Chapter 33
Selenium and Endocrine Tissues

Josef Köhrle

Abstract Selenium (Se) status and individual selenoproteins are important regulators of hormonal homeostasis during development and adulthood. Because endocrine cells and organs are highly perfused and continuously involved in hormone secretion and feedback sensor function, adequate control of their redox state is required to sustain the hormone secretory machinery. Several selenoproteins contribute to this essential function, which might explain the high relative Se content in endocrine tissues. Specifically, hypothalamus-pituitary-feedback regulation is responsive to Se, and the thyroid, islets of Langerhans in the pancreas, adrenal cortex, and gonads are strongly affected by Se status. Deiodinase selenoproteins contribute to the hypothalamic control of satiety, food intake, and energy expenditure, as well as to the development and proper function of several endocrine tissues. Inadequate Se status is linked to autoimmune diseases of the thyroid, impaired insulin secretion and resistance, delayed chondrocyte differentiation, defective bone formation, and reduced gonadal function. Single-nucleotide polymorphisms of several selenoprotein genes affect nutritional Se status and several hormonal axes. An inactivating mutation of thioredoxin reductase 2 causes familial glucocorticoid deficiency. Thus, adequate Se supply is crucial for the appropriate function of the endocrine system and hormone action.

Keywords Adrenal • Antioxidant defense • Autoimmune disease • Bone • Cancer • Deiodinase • Diabetes • Gonad • Kashin-Beck disease • Pancreas • Redox regulation • ROS • Selenoprotein • Testes • Thyroid

33.1 Introduction

Endocrine tissues in rodents stand out by their high relative selenium (Se) tissue content per weight and thyroid, kidney, and pituitary show highest concentrations [1–3]. Experiments involving dietary Se depletion, ^{75}Se labeling, and Se repletion indicate a remarkable hierarchy of Se distribution, retention, and repletion for endocrine organs and the brain, compared to large parenchymal tissues and organs, such

J. Köhrle (✉)
Institut für Experimentelle Endokrinologie, Charité-Universitätsmedizin Berlin, Campus Virchow Klinikum, Augustenburger Platz 1, 13353 Berlin, Germany
e-mail: josef.koehrle@charite.de

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as the liver, muscle, and adipose tissue [1]. Analysis of the expression or function of various selenoproteins in endocrine tissues during these nutritive manipulations revealed a further superimposed 'hierarchy' among individual selenoproteins within these tissues. Endocrine tissues are highly vascularized and perfused to allow rapid delivery of their hormones via circulation to target tissues. Thus, they are also strongly exposed to heavy metals and other adverse agents that circulate in the blood and affect tissues. The accumulation and precipitation of insoluble heavy metal selenides in endocrine tissues and kidneys may account for a fraction of the observed high Se content. However, even a correction for Hg, Cd, and Pb tissue content [4–6] leaves endocrine tissues and kidneys among those that rank the highest with respect to their relative Se content and bioavailability.

In the meantime, several other factors contributing to the observations of high Se content in endocrine tissues have been identified, such as i) distinