coexistence of goitrous subjects with myxedematous subjects having a destroyed thyroid. Iodine deficiency leads to high TSH, thyroid proliferation, and goiter formation to such an extent that goiter by itself impairs efficient use of iodine and thyroid hormone synthesis and thus becomes a maladaptation to iodine deficiency (182). In the peculiar condition of Central Africa (Se deficiency, thiocyanate exposure) pronounced TSH stimulation leads to significant thyroid necrosis, which further increases thyroid proliferation. Thyroid necrosis promotes fibrosis within the wounded thyroid, which may impede proliferation and tissue repair (183). As a result, the evolution of hypothyroid subjects to develop a big goiter or to experience gland destruction depends on which of the two processes, proliferation or fibrosis, wins. The destruction process affects the population on a large scale. In severe cases people become deeply hypothyroid and develop myxedema. Thyroid damage within the rest of the population decreases the efficacy of iodine supplementation programs (181) by decreasing iodide trapping and impairing the adaptive mechanisms (162). Although some myxedematous cretins may improve their thyroid status and even resume a euthyroid status under high iodine supplementation, others may not (168, 169, 180, 184). The fibrotic process may be important for the irreversibility of thyroid destruction by impeding repair through the cell proliferation that follows necrosis in a process akin to liver cirrhosis (179).

4. Biochemical relation of Se deficiency to thyroid destruction. Other trace element deficiencies could act together with iodine deficiency in inducing thyroid destruction (173). Trace elements involved in GPx and superoxide dismutases enzymes activities—*i.e.*, Se, magnesium, copper, and zinc—were lacking in Idjw Island (Central Africa) in two comparably, iodine-deficient areas, one with prevalent myxedematous cretinism, the other without. Only Se deficiency correlated both with the geology and with the distribution of myxedematous cretinism.

The underlying hypothesis was that the thyroid gland, which produces H_2O_2 for thyroid hormone synthesis, is exposed to free radical damage if H_2O_2 is not properly reduced to H_2O by intracellular defense mechanisms or during the hormone synthesis process (185). H_2O_2 is essential for the TPO enzyme in the process of iodide oxidation. In the human thyroid gland, the H_2O_2 generating system is under the control of TSH through the stimulation of the phospholipase PIP_2-IP_3-Ca^{2+} cascade (186, 187). When iodine supply is sufficient, this H_2O_2 generation is thought to be the limiting step for thyroid hormone synthesis; H_2O_2 is reduced to H_2O during the process of synthesis. However, the K_M of TPO for H_2O_2 is high, and much higher amounts of H_2O_2 are produced than consumed by the iodination process (188, 189), potentially exposing the thyroid gland to free radical damage (185). The H_2O_2 exposure is greatest with maximal TSH stimulation. In human thyroid slices, high levels of TSH increase the generation of H_2O_2 up to 13 times the level
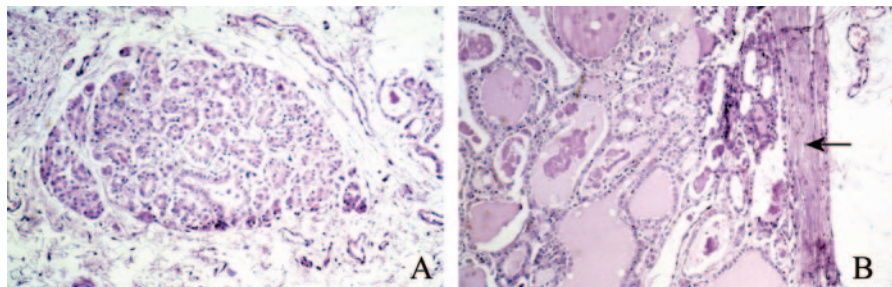
FIG. 6. Fibrotic thyroid of a myxedematous cretin. Paraffin sections from an African cretin. The thyroid structure was modified and highly fibrous. A, , Some nodules had a reduced size and comprised small follicles with cuboidal cells (×150). They were surrounded by a prominent and loose connective tissue, richly vascularized. B, Other greater nodules were made of large follicles compressed by a thick fibrous capsule (*arrow*) (×150). Their colloid was heterogenous, containing cell debris and dense aggregates of Tg or calcified psammoma bodies. (B. Contempré and I. Salmon, unpublished observations).

produced by activated leukocytes (188, 189). TSH secretion is acutely stimulated at birth with the postnatal TSH rise and chronically at all times under iodine deficiency conditions.

Protection against H_2O_2 and resulting free radicals entails vitamins C and E and enzymes such as catalase, superoxide dismutase, and Se-containing enzymes. Originally, GPx was the only identified selenoenzyme (4, 5, 173, 190). However, other Se-dependent enzymes are present in the thyroid and involved in antioxidant defenses (4, 74, 107, 191–193). PHGPx is an example (194, 195). Thus, iodine deficiency increases H_2O_2 generation, whereas Se deficiency decreases H_2O_2 disposal.

5. Epidemiological studies. Epidemiological surveys suggested concomitant Se and iodine deficiencies where myxedematous cretinism is highly prevalent in Central Africa, *i.e.*, in the goiter belt crossing the Congo/Zaire (173, 176, 196). However, a similar association of iodine and Se deficiency in Tibet and in China does not lead to myxedematous endemic cretinism. Thus, iodine and Se deficiencies do not appear sufficient for thyroid destruction. Another important factor in the pathogenesis of endemic goiter in Africa had already been well identified and documented: thiocyanate. Thiocyanate overload results from cassava consumption, a staple in Central Africa, but not Tibet and China. Cassava roots contain the cyanogenic glucoside linamarin (197, 198). Linamarin metabolism releases cyanide, which is detoxified to thiocyanate, a known goitrogen (198). It competes with iodide for trapping by the sodium iodide symporter and for oxidation by the TPO (199). Thiocyanate induces both a release of iodide from the thyroid cell and a decrease of thyroid hormone synthesis. Experimental and epidemiological studies have shown that thiocyanate overload aggravates the severity of iodine deficiency and worsens its outcome (177, 198, 200). However, the common association of these two factors in Central Africa is not sufficient to explain the more restricted prevalence of myxedematous cretinism (196).

6. Se deficiency increases the sensitivity to necrosis in various models. Neither in the thyroid nor in other tissues have experiments shown a deficiency restricted to Se (177, 201, 202). Obvious necroses have only been documented when Se deficiency combines with vitamin E deficiency or additional stressors that lead to an additional decrease in cell defense (202–207). Under these conditions, agents such as paraquat, diquat, or carbon tetrachloride induce necrosis in the liver (202–207).

Myopathy has also been reported in Se-deficient calves that have exercised to excess (208, 209). In the cardiomyopathy of Keshan disease described in China in association with Se deficiency, the proposed additional stress is more complex. Se deficiency would first facilitate somatic viral mutations in the coxsackie B3 virus, which in turn would become more aggressive for the Se-deficient heart and induce necrosis (202, 210). Water pollutants, *i.e.*, fulvic acid, leading to superoxide production, can induce joint damage in mice (202, 211–213). In this disease, aflatoxins may also play a role. Moreover, a statistical relation between iodine deficiency in association with Se deficiency has been recently shown in the Kashin-Beck disease, suggesting that iodine deficiency plays

a role in the etiology (214). Thus, Se deficiency *per se*, in the thyroid as in other tissues, is not sufficient for, but facilitates tissue destruction.

B. Experimental thyroid model

Experiments in rats failed to reproduce major thyroid damage from the single association of Se and iodine deficiencies (15). However, Se deficiency increases the sensitivity of the thyroid gland to necrosis caused by iodide overload in iodine-deficient thyroid glands (215–220). Another group failed to repeat this finding (221). Se deficiency increases the inflammatory reaction initiated by iodide overload that then evolves to fibrosis, whereas the non-Se-deficient thyroid exhibits no fibrosis (222). Fibrosis was associated with increased fibroblast proliferation and decreased thyroid follicular cell proliferation (222). TGFβ was prominent in thyroid macrophages in Se deficiency and was proposed to be responsible for both effects (177, 183). Indeed, TGFβ stimulates the proliferation of fibroblasts and promotes fibrosis, and on the other hand it impairs TSH-induced proliferation (223). TGFβ-blocking antibodies do the reverse, blocking the evolution of the thyroid to fibrosis (177, 183).

The overload of iodine in iodine- and Se-deficient rats does not mimic conditions leading to myxedematous cretinism. Thiocyanate overload instead of iodine might elicit the necrosis. It would aggravate the effects of iodine deficiency by competing with iodide for transport and generate toxic derivatives as well. Indeed, thiocyanate administration to iodine- and Se-deficient rats causes acute inflammation of the thyroid followed by extensive and prolonged fibrosis and atrophy of thyroid follicles.

The association of three factors, *i.e.*, iodine and Se deficiencies plus thiocyanate overload, mimics in rats the phenotype of Central Africa myxedematous cretinism (177). Correction of the iodine and Se deficiencies appears the logical prevention strategy. Correcting the Se deficiency first would be a daring strategy, because it induces T_4 deiodination and consequently increases loss of scarce iodine, which worsens the hypothyroidism and might lead to catastrophic thyroid failure (224).

C. Selenium deficiency and neurological cretinism

All three iodothyronine deiodinases are selenoenzymes, and Se deficiency decreases the type I and II enzyme activities by two different mechanisms (see *Section VI*). Type II and III deiodinases appear more resistant to Se deficiency. The low relative incidence of neurological cretinism in Africa might result from Se deficiency; low T_4 deiodination in the mother and in the embryo would allow higher net T_4 supply to the fetal brain, thereby mitigating at this level the decrease in maternal T_4 due to iodine deficiency (166, 167, 180, 224). However, experiments in rats did not demonstrate higher T_4 or T_3 levels in fetal brains of Se-deficient mothers with iodine deficiency (225). Although this evidence does not exclude the postulated mechanism in humans, it certainly does not support it.

VI. Selenoproteins and the Thyroid Axis

A. Deiodinase enzymes—selenoproteins activating and inactivating thyroid hormones

The deiodinase isoenzymes constitute the second family of eukaryotic selenoproteins with identified enzyme function. Deiodinases catalyze the reductive cleavage of aromatic C-I bonds in ortho position to either a phenolic or a diphenylether oxygen atom in iodothyronines (Fig. 3). The exact mechanism of these reactions and their possible physiological cofactors remain unknown. *In vitro*, strong dithiol reductants such as DTT or dithioerythreitol (DTE) act as cosubstrates in this ping-pong sequential two-substrate reaction releasing free iodide from the enzyme intermediate or iodothyronine substrate. Three enzymes catalyzing iodothyronine deiodination have been identified, which differ in their substrate preference, reaction mechanism, inhibitor sensitivity, tissue- and development-specific expression, and regulation by their substrates or products as well as by other physiological factors and susceptibility to pharmacological agents (226–228).

1. The selenoprotein D1. Type I iodothyronine D1 is the most abundant and best characterized of the three deiodinases (Table 3). D1 was established as a selenoprotein by a combination of metabolic *in vivo* labeling of the protein in Se-deficient rats with 75-selenite and concomitant *in vitro* affinity labeling of its active site with *N*-bromoacetyl derivatives of thyroid hormones (11, 12). These studies revealed the 27-kDa substrate binding subunit of D1 (229), which only functions as intact homodimer (230, 231), and

established that one Se atom was present in the 27-kDa subunit active site (11). The tissue distribution and regulation of this 27-kDa subunit parallels that of the D1 activity in the rat, various cell lines, and other species. The cloning of the cDNA encoding the D1 27-kDa subunit and the identification of an in-frame UGA codon and a 3'-utr SECIS sequence, essential for translation of a functional D1 enzyme, confirmed the selenoprotein nature of D1 and later of other eukaryotic selenoproteins (13, 60). Subsequently, D1 genes have been cloned, and their products have been characterized in many eukaryotic species (232, 233). The 17.5-kB gene of the human D1 has been mapped to chromosome 1p32–33 and contains four exons (234). So far, no splice variants, mutants, or human D1 gene defects have been reported. However, polymorphisms in the 3'-utr or the human D1 gene have been associated with altered thyroid hormone and IGF-I serum levels (235, 236). Several kilobases of the promoter of the human gene have been cloned and partially characterized (237–240). A series of putative regulatory consensus elements were postulated, and two complex thyroid hormone and retinoid-responsive elements have been functionally characterized in the human D1 promoter (63, 237–239). These comprise a direct repeat of three consensus half-sites (DR4 + 2) with a spacer of four bases conferring T_3-response (DR4) and a spacer of two bases mediating retinoid response (DR2). A further combined T_3 and retinoid-responsive direct repeat element with a spacing of 12 bases (DR12) is located downstream in the proximal promoter. Both elements act in tissue-specific context with respect to T_3 and/or retinoid regulation of D1 reporter gene constructs. These elements can explain

TABLE 3. Properties of the three deiodinase enzymes

Enzyme characteristics	Type I 5'-deiodinase	Type II 5'-deiodinase	Type III 5'-deiodinase
Function	Systemic > local T_3 production, degradation of rT_3 and sulfated iodothyronines	Local > systemic T_3 production	Inactivation of T_4 and T_3
Expression	Liver, kidney, thyroid, pituitary, heart	(Hypothyroid) pituitary, brain, brown adipose tissue, skin, placenta; thymus, pineal and harderian gland; glial cells and tanycytes	Placenta, brain; many tissues; except pituitary, thyroid, kidney, adult healthy liver
Cosubstrate	DTT or DTE *in vitro* (K_M, 2–5 mM); not glutathione or thioredoxin *in vivo*	DTT or DTE *in vitro* (K_M, 5–10 mM); higher concentrations than for 5'D1	DTT or DTE *in vitro* (K_M, 10–20 mM); higher concentrations than for 5'D1
Subcellular location	Endoplasmic reticulum in liver, inner plasma membrane in kidney and thyroid	Inner plasma membrane; p29 subunit associated with F-actin respectively perinuclear vesicles	Endoplasmic reticulum
Cloned in species	Human, rat, mouse, dog, chicken, not expressed in *Rana catesbeiana*, *Oreochromis niloticus* (tilapia), rainbow trout	Human, rat, mouse, chicken, *R. catesbeiana*, *Fundulus heteroclitus* (teleost), rainbow trout	Human, rat, mouse, chicken, *R. catesbeiana*, *Xenopus laevis*
Essential amino acid residues	Histidine, selenocysteine, cysteine, phenylalanine	Selenocysteine	Selenocysteine
Enzyme induction	T_3, retinoids; TSH and cAMP in thyroid only; testosterone in liver	cAMP; FGF; phorbolesters via PKC; ANP and CNP via cGMP in glial cells	T_3, FGF, EGF
Stimulation	Se, carbohydrate	β-adrenergic agonists, nicotine	Se
Repression	Ca^{2+}-PI pathway in thyroid; dexamethasone	T_3	
Inhibition	PTU, iodoacetate, aurothioglucose, iopanoate	T_4, rT_3, iopanoate	Iopanoate

ANP, Atrial natriuretic peptide; CNP, C-type natriuretic peptide.

T_3 stimulation of D1 expression in many tissues and non-transformed cell lines as well as retinoid induction of D1 in tumor cells (see *Section VI.A.1*).

Cysteine mutants of D1 are poor catalysts of 5′-deiodination of T_4. Similar to GPx or TrxR, k_{cat} or reaction velocities are two to three orders of magnitude lower than for the wild-type selenoprotein (241). The active site also contains a histidine residue (probably arranged as a selenolate-imidazolium ion pair), as well as aromatic amino acids and a cysteine residue (242–247). A potential membrane insertion domain in the N-terminal part of the highly hydrophobic protein has been partially characterized (248). So far, no *in vitro* translated purified p27 kDa subunit or purified functional D1 protein has been produced. Construction of eukaryotic expression vectors for D1 using its own or heterologous SECIS elements of other selenoproteins enabled identification of the ^{75}Se-labeled p27 protein and determination of D1 enzyme activity in transfected cell lines. The translation efficiency of the D1 expression vectors is low and can be increased by fusion of a SECIS element to the D1 open reading frame, which is "stronger" than the natural D1 SECIS structure (*e.g.*, SePP).

D1 catalyzes the 5′-deiodination of L-T_4, rT_3, and other iodothyronines (Fig. 7) or their sulfoconjugates. D1 also removes iodide from the 5(3) position of the tyrosyl ring at alkaline pH (249). Liver and thyroid D1 are assumed to produce most of the circulating T_3 under normal conditions. D1 also participates in the local production of T_3 from T_4 in some organs. However, the extent is difficult to determine because many tissues express specific T_3-carrier or transport systems as well as D2 (250–253).

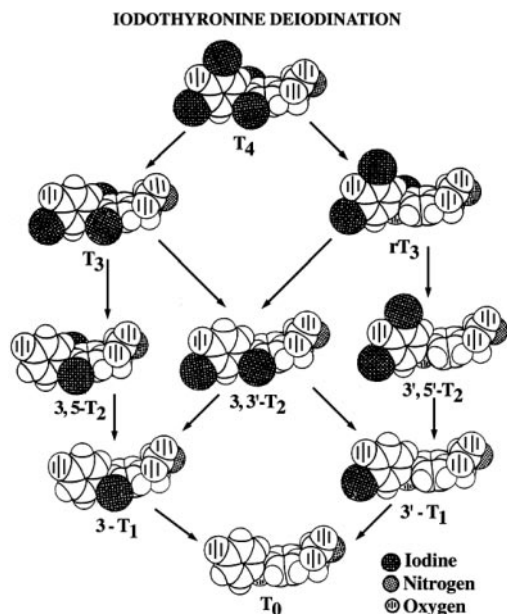D1 is extensively expressed in the liver, kidney, thyroid, and pituitary of adult higher mammals (228, 254). It is an integral membrane enzyme localized in the endoplasmic reticulum of the liver with its active site facing the cytosol. In the kidney and thyroid, D1 is found in the basolateral plasma membrane again with the active site directed toward the cytosol (255–257). The domains directing these tissue-specific differences in subcellular distribution have not been mapped completely (228, 258).

Many hormonal, nutritional, and developmental factors modulate the expression and activity of D1 (226, 227, 259, 260). The substrate and/or products of the enzyme (T_4, T_3, 3,3-T_2) induce its expression, whereas hypothyroidism decreases its activity in most tissues (226, 227, 261–267). In the thyroid, TSH and its cAMP-protein kinase A-signaling cascade increase D1 activity in several species (268–270). Se supply might affect this regulation because TSH enhances D1 mRNA abundance in Se-deficient rats but decreases it in Se-adequate conditions in FRTL-5 cells (269). Sex steroids exert tissue-specific effects on D1 expression. Although hepatic D1 is induced by testosterone, D1 activity is higher in pituitaries of female rats (271–273). Corticosteroid regulation of D1 expression and activity depends on the system and model investigated. Whereas most *in vivo* animal experiments reveal inhibition of D1 activity, dexamethasone stabilizes D1 mRNA and enhances T_3 stimulation of D1 enzyme activity in some *in vitro* models (264, 265).

D1 activity is also increased by stimulation of the GH-IGF-I axis in most species and models analyzed (274–283). It is not yet clear whether GH has a direct stimulatory effect independent of IGF-I. Increased serum T_3/T_4 ratio is interpreted as stimulation of hepatic D1 by GH. GH/IGF-I and their binding proteins also interfere with the Se homeostasis, and conversely, growth curves of Se-deficient animals are affected (78, 284). However, growth can be restored in Se-deficient rats by injections of 1 μg Se/100 g body weight, too low to normalize serum thyroid hormone levels, and the infusion of T_3 alone does not increase the growth rate (284).

Fasting decreases and carbohydrate feeding markedly stimulates hepatic D1 activity, but the exact mechanisms involved remain elusive. In diabetic rats, expression of hepatic D1 is reduced but can be restored by T_3 or insulin administration (285). Proinflammatory cytokines down-regulate D1 in liver and thyroid and up-regulate it in liver and pituitary (267).

Severe Se deficiency reduces D1 protein and activity in a tissue-specific manner, and repletion increases it (97) by combinations of mechanisms involving both D1 mRNA steady-state levels and posttranscriptional regulation (286, 287). Systematic analysis of modulation of the tissue-specific expression of various Sec-containing enzymes and proteins revealed a pronounced hierarchy in Se responsiveness and Se supply to individual selenoproteins in tissue-specific manner (98, 269, 288). In general, D1, an enzyme of low abundance, seems to hold a high rank in this hierarchy, at least above cGPx, enabling local and systemic production of T_3 from T_4 even at low available Se concentrations (97). In a cell culture model, D1 may even recruit Se liberated from the turnover of the more abundant selenoprotein cGPx for incorporation into newly synthesized D1 (97). Several tissues exhibit a further hierarchy. Whereas liver, kidney, heart, skin, and muscle are rapidly depleted from Se during severe defi-

IODOTHYRONINE DEIODINATION

● Iodine
○ Nitrogen
◎ Oxygen

FIG. 7. Monodeiodination cascade of T_4 via iodothyronines to T_0. T_4 and the lower iodinated tri-, di-, and monoiodothyronines undergo sequential 5′(3′) or 5(3)-monodeiodination to the iodine-free thyronine (T_0), which is found in the urine. Also 4′-sulfated iodothyronines are substrates for the deiodinases.

ciency, the thyroid, several other endocrine organs, the reproductive system, and the brain retain Se to a remarkable extent. In adult Se-deficient animals, PHGPx and even more D1 activity are kept at high levels in the thyroid (98).

Stabilized organoselenenyl iodides were used to mimic the Sec-containing active site of D1 and its reaction mechanism as enzyme-mimetic substrates. Propylthiouracil (PTU) reacts with the oxidized E-SeI enzyme intermediate, but not the native enzyme. Basic residues in the active site, such as the proposed histidine, which can form a selenenolate-imidazolium ion-pair (242), kinetically activate the SeI bond. Hydrogen-iodide-catalyzed disproportionation of E-SeI intermediates to diselenides may occur if sterically feasible in the enzyme. An E-SeI reaction with a selenol is much faster than with a thiol, and these factors might account for insensitivity toward PTU inhibition of D2 and D3 (289–291). PTU is inactive toward diselenides.

2. Type II 5'-deiodinase—a second selenoprotein involved in deiodination of T_4 to T_3. The D2, like the D1, enzyme generates T_3 from the prohormone T_4 (Table 3). D2 has a higher affinity for T_4 than D1 ($K_{Mapp} = 2$ nM T_4), and shows high specificity for T_4. Furthermore, D2 is rapidly inactivated by its substrate T_4, but also by rT_3 (292). Its transcription is inhibited by T_3; thus, regulation is inverse to that of D1 and D3 (293). Tissue distribution, developmental profile, and regulation by hormones and other signals are distinct from that of D1 (294, 295). Therefore, D2 is assumed to generate T_3 from local T_4 sources for intracellular demands independent from circulating T_3, and the contribution of D2 to circulating T_3 is considered to be limited. The latter assumption has been thrown into question by the findings of significant mRNA and enzyme levels in the human thyroid and muscle and cells derived therefrom (296, 297). D2 activity was found in neonatal rat thyroid, but not in adult rat thyroid (294), and mRNA levels do not in all instances reflect expression and activity of the enzyme (298–301).

In vitro determination of D2 activity takes advantage of its weak inhibition and the strong inhibition of D1 by the PTU drug. The mechanism of D2 reaction proceeds via a sequential two-substrate reaction without intermediate formation of an oxidized selenenyl residue (Fig. 2). D2 is thought to be unaffected by PTU, which forms a covalent intermediate with the oxidized selenenyl residue of D1 and reacts in a two-substrate ping-pong mechanism with formation of an oxidized enzyme intermediate (289–291).

The selenoprotein nature of D2 has been questioned, because several models have found no clear Se-dependent expression of D2 (287, 302). The identification of a functional SECIS element in the 3'-utr of the long D2 mRNA has only recently been achieved. Cloning of highly conserved orthologs to the D2 transcript, identification of full length cDNAs, characterization of the human D2 gene on chromosome 14q24.2–3 (303–307), and several *in vivo* and *in vitro* findings suggest that the D2 transcript encodes a functional D2 enzyme with a mass of 200 kDa (308). Strong experimental evidence for the selenoprotein nature of D2 encoded by the SECIS-containing D2 transcript was provided by experiments with a human mesothelioma cell line. High levels of expression of D2 transcripts, Se-dependent functional activity of D2, and ^{75}Se-labeling of a p31 subunit were found (309). One study compared the expression and location of the D2 selenoenzyme transcript and the transcript of the cAMP-responsive p29 nonseleno T_4 binding subunit (300). A different location of the two transcripts was reported in the rat brain; p29 was expressed in neurons and in all the regions of the blood-cerebrospinal fluid barrier, but in different cell types than the D2 selenoprotein transcript, with the exception of the tanycytes. This does not support the assumption that p29 has a functional relationship with D2 (310).

Whereas the human D2 gene encodes for two SeCys residues in the protein, in most other species only one highly conserved active-site SeCys residue is found. The second SeCys residue 266 in the human D2, located seven codons upstream of the stop codon, is not essential for enzyme function. Site-directed mutagenesis to a cysteine residue or a stop codon had no effect on enzyme activity but modified Se incorporation (311).

D2 is highly expressed in the central nervous system (CNS), with the highest levels in astroglial cells and tanycytes. Neurons, in which most of the T_3 receptors are expressed, show rather low D2-enzyme activity. D2 transcripts have also been localized to tanycytes (312–314). Thus, D2, locally generating the active hormone T_3 from its precursor T_4, and the nuclear T_3 receptors, mediating most of thyroid hormone action, are localized within different cell types. This suggests a regulated efflux and transport of T_3 from its intracellular site of production in glial cells to surrounding neurons containing T_3 receptors (253). Cell-specific membrane transporters such as MCT-8 (315) and OATP14 (316) might independently control influx and efflux of T_4, T_3, and their metabolites. Both T_4 and rT_3 but not T_3 are potent regulators of D2 inactivation (317). Nonnuclear receptor-mediated mechanisms of thyroid hormone action might also play an important role in hormone action (318). Thyroid hormones also regulate neuronal migration and neurite outgrowth as well as laminin expression in rat astrocytes and within the rat cerebellum (319, 320). Because laminin is produced and secreted by astrocytes, which have low numbers of thyroid hormone receptors but high D2 activity, thyroid hormone-dependent alteration of laminin secretion might be mediated by an extranuclear thyroid hormone effect independent of T_3 receptors.

In the hypothalamus, *in situ* hybridization in combination with immunohistochemistry for the glial cell marker glial fibrillary acidic protein revealed a colocalization of D2 transcripts in glial cells of the median eminence and the arcuate nucleus, but not the paraventricular nucleus. This indicates a close relationship between local thyroid hormone production in the hypothalamus and neuroendocrine TRH-producing cells in the paraventricular nucleus (321).

In the hypothyroid rat brain, D2 transcripts were found elevated in relay nuclei and cortical targets of the primary sensory and auditory pathways (322). The occurrence of D2 transcripts in the cochlea of the developing rat suggests a major function of locally formed T_3 in this structure (323). Thyroid hormone receptor (TR) is expressed in the sensory epithelium, whereas D2 is found in the periostal connective tissue, which might thereby control T_4 deiodination and T_3 release for action in the epithelium in a paracrine manner.

cAMP stimulation of D2 activity and expression has been demonstrated in glial cells, human thyroid, and brown adipose tissue of rodents (309, 324–326). In brown adipose cells, D2 is highly expressed and generates T_3 essential for stimulation of expression of uncoupling proteins and thermogenesis in synergism with catecholamines. A cAMP-responsive element has also been identified in the human D2 gene and functionally characterized in thyrocytes (327, 328). In rat astrocytes, cAMP stimulation of D2 activity has been linked to the recruitment of a 60-kDa cAMP-dependent protein to the p29 catalytic subunit affinity-labeled by BrAcT4 to yield the 200-kDa holoenzyme complex. During this cAMP-dependent stimulation of D2 activity, its p29 subunit is translocated from the perinuclear space to the inner leaflet of the plasma membrane coincident with appearance of deiodinating activity (325). The promoter of the human, but not the rat, D2 gene contains a functional TTF-1 response element (329). Stimulation of glial cell D2 by nicotine and its inhibition by mecamylamine, which blocks nicotine binding to nicotinic acetylcholine receptors, could influence brain function via modulation of local T_3 production (330).

A study reports a transgenic mouse model in which an artificial gene construct comprising the coding region of the human D2 and the rat SePP SECIS element flanked by the human GH polyadenylation signal was expressed under the control of exons I and II of the mouse α-myosin heavy chain gene promoter (331, 332). These mice had elevated cardiac D2 activity, unchanged cardiac T_3 levels, and unaltered plasma hormone levels and growth rate. Nevertheless, signs of cardiac hyperthyroidism were observed associated with increased adrenergic responsiveness. Conversely, targeted deletion of D2 in mice revealed a mild phenotype (increased serum levels of T_4 and TSH, but normal T_3), mild growth retardation in males, and impaired cold adaption (333, 334). This indicates either functional redundancies among the deiodinases or efficient adaption of the components of the thyroid hormone network to failure of a component.

The novel identification of mutations in the human SBP2 gene (22), which led to a phenotype of the thyroid hormone axis resembling that of D2 knockout mice (333), illustrates the importance of Se in thyroid hormone economy and especially for adequate function of D2. Elevated serum TSH, T_4, rT_3, and low T_3 are accompanied by low serum levels of Se, GPx, and SePP, indicating a major disturbance of Se homeostasis but an early manifestation of this genetic defect in the thyroid hormone axis.

In animal models of Se deficiency, only minor alterations of Se content are observed in most endocrine organs and in the CNS. Similarly, only minor alterations of D1, D2, and D3 activity were found in the CNS under Se depletion and repletion (335). The major regulator of D2 expression in the brain is the thyroid hormone status itself. In hypothyroidism, D2 mRNA is increased severalfold in glial cells and in interneurons in the regions related to primary somatosensory and auditory pathways (322). Because the brain strongly depends on T_4 supply from the thyroid and circulating serum T_3 probably reaches the brain only in limited quantities or under pathological conditions, proper thyroid function, and hence adequate Se supply, is crucial both during development and in the adult organism. Apart from thyroid hor-

mone, stress, circadian rhythm, and several neuroactive drugs affect brain deiodinase enzymes and local thyroid hormone levels strongly (336–339).

Se deficiency is known to impair cold tolerance in animals, which might be related to lower expression of D2 in brown adipose tissue associated with decreased T_3 production and subsequent reduction of uncoupling protein expression and catecholamine-stimulated thermogenesis (340). A rat astrocyte culture model has shown that the Se status modulates cAMP stimulation of D2 expression (302).

3. Type III 5-deiodinase—the selenoprotein catalyzing T_4 and T_3 inactivation. The selenoenzyme D3 inactivates thyroid hormones, both the prohormone T_4 and its active metabolites such as T_3 or 3,5-T_2. D3 does not metabolize T_4-sulfate and T_3-sulfate (341). The products of deiodination of iodothyronines at the tyrosyl ring in 5-(or 3-) position (Fig. 3) are devoid of thyromimetic activity and do not bind to nuclear T_3 receptors. The main metabolite of D3, rT_3, competes for T_4 deiodination by D1 and thus might have a regulatory function in thyroid hormone metabolism. Because circulating rT_3 levels are in the range of T_3 and high rT_3 formation is found in the CNS (342), a biological role for this metabolite during brain development, such as modulation of the polymerization state of the actin cytoskeleton, neuronal migration, and neurite outgrowth, has been suggested (320).

D3 activity is expressed in many tissues; particularly in developing brain, in pregnant rat uterus, and in fetal human liver. In adulthood, high D3 levels are maintained in the brain and skin, several other tissues, and the placenta (301, 343–347). No D3 expression is found in the normal adult liver and kidney, *i.e.*, tissues with high D1 or D1 and D2 activity. D3 is thought to prevent inappropriate exposure (*i.e.*, in time, space, or concentration) of cells or tissues to the active hormone T_3. Placental and uterine expression of D3 might play a major role in protection of the conceptus from excessive thyroid hormone exposure during implantation (348, 349). Unusual expression of D3 in pathological tissues, perhaps as a response to impaired perfusion and hypoxia, has recently been shown for liver, pituitary, heart, and lung (350–352).

In the neonatal brain, D3 transcripts are selectively and transiently expressed in areas involved in sexual differentiation such as the bed nucleus of the stria terminalis and preoptic nuclei (353). In the adult rat brain, focal expression of D3 transcripts has been described in hippocampal pyramidal neurons, granule cells of the dentate gyrus, and layers II to VI of the cerebral cortex (354). Transcript levels increase during hyperthyroidism, suggesting increased degradation of excess thyroid hormone. No evidence for regulation of brain D3 expression by the Se status and very minor evidence for placenta has been presented (343, 355). These observations suggest either efficient Se supply to D3 in these tissues or a high rank of D3 in the Se hierarchy of supply during manipulation of Se status.

The selenoprotein D3 is encoded by a gene on human chromosome 14q32 and consists of only one exon (356). A similar structure has been reported for the mouse gene, which has two transcriptional start sites and whose functional promoter contains consensus TATA, CAAT, and GC-

boxes (357). The D3 gene appears to be imprinted and preferentially expressed from the paternal allele in the mouse fetus (358). *In vitro*, Se-dependent expression of D3 has been demonstrated in rat astrocytes (359). Various growth factors [basic fibroblast growth factor (bFGF)], the MAPK kinase-ERK cascade, cAMP, phorbol esters, thyroid hormone, and retinoic acid may induce D3 expression via defined response elements in its promoter (359–362).

The essential role of D3 in control of active thyroid hormone levels has recently been demonstrated in the model of metamorphosis of *Xenopus laevis* tadpoles (363, 364). The metamorphosis program is strictly controlled by thyroid hormones and their receptors (364–367). These regulate cell proliferation and apoptosis, tissue remodeling and resorption, and switches in metabolic pathways related to the transit from aqueous to terrestrial habitats. Overexpression of D3 in these tadpoles enhances T_4 and T_3 inactivation, retards the development in premetamorphosis, slows the process of gill and tail resorption, and eventually leads to death after arrest of metamorphosis (363, 368). Expression of D3, which degrades thyroid hormone, and D2, which locally generates T_3, in a given tissue is highest when metamorphic and metabolic changes occur in tadpoles of *Rana catesbeiana* (369). Strict local control of active thyroid hormone concentration seems mandatory for normal frog development. Tissue-dependent expression of D3 and TRβ, also regulated by T_3 and highly expressed at metamorphosis, shows different time profiles in *Xenopus* tadpoles (364). Whether Se supply modulates expression and function of the deiodinase selenoproteins in amphibia and thereby limits metamorphosis is unknown.

B. Selenium and thyroid function—the role of selenium in thyroid hormone synthesis

1. Antioxidant defense and expression of selenoproteins in the thyroid. Thyroid hormone synthesis requires adequate supply with the essential trace element iodide as well as continuous production of H_2O_2 (188, 189, 370). This is necessary for iodide oxidation, tyrosine iodination, and coupling of iodinated tyrosine residues to iodothyronine under the control of the pituitary hormone TSH. Appropriate antioxidative defense systems are essential to resist this lifelong oxidative stress. One element in this defense strategy is the production of H_2O_2 in the extracellular space, *i.e.*, the colloid lumen at the surface of the apical membrane (Fig. 8). The active site of the integral membrane enzyme TPO is also oriented toward this compartment, thus avoiding exposure of intracellular compartments and membranes to H_2O_2 and other ROS. Another element is the expression of catalase at high levels in thyrocytes (371). Because the K_M of catalase for H_2O_2 is in the millimolar range, a second defense line is required to deal with lower micromolar concentrations (185, 372–374). Therefore, it was not surprising to find high Se levels in the thyroid tissue (375). GPx is involved in H_2O_2 degradation at up to 0.1 mM concentrations, whereas peroxisomal catalase is also involved at higher H_2O_2 levels (371).

Most of the trace element Se is incorporated into proteins of thyrocytes. Table 4 summarizes our current knowledge on the expression and function of selenoproteins in thyroid tissue. Apart from D1, recent evidence suggests expression of D2 in the adult human and fetal rat, but not adult rat thyroid
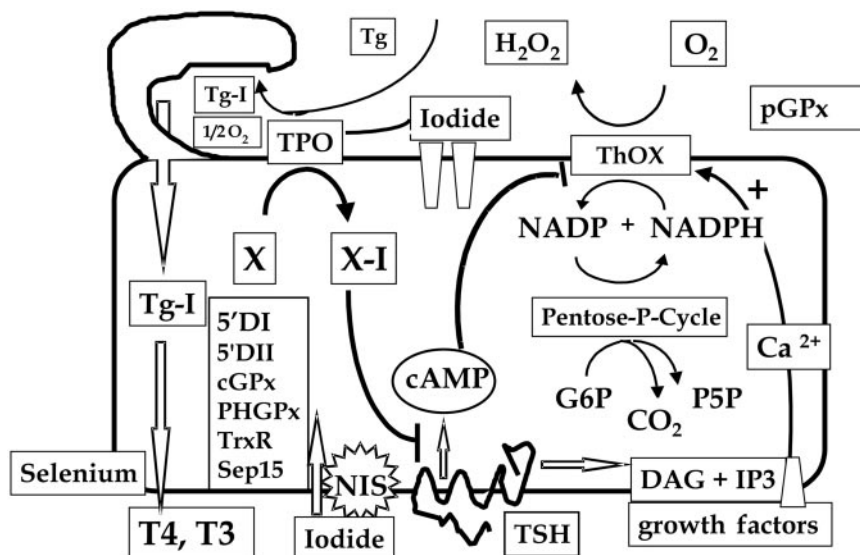
FIG. 8. Schematic presentation of selenoproteins in thyrocytes and thyroid hormone synthesis. Among 11 protein bands metabolically labeled by 75-selenite, the selenoproteins type I and type II 5′-deiodinase, cGPx and pGPx as well as TrxR and Sep15 have been identified in thyrocytes (5′DI, 5′DII, cGPx, TrxR). pGPx is secreted across the apical membrane into the colloid lumen. The sodium iodide symporter (NIS) transports iodine into the thyrocyte, which after passage of the apical membrane is incorporated into Tg in a reaction catalyzed by the hemoprotein TPO, an integral membrane protein in the apical membrane. H_2O_2 required as substrate by TPO for the iodination and coupling of tyrosyl residues in Tg is generated by the NADPH-dependent thyroxidase (ThOx). NADPH is provided by the cellular pentose phosphate cycle. Intracellular unknown compounds iodinated by TPO (X-I) might inhibit TSH-receptor signaling. TSH and several growth factors regulate thyrocyte function and thyroid hormone synthesis by cAMP and PKC- or Ca^{2+}-mediated signaling cascades via receptors of the basolateral plasma membrane. T_4 and T_3 are released via the basolateral membrane into circulation by yet unknown mechanisms. DAG, Diacylglycerol; IP3, inositoltriphosphate; G6P, glucose-6-phosphate; P5P, pentose-5-phosphate.

TABLE 4. Selenoproteins expressed in the thyroid

Selenoprotein	Characteristics	Location	Ref.
Type I 5′-deiodinase	Activation of T_4 to T_3	ER or basolateral membrane	193, 256, 257, 270
Type II 5′-deiodinase	Local activation of T_4 to T_3		296, 668
cGPx	H_2O_2 degradation	Cytosol	85, 379
pGPx	H_2O_2 degradation	Apical colloid	378, 379
TrxR			107
Sep15	Chaperone	ER	64, 67, 593
SePP			J. Köhrle, unpublished data
Several 75-labeled bands			11, 85

ER, Endoplasmic reticulum.

(193, 259, 296, 376). D3 is not expressed in thyroid tissues or 6thyroid cell lines. Three of the five GPxs, cGPx, pGPx, and PHGPx, as well as TrxR (107) and the selenoproteins of unknown function p15 and SePP (Table 4) are also expressed in thyrocytes and thyroid tissue (269, 377, 378). Whereas cGPx is found at high levels in thyrocytes, pGPx appears to be secreted across the apical membrane into the colloid lumen (379). Elegant studies using primary human thyrocytes in culture and thyrocyte cell lines suggest a distinct regulation of expression and secretion or function of the various selenoproteins D1, D2, cGPx, PHGPx, pGPx, and TrxR by signaling cascades, controlling thyrocyte growth, differentiation, and function (107, 193, 288, 377, 379–385).

2. Regulation of thyroid selenoproteins. Thyrocyte D1 activity is enhanced by the TSH-cAMP-protein kinase A cascade in several *in vitro* and *in vivo* models and species (193, 259, 268, 270, 386) and is negatively regulated by activation of the Ca^{2+}-phosphoinositide (PI)-cascade (270). TSH stimulation leads to a large increase in D1 mRNA in Se-depleted FRTL-5 cells, but to a small decrease in Se-repleted cells (269). Treatment of human thyrocytes in primary culture with the calcium ionophore A 23187 diminished the amount of pGPx secreted, but TSH and cAMP had no significant effects on its production or secretion (379). In FRTL-5 cells, Se depletion reduces expression of cGPx mRNA and activity, but no alterations of PHGPx and D1 mRNA were observed (269). Expression of the TrxR protein, identified by ^{75}Se labeling and Western blot analysis as a 57-kDa band, is stimulated by the calcium ionophore A 23187 and the phorbolester phorbol 12-myristate 13-acetate, but not by TSH or cAMP derivatives. Because activation of the calcium-PI cascade and of the PKC pathway also activates the apical pendrin iodide channel and stimulates NADPH-dependent H_2O_2 production at the luminal surface of the apical membrane, the simultaneous activation of the antioxidative defense system might be required. Taken together, these divergent effects of potent regulators of thyrocytes suggest an important role for selenoproteins. TSH and cAMP stimulate expression of the selenoproteins D1 and D2 and of other proteins involved in iodide transport, thyroid hormone synthesis, and secretion.

3. Expression of thyroid selenoproteins in combined iodine and Se deficiency. Even more complex is the regulation of selenoproteins by combined iodine and Se deficiency in the fetal and adult thyroid gland. Here, divergent alterations are observed at the mRNA and protein level as well as in fetal *vs.* adult thyroid glands. In thyroids of Se-deficient rat pups, mRNA levels of selenoproteins D1, cGPx, and PHGPx are not altered, whereas D1 activity is decreased to 61%, cGPx to 45%, and PHGPx activity to 29% (288). In the thyroid of adult Se-deficient rats, D1 and PHGPx mRNA and activity are increased or unchanged (98, 288) or unchanged (288) or decreased (98, 288). These differences in results from the same group might result from different degrees of Se deficiency or the analysis of first- and second-generation Se-deficient rats. In iodine-deficient fetal glands, mRNAs for all three selenoproteins are significantly increased, as were activities of D1

TABLE 5. Biochemical and physiological functions and diseases associated with Se or its deficiency

Disease or metabolic pathway	Possible mechanisms involved
Keshan disease	Cardiomyopathy of children and adolescents, increased cardiotoxicity of Coxsackie B3 viruses
Kashin-Beck disease	Osteoarthropathy of joints, in connection with iodine deficiency, exposure to fulvic acid and infections
Myxedematous cretinism	Combined Se and iodine deficiency leads to pre- and postnatal destruction of thyroid tissue
White muscle disease (muscular atrophy, vacuoles in fibers, enlarged mitochondria, amorphous white matrix deposits)	Severe long-standing Se deficiency in anorexia nervosa or long-term total parenteral nutrition (669)
Relationships to coronary heart diseases	Expression of selenoproteins in vascular smooth muscle cells and (cardio-) myocytes, antioxidative function of selenoproteins
Impaired immune response	Impaired function of the cellular and humoral immune system
Anticancer effects of Se supplementation	Modulation of initiation, progression, and proliferation; via alteration of Se-dependent antioxidant enzymes (GPx) and thioredoxin reductases (TrxR), cell proliferation, and apoptosis
Se deficiencies in low-protein diets (phenylketonuria), long-term total parenteral nutrition, cystic fibrosis, chronic dialysis, anorexia nervosa	Various side effects characterized by enhanced oxidative stress, myopathies, disturbance of thyroid hormone economy
Impaired spermatogenesis	Role of PHGPx as structural protein of the sperm mitochondrial capsule for thiol-protamine cross-linking (575, 583)

and cGPx (288), whereas PHGPx activity was decreased. In combined iodine and Se deficiency, thyroid transcript levels of selenoproteins were also increased, but D1 activity was elevated, cGPx activity was unchanged, and PHGPx activity was decreased (288). Alterations in the adult maternal thyroid gland followed the same directions as observed in the fetal thyroid (98, 288). Also, in thyroids of cattle, iodine deficiency leads to marked induction of the selenoprotein D1, accompanied by elevated cGPx activity (377). The compatibility of these disparate results in different rat systems with the clear *in vivo* pathogenesis of thyroid destruction in human myxedematous endemic cretinism (Table 5) is unclear.

4. Cellular integrity and Se-dependent transcription regulation. Using a polarized pig thyrocyte culture system, the role of Se-dependent expression of GPx activity for thyrocyte integrity and protein iodination has clearly been demonstrated. Whereas Se-depleted thyrocytes with low GPx activity presented cytoplasmatic iodination of proteins after H_2O_2 exposure, iodination of proteins was restricted to the apical surface in Se-adequate thyrocytes with sufficient GPx activity, whether exogenous H_2O_2 was added or not (387). This crucial finding indicates that Se-depleted cells devoid of sufficient antioxidative defense capacity might experience aberrant intracellular iodination of proteins, leading to deleterious events such as apoptosis, exposure of unusual epitopes, recognition by the immune system, or aberrant targeting and processing of iodinated proteins. Se also has a protective role against cytotoxic H_2O_2 effects mediated by caspase-3-dependent apoptosis in such thyrocytes (388). These observations might provide an experimental biochemical basis for the pathogenesis of myxedematous endemic cretinism and a rationale for beneficial effects of Se supplementation reported in prospective controlled studies in patients with Hashimoto's autoimmune thyroid disease (389, 390).

5. Se content in thyroid cancer tissues and nodules—associations or causal relationships? The human thyroid in adults and children contains the highest Se concentrations per unit weight among all tissues (375, 391–395). An inverse correlation between whole body Se status, Se content of the thyroid, and incidence of human thyroid carcinoma has been postulated in case-control studies of the Norwegian Janus cancer survey (393, 396, 397); prediagnostically low serum Se levels were highly correlated to the incidence of thyroid cancer, but no direct relationship between actual tissue or serum Se content and thyroid cancer manifestation at the time of diagnosis could be found. In cold nodules of nine patients, Se, iodine, and cadmium contents were lower than in residual nonaffected thyroid tissues, but due to high variations in Se content of surrounding residual tissues, this difference did not reach statistical significance for Se (398). In contrast, Se content in seven untreated autonomous adenoma was significantly lower than in residual surrounding tissue, and pretreatment of patients with Se markedly increased Se content in five adenoma, whereas no increase was found in "normal" surrounding tissue (398). Iodine content in these autonomous adenoma was higher than in normal residual tissue.

A serial analysis of age-dependent Se and cadmium con-

tents of human thyroid, liver, and kidney was performed in autopsy tissues in the same region of Styria (Austria), an area with low Se supply (394). Se content increased from 1.6 in newborns up to 6.2 nmol/g wet tissue in thyroid from adults (45 to 59 yr of age) and decreased in old age. Similar results with very heterogeneous distributions (399) were obtained in Praha (400). Liver Se content showed no significant alterations in the range between 1.5 and 2.9 nmol/g with increasing age, whereas kidney Se steadily increased with age from 1.9 up to 7.3 nmol/g, probably due to accumulation of insoluble mercury and cadmium selenides. Cadmium content increased in all three tissues with age, but no correlation was found between Se and cadmium content in the thyroid of adult, suggesting a deposition as insoluble cadmium selenide (394). Se concentrations were decreased in hyperthyroid, carcinoma, and adenoma thyroid tissues compared with control tissue (399).

In one study, but not another (401), significant correlations were found between Se indices and serum TSH (positive), serum thyroid hormone levels (negative), thyroid volume (negative), and peripheral endpoints of thyroid hormone action.

Evolution with age, or heterogeneous distribution of Se in the thyroid, as well as Se content differences between normal and cancer thyroid tissues, have not been found in Russia (402). Differences are found in normal, compared with nodular thyroid tissues. Increased TSH is associated with higher iodine, zinc, and Se content in nodular tissue, whereas iodine and Se content decrease in normal thyroid tissue with increasing TSH, suggesting redistribution or altered turnover of trace elements between functionally active and nodular areas (403).

6. Speciation of selenoproteins in normal and pathological human thyroid tissues. To better understand the role of Se and individual selenoproteins in thyroid hormone cancer, we analyzed Se content and activity of the selenoproteins D1 and GPx in the same samples from several thyroid tumors, adenoma, and goiters as well as C cell carcinoma or parathyroid adenoma. We found highest Se concentrations in tissue samples derived from follicular cells. Se content was diminished in tumor samples compared with normal tissues, adenoma, or goiter. No correlation was found between Se content and activities of the selenoenzymes D1 and GPx. Activities of D1 vary by four orders of magnitude and were decreased in thyroid carcinoma and elevated in thyroid adenoma. Variations of GPx activity were observed around only one order of magnitude and did not correspond to alterations of either Se content or D1. Elevated GPx activity was observed in autonomous adenoma tissue and some carcinoma, whereas significantly decreased activity was observed in autoimmune thyroid tissue (404, 405) (J. Köhrle, unpublished data). These studies indicate that no direct conclusion can be drawn from serum or tissue Se levels about the expression of individual selenoproteins in the corresponding thyroid tissue. Furthermore, the large variation of D1 activities compared with that of GPx and the lack of correlation between these two enzyme activities suggests that different regulators control their expression in the same tissue and override the regulatory influence of tissue Se status *in vivo*. Comparative

analyses of several trace elements and minerals found in thyroid tissue suggest several interactions beyond that known for iodine and Se. Especially, zinc, rubidium, and the toxic metals cadmium and mercury might interact with or impair the function of Se in thyroid physiology.

7. Se, iodine, zinc, and iron interactions in the rat thyroid. Feeding rats on diets deficient in one or more of the trace elements Se, iodine, and zinc revealed complex interactions (406). Whereas serum total and free T_4 was lower and TSH was higher in iodine-deficient rats than in control rats regardless of zinc and Se status, T_3 was lower in zinc-deficient, zinc- and Se-deficient, and Se- and iodine-deficient rats. As expected, total thyroid GPx activity was reduced in Se-deficient and Se- and zinc-deficient rats and increased in iodide-deficient groups. No major structural alterations were found in the Se-deficient thyroids. Iron deficiency also leads to decreased cGPx activity in several rat tissues (407), and T_4 and T_3 disposal rates were also decreased (408). Impaired efficiency of thyroid hormone synthesis in iron-deficient goitrous children and adults has been recently reported and reviewed (175, 409), indicating that not only adequate Se but also sufficient iron supply is required for effective thyroid hormone synthesis after iodide supplementation. Iodine deficiency, independent of concomitant Se or zinc deficiency, leads to the expected changes known for goitrogenesis overriding the alterations observed in other deficiencies. Interstitial fibrosis was found in the Se-deficient groups similar to the studies described before (183).

8. Se status affects thyroid hormone economy by altering conjugation reactions. Kinetic studies have revealed a marked shift of T_3 and T_4 into sulfation pathways in Se-deficient rats (410), which might lead to enhanced enterohepatic recycling of sulfated iodothyronine metabolites as well as to altered tissue distribution and accessibility of these conjugated metabolites compared with the free iodothyronines (411). Moreover, due to decreased hepatic D1 activity, the metabolic clearance rates of iodothyronine sulfates are reduced in Se-deficient rats (249, 412).

9. Se treatment in autoimmune thyroid disease. A European cross-sectional study (413) found an inverse association between Se and thyroid volume and a protective effect of Se against goiter. Recently, several studies reported on the benefit of Se treatment in autoimmune thyroid disease, both Hashimoto thyroiditis and Graves' disease (389, 390, 414). In two of these blind, placebo-controlled prospective studies, serum levels of thyroid anti-TPO autoantibody decreased, and patients' self-assessment of the disease process improved, compared with a placebo group, after 3 to 6 months of treatment with 200 μg/d sodium selenite or selenomethionine. All patients were substituted with L-T_4 to maintain TSH within the normal range. Se substitution may improve the inflammatory status in patients with autoimmune thyroiditis, especially in those with high activity. These studies were performed in areas of Europe with limited nutritional Se supply (Germany, Greece, and Croatia), and Se supplementation led to increased plasma Se and GPx activity. This suggests a phenomenology akin to the pathogenesis of myx-

edematous endemic cretinism with local mechanisms in the thyroid or via the immune system (415).

C. Selenium status and supplementation in "low-T_3 syndrome," nonthyroidal illness, sepsis, and related pathophysiological conditions

Initially, the discovery of D1 as a selenoenzyme with high expression in the liver (11, 12) led to the assumption that the observed disturbance of Se metabolism in severe illness, sepsis, burns, or other nonthyroidal illnesses associated with the euthyroid sick syndrome (ESS) or low-T_3 syndrome, might lead to impaired hepatic T_3 production and to the decreased serum and tissue T_3 levels observed under these conditions (226, 259, 416–422). A significant part of circulating T_3 is formed by hepatic deiodination of T_4 to the active hormone form T_3 via D1 expressed in this tissue. Furthermore, elevations of rT_3 serum levels observed under these conditions result from impaired 5'-deiodination of rT_3 by hepatic D1. Production of rT_3 in extrahepatic tissues by D3 is not affected, but reexpression of D3 in several tissues of critically ill patients might contribute to T_3 degradation and rT_3 production (352). No significant alterations have yet been described in ESS for expression and activity of D2, which also forms T_3 from T_4 but is not expressed in adult mammalian liver. These severe illnesses are accompanied by acute-phase responses and activation of the stress axis, enhanced secretion of proinflammatory cytokines, and disturbances of several serum-binding proteins including those of hormones (423, 424). Reduced tissue T_3 levels (except in skeletal and cardiac muscle) and reduced hepatic T_4 levels with normal T_4 in other tissues and normal circulating TSH in patients who died from nonthyroidal illness indicate a major role for decreased hepatic D1 activity combined with reduced hepatic T_4 uptake in this syndrome (421).

The reasons for this disturbance in thyroid hormone metabolism in severe disease, the mechanisms involved, and the relation to Se economy are still not understood (352, 418, 419, 425–428). Plasma Se is localized mainly within two proteins, pGPx and the plasma glycoprotein SePP (429, 430). The majority of pGPx is produced by the kidney (431), but no evidence for decreased pGPx production and activity has been observed under the ESS conditions. Expression and secretion of SePP is affected by proinflammatory cytokines and TGFβ, at least in the model of the human hepatocarcinoma cell line HepG2 (238, 432–435). SePP contributes up to 70% of plasma Se, and both proinflammatory cytokines and TGFβ are involved in pathogenesis of severe illness and acute phase response. Thus, inhibition of production and/or secretion of SePP might be a major factor of disturbed Se economy in severe illness. The expression of hepatic DI is also inhibited by proinflammatory cytokines, as shown in several cell and animal models (424, 432, 436). The human D1 promoter in HepG2 cells is also inhibited by the proinflammatory cytokines IL-1β, TNFα, and interferon-γ, but not by IL-6 (432). Se inhibits activation of the transcription factor NFκB, which regulates genes encoding proinflammatory cytokines (437). Therefore, decreased hepatic Se might lead to synthesis of positive (such as C-reactive protein) and decrease negative (*e.g.*, SePP and D1) acute phase proteins (422). *In vitro* ex-

periments support Se-dependent expression of both the selenoproteins D1 and SePP in HepG2 and other cell types (432). No direct link between Se supply and the pathogenesis of the ESS or low-T_3 syndrome has been shown.

Recent clinical studies support these findings (438, 439). In a prospective, randomized pilot study, initially high and subsequently moderate supplementation doses of sodium selenite were administered to patients with systemic inflammatory response syndrome. Several clinical chemical and thyroid hormone parameters as well as intensive care medicine scores such as APACHE II and III were analyzed. No significant alterations of serum thyroid hormone levels could be linked to Se supply and clinical outcome. However, an improved survival, APACHE score, and significant clinical benefit were found in the group supplemented with Se. Thyroid hormone levels responded to clinical improvement with some delay but were not altered directly with Se supplementation. This suggests that impaired hepatic T_3 production by D1 in ESS or low-T_3 syndromes might represent adaptive changes and not causal events for the impaired clinical situation. Se administration, by yet unknown mechanisms, might be beneficial in systemic inflammatory response syndrome and sepsis patients, in addition to other measures of intensive care. A prospective, controlled, multicentric clinical study expands these findings and addresses possible mechanisms. Similar beneficial effects of selenite supplementation on clinical outcome were observed in trauma patients and preterm neonates, where normalization of thyroid hormone serum levels correlated closely to improved clinical condition but not to plasma Se status (440, 441). Disturbed serum Se status and altered thyroid hormone serum levels are also found in other ESS-like patients on protein-poor diets (*e.g.*, phenylketonuria), on long-term parenteral nutrition, or suffering from cystic fibrosis, and in animal models, *e.g.*, during lactation or intoxication by heavy metals (mercury, cadmium) (442–447).

Alterations of serum thyroid hormone levels compatible with decreased hepatic D1 activity have been reported in children (442) and elderly with insufficient Se supply (448). In children undergoing cardiopulmonary bypass, a significant reduction of plasma Se with unaltered pGPx activity was accompanied by decreased serum free T_3/free T_4 ratio, indicating impaired D1 activity and SePP secretion (449). In elderly persons, Se supplementation (100 μg sodium selenite/d for 3 months) decreased serum T_4 levels and improved serum Se and GPx activity in erythrocytes (448). This result needs confirmation (450). No general recommendations can be given for normalization of altered serum thyroid hormone levels by Se supplementation. Exceptions include: 1) long-term parenteral nutrition in children and adults; 2) children on protein-poor diets (*e.g.*, phenylketonuria or cystic fibrosis); and 3) patients on chronic hemodialysis with frequent serious deficits in Se supply leading to enhanced oxidative stress and alterations of thyroid hormone levels as indicators of ESS or low-T_3 syndrome (451).

A selenomethionine supplementation study in euthyroid T_4-substituted children with congenital hypothyroidism who had decreased Se, Tg, and T_3 concentrations and increased TSH, rT_3, and T_4 levels found no effect on serum thyroid hormone concentrations. However, elevated Tg and

TSH levels returned to those of controls after a 3-month Se treatment (452). The authors interpreted these observations as evidence against a direct effect of Se supplementation on peripheral deiodinases, whereas pituitary feedback control of TSH by local 5'-deiodination might be normalized.

Combined administration of TRH and GHRH to critically ill patients can restore pituitary and thyroid function and metabolic conditions, suggesting, that decreased serum Se levels are not the causal factor for low-circulating T_3 levels in this condition (453). High doses of GH administered to patients with prolonged critical illness increase both morbidity and mortality (454). Previous attempts to substitute low T_3 in patients with the low-T_3 syndrome led to inconclusive results and were halted due to increased nitrogen loss, fear of cardiovascular complications, and unwanted side effects (436, 455–458). A potential role of selenoproteins, other than hepatic D1, in the pathogenesis of the ESS or low-T_3 syndrome needs to be considered.

Exposure to high Se supply in Se-rich areas of Venezuela showed an inverse correlation between serum Se and free T_3 levels, whereas free T_4 and TSH were unaltered (459). A study of healthy men, fed a diet for 120 d either low or high in Se, observed in the high-Se group (300 μg/d) decreased serum T_3, elevated TSH, and weight gain, whereas the low-Se group (47 μg/d) had elevated serum T_3 and lost body fat (460). These observations might indicate a negative effect of excessive selenite supply on hepatic D1, similar to inhibition of D1 in epithelial kidney cells at selenite concentrations above 200 nmol/liter (97).

D. Selenium, the thyroid axis, and chronic hemodialysis

Metabolic disturbances in chronic hemodialysis involve several minerals and trace elements—most importantly, decreases in serum Se and serum GPx levels. Decreased levels of its activity combined with decreased total serum Se seem plausible, because pGPx originates from kidney tubular cells and contributes up to 30% of plasma Se content (431). However, biological data also indicate a condition similar to the ESS or the low-T_3 syndrome. Because the kidney contributes only slightly to circulating T_3 levels, this suggests interference of this metabolic condition with liver and or thyroid function. The association of low serum Se and low T_3 values with normal to elevated T_4 and normal, decreased, or increased TSH initially suggested causal relationships between low Se and decreased hepatic D1 activity (461–464). Attempts of Se supplementation normalized serum Se levels partially, but had variable or no effect on serum thyroid hormone parameters (451, 462). Factors other than dialysis might interfere with pituitary and thyroid function, such as interference by uremia at several levels of hormonal regulation (465, 466). Nevertheless, Se supplementation might be beneficial to counter oxidative stress with its long-term role in the cardiovascular defects, cancer incidence, and elevated mortality in dialysis patients (467).

VII. Selenium and the Endocrine System

A. Selenium and the pituitary hormones

Toxic effects of Se observed in livestock were growth reduction, disturbance of the reproductive axis in males and

females, and intrauterine resorption of fetuses (468). In several species, Se accumulates in the pituitary more than the brain (468–475). Se in drinking water (2.5 to 15 ppm) or ip injection of 5 to 20 mg/kg produced dose-dependent Se deposits in secretory granules and lysosomes mainly in somatotrophs, and in thyrotrophs, corticotrophs, and gonadotroph cells, whereas nonsecretory cells were unaffected (468, 471, 472). Because the pituitary contains large amounts of zinc, formation of zinc-selenite or zinc-selenide in the secretory organelles was assumed to cause these deposits (468). In anterior pituitaries of human accident victims, no differences in Se content (2.4 ± 1.0 μg/g dry weight) were found between females and males, but the concentration varied from below the detection limit to double that of other endocrine organs. Peak levels of Se were observed 2 h after a single injection of 5 mg/kg sodium selenite (^{75}Se) and were excreted in a biphasic manner in the pituitary as in other tissues (472). No differences were found in Se contents between control and Alzheimer disease pituitaries (0.86 ± 0.19 *vs.* 0.92 ± 0.11 μg/g wet weight), but there was a significant correlation between Se and mercury content, suggesting complexation of both elements (476).

Both excess and deficiency of Se supply lead to impaired growth. Long-term treatment of rats with sodium selenite in drinking water decreases serum GH, IGF-I, and IGF binding protein-1, -2, and -3 levels and results in growth retardation (477, 478). The exact mechanisms involved are not fully elucidated, but inhibition of GH secretion might be caused by Se accumulation in secretory vesicles. Tibia and tail length also decreased. Withdrawal of the excess selenite during the growth spurt from d 21 and 42, respectively, to d 63 restored growth and normalized GH response to GHRH in rats 3 wk after withdrawal, but IGF-I production remained decreased, and signs of liver damage also persisted, including elevated alanine aminotransferase, and reduced albumin (479). High doses of GH administered to rats during excess selenite exposure also restored growth, indicating that circulating levels of IGF-I do not reflect local events at the growth plates and suggesting direct action of GH or paracrine GH-dependent mechanisms (477). On the other hand, Se deficiency also impairs growth in rats and results in increased T_4 (67%) and decreased T_3 (23%). Using second-generation Se-deficient male and female weanling rats maintained on adequate vitamin E and methionine levels, administration of Se in concentrations of 0.1 or 0.2 μg/g diet normalized serum thyroid hormones, liver Se content, and GPx activity (284). T_3 injection to these animals restored normal thyroid hormone levels but did not restore growth, suggesting that additional factors apart from serum T_3 are involved in growth disturbance.

B. Selenium accumulation in the pineal gland

Se accumulates in the pineal gland (480). It is probably required for the highly active D2 (481, 482) and for a strong antioxidative capacity against the ROS produced in melatonin synthesis (483).

C. Selenium and selenoproteins during lactation and in the mammary gland

The lactating mammary gland is an essential source of trace elements for the newborn suckling baby. Both iodine and Se are highly enriched in milk and actively concentrated and secreted by the lactating gland (484–489). The Se content of colostrum is high (25.5 ± 16.6 μg/liter), and human milk contains 5 to 15 μg/liter depending on the Se supply of the mother. The newborn baby receives 5–12 μg Se/d from breast milk and significantly less from formula. Formula-fed babies also exhibit lower Se and GPx blood levels until they consume fish or meat products (485, 487, 490). In extremely low-birth weight infants and premature babies, these deficiencies are more pronounced. However, specific deficits associated with lower Se supply in this population have not been found (484, 488). Surprisingly and in contrast to other supplementation experiences, selenomethionine-containing yeast does not lead to increased GPx activity in milk as does maternal supplementation with selenite (487).

Several reports have been published indicating a specific cell-, proliferation-, and differentiation-specific distribution of the selenoproteins D1 and D2 in the lactating mammary gland of rats. During lactation, D1 expression is increased in the lactating gland and decreased in liver (446). Expression of D1 is restricted to the differentiated alveolar epithelium in the gland and stimulated by suckling (491, 492). Norepinephrine enhances both mRNA levels and enzyme activity, whereas prolactin increases D1 activity but not transcript levels. GH and oxytocin have no effect (491). Constitutive expression of D2 is confined to the nonepithelial cells, fibroblasts, and fat pads in the mammary gland. Breast D2 activity varies along the estrous cycle, with the lowest activity in diestrus. In lactating cows and pigs, D2 expression and its control by GH have been observed (493, 494). Apparently, increased expression of deiodinase activity and T_3 production is essential to maintain the local thyroid hormone requirements of the mammary epithelium during high milk production, when liver deiodinase and circulating hormone levels tend to decrease. The changes in D1 expression in the lactating mammary gland parallel increased 5′-deiodinase activity in the hypothalamus and pituitary, where hyperplasia and hypertrophy of lactotroph and somatotroph pituitary cells are observed.

Pregnancy and lactation lead to major tissue redistribution of Se as well as altered expression of selenoproteins and various chemical forms of supranutritional Se supply. They influence Se load of the milk and tissue selenoprotein expression (495). Several selenoproteins have been identified in milk and might contribute to the beneficial effects of Se, which reduces infections and mastitis and improves milk production in farm animals (487, 489, 496). Metabolic labeling with 75-selenite of mouse mammary epithelial cells *in vitro* and *in vivo* identified 11 different selenoproteins resolved into 25 different spots after 2D-gel electrophoresis. GPx constitutes a major fraction of these proteins (497). Se exerts inhibitory effects on growth of mouse mammary tumor cells. This inhibition has been linked to the expression of an acidic 58-kDa protein (498–500) and to a mouse 56-kDa protein (501, 502). The 56- or 58-kDa proteins reversibly bind

Se and do not contain Sec residues. The 56-kDa protein, also found recently in human tissues and shown to be repressed by androgens, exerts growth inhibitory properties and might be of importance in antiproliferative action of Se compounds (503) (see *Section VII.G.3*). TrxR, assumed to be involved in regulation of normal and tumor cell growth, has recently been identified in mammary tumor cell lines, and its expression is markedly stimulated (37-fold) by selenite treatment (149). The functional relevance of these findings for tumor cell growth and gene expression is of interest because not all tumor cells express TrxR, and Se-dependent apoptosis, cell and tumor growth, and stimulation of TrxR activity differ significantly between cell lines and among various tumors. Recent studies found inhibitory effects of both low (<0.1 ppm) and high (2.25 ppm) selenite supply on tumor development, which is accelerated in a transgenic mouse model coexpressing TGFα and c-myc in hepatocytes (504). Expression of several selenoproteins was altered, and 3β-hydroxysteroid dehydrogenase as well as other enzymes involved in detoxification reactions were expressed at higher levels. These observations caution against indiscriminate Se administration for prevention or treatment of all tumor forms.

D. Selenium and the adrenals

Se readily accumulates in the adrenals where it is retained during Se deficiency (472, 480, 505). Rat adrenals express significant levels of D2 activity, which are enhanced in hypothyroidism (506, 507). A nyctohemeral rhythm of D2 expression has been found in the adrenals, the pineal, and the pituitary gland (506). Se deficiency causes a marked decrease in GPx activity in an adrenal cell line associated with decreased steroid hormone production (508). High expression of mitochondrial TrxR has been found in bovine adrenal cortex (509).

E. Selenium, pancreas, and diabetes

TrxR 1 and Trx expression have been shown in mouse exocrine and endocrine pancreas, GPx activity and 5'-deiodinase in rat islet cells, and SePP in β-cells (510–514). TrxR expression increased in the islet cells during starvation (515). Glucose stimulates T_3 production in TR-expressing islet cells (511).

β-Cells are sensitive to oxidative stress while showing a low capacity of antioxidative systems. Se-deficient animals have low serum insulin levels, and their islet cells show impaired protein secretion that is normalized by Se and vitamin E (516). Pancreas islets from patients with Keshan disease and from Se-deficient rats show atrophy and degeneration. Diabetogenic drugs like alloxan and streptozotocin induce β-cell degeneration through production of ROS. Overexpression of β-cell-targeted copper/zinc superoxide dismutase enhanced resistance to the effects of diabetogenic drugs in mice (517). Inactivation of copper/zinc superoxide dismutase by glycation may be a factor in diabetic complications (518). High glucose concentrations up-regulated superoxide dismutase and GPx in rat islet cells, but not catalase activities (510). Earlier, the induction of cGPx in endothelial cells suggested a defense against glucose toxicity (519).

TNFα and IL-1β are mediators of β-cell damage in autoimmune diabetes. Ebselen, a synthetic Se-containing compound mimicking GPx activity, prevented the increase in nitrite production by human islets exposed to TNFα, IL-1β, and interferon-γ, and partially inhibited inducible nitric oxide (NO) synthase expression in rat insulinoma cells. It failed to inhibit NFκB activation and long-term IL-1-induced inducible NO synthase expression (520). Similarly, β-cell targeted catalase overexpression did not impair but protected β-cell function against hydrogen peroxide and streptozotocin but not IL-1 (521). In contrast, stable expression of manganese superoxide dismutase in insulinoma cells prevented IL-1 β-cell toxicity and reduced NO production (522). The new selenoprotein SelS is induced by glucose deprivation and endoplasmatic reticulum stress in liver cells and upregulated by insulin injection in adipose tissue and muscle of diabetic, but not control subjects (523). Its overexpression increased resistance to oxidative stress in mouse β-cells (Min6) (524).

Diabetic patients and animal models show decreased serum Se levels, lower GPx activities and increased cellular oxidative stress (525, 526). Data on beneficial effects of Se supplementation are controversial. In streptozotocin-induced diabetic rats, Se supplementation reduces blood glucose levels and lipid peroxidation (527) and brings decreased blood and liver GPx activities, GSH levels, and Se concentrations to normal.

Se supplementation to diabetic rats prevents TGF-β1-mediated renal injury associated with diabetes (526). This is analogous to iodide-induced thyroid fibrosis in Se-deficient rats (183). Several reports suggest an insulin-like effect for selenate similar to vanadate in *in vitro* and animal experiments (528–532). Direct inhibition of phosphatases involved in insulin signal transduction can be shown in β-cells, adipocytes, and muscle cells. In the db/db mouse model, genetically predisposed to develop type II diabetes, administration of selenate (SeVI) revealed an insulinomimetic role, whereas selenite (SeIV) or Se deficiency aggravated diabetes (533). The development of insulin resistance and syndrome X-like metabolic alterations in mice overexpressing GPx-1 suggests interference with insulin action through ROS (534). This insulin resistance was associated with a reduction in the insulin-stimulated phosphorylation of insulin receptor and of Akt. In addition to the weight gain reported in healthy men with high-dose Se supplementation, studies suggest (460) that selenoproteins protect both the exocrine and the endocrine pancreas (535, 536). There is evidence for protective effects of Se supplementation on surrogate parameters (*e.g.*, NFκB in monocytes) for adverse cardiovascular events (537) and diabetic complications (*e.g.*, neuropathy and retinopathy) (538–541).

F. Selenium and selenoproteins in the female reproductive tract

1. Placenta and uterus. Se excess in rats results in reproductive failure due to toxic Se effects in females, but not males; it causes injury to the fetus followed by absorption (10). Se concentrations are higher in maternal than fetal human plasma, and placental tissue concentrations are high (542,

543). Whether Se rapidly passes the human placenta or is actually concentrated in placental tissues remains controversial (544).

High expression of SePP mRNA has been found in the mouse uterus and placenta, and expression levels markedly increase 4 d before birth, reaching maximal levels at term (545). Fetal liver also expresses SePP mRNA before term (545). Rat placental Se content and expression of selenoproteins gradually increase during gestation (546). Placental Se uptake during pregnancy is saturable and affected by several inhibitors (89). SePP might be involved, as it is in passage, fetal deposition, and complexation of mercury (70, 71, 547–549). Selenite, but not selenate or the GPx mimic ebselen, interferes with the metabolism and action of prostanoids (550). Se deficiency and decreased expression of GPx and other enzymes involved in antioxidative defense have been observed in placental insufficiency and in tissues of pregnancies with complications such as preeclampsia (551–554).

Pregnant rat uterus expresses extremely high levels of the selenoprotein D3 mRNA immediately after implantation (348). D3 is localized to epithelial lining cells of the uterine lumen surrounding the fetal cavity. D3 mRNA and activity were found by gestational d 9 at the implantation site (348). This regiospecific and time-dependent expression of D3 suggests an important role for D3 in the control of thyroid hormone availability to the conceptus. The high expression of D3 at the implantation site is assumed to prevent exposure of the developing fetus to excess thyromimetic T_3. The preferential supply of Se to D3 and the high Se content of the placental membranes prevent modulation of its activity even under marked Se deficiency. D3 activity increases in the human placenta as a function of gestational age, and elevated rT_3 levels are observed in the amniotic fluid (301). In the epitheliochorial porcine placenta, D3 activity is higher in the fetal compared with the maternal part (345). This probably limits but does not completely prevent maternal-fetal thyroid hormone transfer during advanced pregnancy. D2 activity is thought to contribute to local T_3 production but not to transfer T_3 to the fetus (298, 301, 555).

Human placenta is a rich source of selenoproteins including TrxR (556). Trx and TrxR are localized histochemically in cytotrophoblasts, decidua, and stromal cells in the stem villi of normal human and rodent placenta and assumed to protect placental tissues during inflammation (557, 558). In the uterus, but not in the liver, of ovariectomized rats, expression of Trx mRNA is stimulated by estradiol, androgen, and 5α-dihydrotestosterone, but not progesterone. The combined treatment by estradiol and the antiestrogen ICI 182780 or by testosterone together with the antiandrogen flutamid attenuated the stimulatory effect of the hormones alone (559, 560). These findings indicate that Trx regulation is mediated via nuclear steroid hormone receptors possibly coupled to growth-promoting effects of steroids in this tissue. In human endometrial stromal cells, rapid Trx expression at the mRNA and protein level is induced by estradiol, augmented by progesterone, and inhibited by tamoxifen. Although Trx itself did not promote endometrial cell growth, it additively enhanced the EGF-induced mitogenic effect (561).

2. Ovarian function, gonadotropins, and Se. Se deficiency leads to degeneration of ovaries and atresy of follicles (562). *In vitro* studies revealed that Se supply and expression of GPx activity, together with other antioxidative enzymes, assist in ovarian function regulation by FSH (563, 564). Selenite not only stimulates proliferation of bovine granulosa cells from small follicles, but also potentiates the stimulatory action of gonadotropins on estradiol secretion. Bovine FSH stimulates estradiol production in cells from large follicles in the absence of Se. Its action on cells from small follicles requires addition of Se. The role of Se in inhibiting NO production remains uncertain, because it decreases bovine FSH-induced NO production in granulosa cells of small follicles. Inhibitors of oxidative stress, such as GPx, mimic the ability of FSH to suppress apoptosis in cultured rat ovarian follicles *in vitro* (563). In cows, degeneration of the ovaries and placental accretion occur in cases of Se deficiency (562). Se deficiency in the developing rat decreases Se levels in the ovary, with no alterations of D1 and D3 (565).

G. Selenium and male reproduction

1. Se deficiency and male fertility. Studies in rats have revealed that after several generations of feeding a Se-deficient diet, male infertility develops (566–568). There was no effect in females (10). With mild deficiency, Se accumulated in testes; it is preferentially found in the midpiece of spermatozoa, which contains mitochondria. Developmental studies in rats showed changes associated with Se deficiency, *e.g.*, changes in the morphology of spermatids and spermatozoa and, finally, complete absence of mature germinal cells (569, 570).

2. Expression of selenoproteins in testes. cGPx and PHGPx are expressed in the testes, the former at a low level, the latter at a high level (571). The onset of PHGPx expression in rat testes was shown to start at puberty and to be gonadotropin-dependent (4- to 6-fold enhancement) (99, 195, 572, 573). The expression was localized close to nuclei and mitochondria of the seminiferous epithelium, as shown by immunohistochemical methods. *In situ* hybridization experiments in mice showed a distinct and stage-specific pattern of expression of PHGPx mRNA in developing spermatids. High expression was found in round spermatids with a peak expression in elongating spermatids, whereas beyond this differentiation stage mRNA signals declined (574). Huge amounts of immunoreactivity for PHGPx were found in the mitochondrial membrane. At least 50% of the keratin-like capsule material obviously consists of enzymatically inactive PHGPx, indicating that during the course of sperm maturation this protein undergoes a functional switch to a matrix constituent, which then lacks enzyme activity (575, 576). PHGPx reportedly plays a role in spermatogenesis in rat and other mammals, including man (577–579). The time course of PHGPx decline after Leydig cell eradication appears comparatively slow, but could be rescued by testosterone substitution. No direct effect of testosterone on the regulation of expression could be demonstrated. In rats, estradiol administration increased and tamoxifen decreased PHGPx mRNA levels both in testes and prostate, but not in the epididymis. These estradiol effects on PHGPx expression might be mediated via

the estrogen receptor β signaling pathway (580). Marked decreases in expression of immunoreactive PHGPx have been observed in infertile males suffering from oligoasthenozoospermia (581).

cGPx does not appear to possess any specific function in spermatogenesis, because cGPx knockout mice are fertile (573, 582). A 34-kDa selenoprotein, the specific sperm nuclei GPx (snGPx), has been identified and cloned (583). This selenoprotein has catalytic properties similar to PHGPx. Structural analysis revealed that snGPx is a PHGPx isoform; it has a different N-terminal sequence encoded by an alternative first exon of the PHGPx gene. This N-terminal sequence contains a nuclear location signal and has high sequence similarity to protamine. snGPx is only expressed in nuclei of late spermatids and acts as protein thiol peroxidase responsible for disulfide cross-linking by reduction of ROS. snGPx influences chromatin condensation and stabilization by acting as a "moonlighting" bifunctional protein (577, 583, 584). Knockout models of PHGPx are lethal at the embryonic period (585, 586). Male infertility is also observed in the SePP-knockout mouse model, which leads to diminished Se content of the testes (78, 79).

An epididymis-specific nonseleno-GPx (GPx-5) was reportedly secreted into the seminal fluid of rodents and other mammals. It was hypothetically associated with the fertilizing capacity of sperm, but some data suggest that no functional transcripts or GPx-5 proteins are expressed in the human epididymis as these transcripts are incorrectly spliced or mutated (59). GPx-5 is a cysteine homolog of the GPx family, which is expressed in several tissues of mammalian species except humans. GPx-5 appears to be up-regulated in mammalian epididymis in case of Se deficiency and might act as a back-up system for the Se-dependent GPx enzymes (55).

At least three different isoenzymes of TrxR have been characterized. TrxR1 is known to be a cytosolic enzyme, whereas TrxR2 and -3 appear to be located in mitochondria. The selenoprotein Trx glutathione reductase (TGR) accumulates in testes after puberty and is particularly abundant in elongating spermatids at the site of mitochondrial sheath formation but absent in mature sperm. TGR might serve together with PHGPx as a novel disulfide bond-formation system, targeting proteins that form structural components of the sperm (587). The specific functions of TrxR1 and -2 in testes have not been characterized. TrxR-catalyzed reduction of critical cysteines in transcription factors like steroid hormone receptors or NFκB and in other nuclear events, like redox-dependent signaling, may be of special importance in testes (135, 138, 143). SePP is exclusively expressed in the Leydig cell fraction and when ethylene-dimethane-sulfonate treatment destroyed the Leydig cells, SePP mRNA disappeared from the testes (588). A link between SePP expression and testosterone production in cultured Leydig cells has been proposed (589). SePP would protect Leydig cells from increased levels of ROS formed after cAMP stimulation in association with increased testosterone production. Serum LH, FSH, and testosterone levels were reduced in Se-deficient mice, along with decreased sperm number and motility, as well as DNA fragmentation. Thus, oxidative stress generated by Se deficiency seemed to impair steroidogenesis, spermatogenesis, and male fertility (590).

Selenoprotein W, which might act as glutathione-dependent antioxidant, also appears in rat testes (591, 592). Selenoprotein p15 mRNA is highly expressed in human and mouse testes (593). However, it is substantially reduced in two malignant cell lines. A high expression of cloned selenoprotein V has been demonstrated in seminiferous tubules of the testes (20).

Sec lyase, the 47-kDa enzyme that specifically catalyzes the degradation of Sec to alanine and elemental Se, is also highly expressed in testes (53). It might cooperate with the similarly abundant selenophosphate synthase, which utilizes the liberated elemental Se (42, 53, 594). High expression of SECIS-binding protein 2 (SBP2) has been reported in testes (27). Purified SBP2 bound to the PHGPx SECIS element proved very effective in mediating Sec incorporation, which is quite universal for selenoprotein synthesis in eukaryotic cells.

3. Selenoproteins of the prostate and prostate cancer. Epidemiological evidence, as well as animal experiments, indicates that low Se supply is linked to the incidence of prostate cancer (2, 595–598). Several selenoproteins have been identified and characterized in the prostate (64, 599–603). The prostate epithelial selenoprotein (PES) is localized in epithelial cells, but not secreted. A 15-kDa Se-labeled subunit is part of a 300-kDa holoprotein (599, 602). At low Se supply, this protein preferentially incorporates Se. Apart from this protein, GPx subunits, SelW, small selenoproteins, and several selenoproteins in the 50- to 70-kDa range are also expressed (592, 599, 603).

A human ortholog (hSP56) of the mouse Se-binding protein SP56 is expressed in androgen-dependent prostate, but not in androgen-independent cancer cell lines (503, 604). Its expression is down-regulated by androgen treatment at low concentrations, whereas prostate-specific antigen (PSA) is up-regulated. In contrast to Sec-containing proteins, SP56 reversibly binds Se (503, 605). Expression of hSP56 is highest in liver, lung, colon, prostate, kidney, and pancreas (503). Low levels were found in testes and brain. This finding is remarkable because Se treatment decreases cancer incidence especially in prostate, lung, and colon tissues (2, 3, 597). A growth-inhibitory action of SP56 has been proposed, and the down-regulation of hSP56 by androgens might relieve this antiproliferative action of hSP56.

A link between Se, androgen regulation, and prostate cancer progression and treatment is probable. Se down-regulates the PSA and androgen receptor (AR) transcripts and protein within hours in the androgen-responsive LNCaP cells and inhibits the trans-activating activity and DNA binding of AR (606). Methylseleninic acid, a potent anticarcinogenic Se compound, inhibits the expression of AR and AR-regulated genes, and thus proliferation, and increases levels of phase 2 detoxification enzymes (607). A recent short time Se intervention study showed a down-regulation of serum-free PSA and testosterone levels (608). Epidemiological retrospective evaluations revealed increased prostate cancer incidence in men with lowest quintiles of serum Se (609). Thus, Se supplementation in men at risk of prostate cancer appears promising (598).

H. Selenoproteins in bone

1. Bone physiology and ROS. Bone is built up and remodeled by the concerted action of mesenchymal and myeloid cells, such as osteoblasts (OB) and osteoclasts (OC). OB secrete extracellular matrix and associated growth factors (*e.g.*, type 1 collagen, osteopontin, osteocalcin, hCYR61),with subsequent mineralization. OC develop from myeloid precursors and are terminally differentiated cells of the monocyte/phagocyte lineage. The receptor activator of NFκB (RANK) and RANK ligand are essential for OC differentiation and activation. The decoy receptor osteoprotegerin modulates RANK ligand availability (610).

When activated, macrophages and related cells undergo an oxidative burst, mediated by the enzyme complex NADPH oxidase (611). Oxidative bursts of different intensity are a source of redox signaling in the cell. Thus, the so-called peroxide tone is important for a balance between signaling, cellular defense mechanisms (intracellular killing of bacteria), and cell damage. This process probably has to be compartmentalized, and we can expect that effective antioxidative systems protect the cells from damage. The main players in this process are superoxides, superoxide anions, and NO. H_2O_2 and NO have been shown to stimulate bone resorption (612, 613). We can assume this oxidative burst and the consecutive reactive oxygen intermediate-mediated signaling necessary for bone resorption in the context of bone remodeling, but leakage or overflow of reactive oxygen intermediate could also impair OB function, thereby propagating bone mass loss and subsequent osteoporosis.

2. Se deficiency, selenoproteins, and bone disease. Se-deficient male rats were shown to develop osteopenia and impaired bone metabolism, growth retardation, and reduction of GH and IGF-I levels (614). Reduced activity of deiodinases in the pituitary may be one reason for these findings (12, 274, 275, 280, 281, 283, 468, 477, 615). Impairment of OB function and reduced sensitivity to PTH and/or 1,25-dihydroxycholecalciferol (1,25-D3) were postulated, because PTH and 1,25-D3 levels were enhanced without enhanced OC formation and bone resorption. Serum calcium levels were unexpectedly lower in the Se-deficient group, and hypercalciuria was noted, indicating an influence of Se deficiency on calcium absorption and/or renal excretion.

Kashin Beck disease is a form of osteoarthritis occurring in regions of Central Africa and China that are known for their low Se supply (Fig. 9). The clinical course of this form of osteoarthritis can be ameliorated by Se supplementation, but the primary cause of the disease remains unclear (214, 616, 617). In rheumatoid arthritis, the TrxRs of monocytic cells have long been targets for antirheumatoid therapy exploiting gold compounds, which can inhibit TrxR activity (618). A report on the influence of antioxidant vitamins E and C on the risk of hip fractures postulated that ROS might exert effects on bone metabolism, but there was no significant effect on hip fracture incidence (619).

3. Selenoprotein expression in OB. [75]Se labeling of human fetal OB (hFOB) cell cultures shows at least nine different proteins that incorporate the radioactive trace element (613, 620).
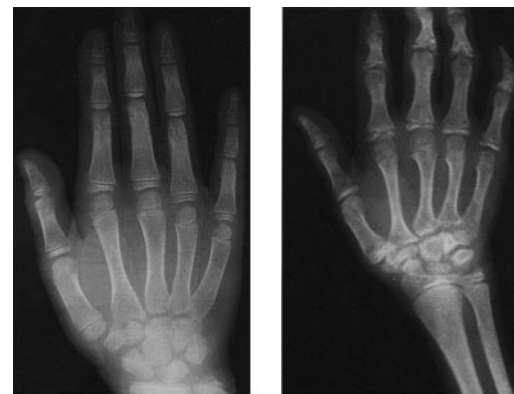
normal   Kashin-Beck

FIG. 9. Kashin-Beck disease. The x-ray figure to the *right* shows marked signs of osteochondropathy of the right hand of a patient suffering from Kashin-Beck disease, in comparison to an age-matched normal control (*left*). [Reproduced with permission from R. Moreno-Reyes *et al.*: *N Engl J Med* 339:1112–1120, 1998 (214) © Massachusetts Medical Society.]

Their respective molecular masses are approximately 80, 70, 56, 54, 24, 21, 18, and 14 kDa (Fig. 10).

The expression of cGPx and pGPx was demonstrated in hFOB (613). [75]Se labeling of hFOB cells showed two compatible bands of 21–24 kDa, and GPx activity was readily measurable. Total GPx activity could be stimulated upon the addition of 100 nM selenite to tissue cultures and decreased by serum deprivation (Fig. 11).

TrxR1 was identified as a 1,25-$(OH)_2$ vitamin D-responsive early gene in hFOB cells (116). Only a transient increase of TrxR mRNA was observed, reaching maximal levels by 4 h after stimulation with 1,25-D3. TrxR2 mRNA was expressed
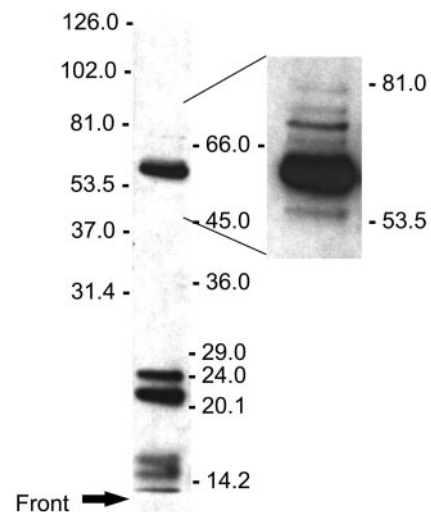
FIG. 10. Autoradiography of Se-75 metabolic labeling in hFOB and separation of radiolabeled proteins. [Reproduced with permission from I. Dreher *et al.*: *Biochem Biophys Res Commun* 245:101–107, 1998 (613).] hFOB-cells were cultured under Se-deficient conditions (serum-free culture for 3 d). 75-Se (specific activity, 1.9 Ci/μg; Research Reactor Facility, University of Missouri, Columbia, MO) was added at 10 nM for 24 h. Positions of molecular weight markers are shown on the *left* and *right*. After gel electrophoresis, the dried gel was exposed to Kodak X-Omat x-ray film for 24 h.
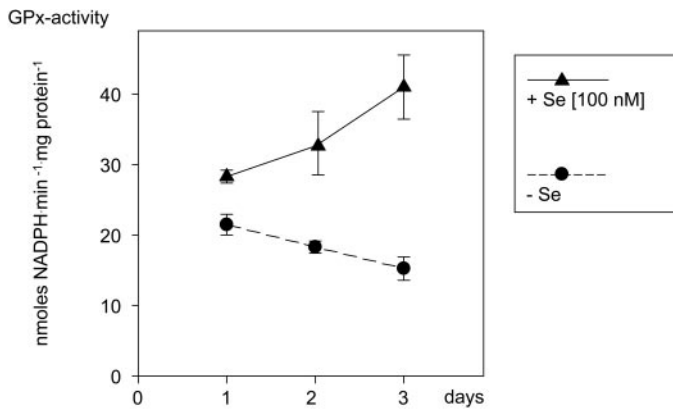
GPx-activity

FIG. 11. Time course of stimulation of GPx-activity by selenite in hFOB. [Reproduced with permission from I. Dreher *et al.*: *Biochem Biophys Res Commun* 245:101–107, 1998 (613).] hFOB cells were cultured in 10% FCS-containing medium. From d 0 onward, cells received serum-free medium plus/minus selenite at 100 nM. GPx enzyme activity was measured from cytosolic extracts prepared after 24, 48, and 72 h. The assay applied does not discriminate between various GPx isoenzymes.

at low levels and did not respond to 1,25-D3 treatment. Total TrxR activity was regulated by the addition of 100 nM selenite to cell cultures, but was not stimulated by 1,25-D3 under conditions of relative Se deficiency (*e.g.*, cell culture conditions without supplementation containing 7.5 nM Se). Only after two passages of cultures in the presence of 100 nM selenite was a significant rise in TrxR activity observed upon 1,25-D3 stimulation (621).

TrxR/Trx in OB could be involved in regulation of the transcription factor (*e.g.*, steroid hormone receptor signaling in OB), the peroxide tone, and antioxidative scavenging. Vitamin K is a substrate for TrxR, and thus TrxR contributes to the activity of vitamin K-dependent proteins like γ-carboxylase itself, osteocalcin, and bone gla protein, the latter two being important regulators of calcification (Refs. 621 and 622 and references therein). Additional functions may comprise the modulation of cysteine-rich signaling proteins of the CCN family of growth factors (*e.g.*, CYR61, CTGF) (623–625).

a. Other selenoproteins in OB. [75]Se labeling in the region of 53–60 kDa (Fig. 10) can be assigned to TrxR1 and SePP in OB and their precursors. A mouse chondrogenic cell line expresses functional D2 and T_3 receptors (626). We found no evidence for deiodinase expression and activity in hFOB cells. Bone development and differentiation are controlled by thyroid hormones acting via local cell-specific expression of deiodinases and T_3 receptors (615, 627, 628). No 5'-deiodinase activity is found in bone extracts of D2 knockout mice, and both 1,25-(OH)$_2$ vitamin D$_3$ and TSH via its adenylate cyclase-coupled receptor, which is expressed in OB, stimulate D2 activity in OB *in vitro* (615, 628). The 14-kDa band may represent the 15-kDa selenoprotein expressed in T cells, which is discussed as a putative cancer-associated factor (629).

4. Selenoproteins and cells of the monocyte/macrophage lineage of differentiation. [75]Se labeling of monocytic THP1 cells yielded the expression of at least nine different selenopro-

teins or selenoprotein fragments. TrxR1 was identified as a vitamin D-responsive selenoprotein in THP1 leukemia cells and in peripheral blood monocytes prepared *ex vivo* (113, 114, 630). There is presently no information available on selenoproteins in mature OC.

I. Selenium, the hormonal system of the skin, and selenoproteins in muscle

Skin locally expresses most components of the endocrine system (631). However, with the exception of expression of GPx-1 in skin and of D2 in keratinocytes, no detailed information on other selenoproteins in skin is available (592, 632–634). Local T_3 production by skin might be an important source of T_3, especially during the fetal period or in hypothyroidism (635). Se depletion reduces skin Se levels in rats and decreases activities of all three deiodinases in embryonic d 21 rats as well as D1 and D3 activity in postnatal d 12 rats (565). Whether Se supply is involved in deposition of glycosaminoglycans in the skin of severely hypothyroid patients has not yet been analyzed. GPx and SelW are expressed in skin of Se-adequate rats (636), and Se deficiency reduced the number of epidermal Langerhans cells that might affect cutaneous immunity and UV protection (634). SelW is expressed in the skin at higher levels in female rats (592, 637). Cre recombinase-dependent inactivation of the Sec tRNA [Ser]Sec gene (Trsp) reduced Sec tRNA [Ser]Sec amounts and the selenoprotein population of skin (GPx-1 and GPx-4, Sep15) (638).

Differential expression of TrxR and PHGPx has been found in human fibroblasts, keratinocytes, and melanocytes (639). Low (1 nM) concentrations of selenite or (10 nM) selenomethionine protect keratinocytes and melanocytes from UV-B-induced cell death *in vitro* (639).

Fibroblasts and muscle cells also express several selenoproteins including deiodinases (297, 328, 640). Functional D1 activity in rat skeletal muscle (641) might generate a significant quantity of daily T_3 production, given the mass of tissue compared with liver, kidney, and thyroid, the other organs contributing to T_3 formation (642). D2 expression, its stimulation by cAMP and β-adrenergic agonists, and inhibition by thyroid hormones and TNFα have been demonstrated in cultured human skeletal muscle cells (297). However, skeletal muscle biopsies of critically ill patients revealed no D2 activity (352). SepN mutations lead to hereditary myopathies, but its exact function in muscle development and physiology remains to be clarified (643).

J. Selenoproteins and the hormonal regulation of endothelial function

Se deficiency has been associated with cardiovascular problems, thrombosis, and atherosclerosis (18, 644–646). Many of the protective effects of Se have been attributed to the action of the GPx family of enzymes (576), which apart from their antioxidative effects modulate the cyclooxygenase pathway, thromboxane production, and eicosanoid metabolism (647). The finding of SePP binding to the inner endothelial surface (73) suggests a protective role of SePP, possibly mediated by inhibition of peroxynitrite formation and

nitrosylation of endothelial proteins (648). Experimental evidence supports the hypothesis that low Se status is linked to enhanced lipid peroxidation, elevated levels of oxidized lipoproteins, and etiology of cardiovascular diseases (537, 646, 649). Several selenoproteins are Se-dependently expressed in bovine arterial endothelial cells (cGPx, PHGPx, TrxR1, TrxR2, TrxR3, SePP) (650). Selenite induces TrxR, protects human endothelial cells from oxidative damage, and affects calcium signaling (651–653). Several other not yet identified Se-containing proteins were found in the arterial wall (p15, p18, p30, p43, p67) (654). Combined Se and vitamin E deficiency increased microvascular permeability in rat heart and eye tissues, but not in others (655). GPx-4 expression in human endothelial cells depends on Se supply and is markedly modulated in a complex manner by fatty acids, cytokines, and other oxidants indicating possible protective links of Se against atherogenic processes (656). The role of Se in the immune system and hormonal influences in the interaction of these key networks in maintaining and regulating communication and information transfer in multicellular systems are beyond the scope of this review (see Refs. 415 and 657–659).

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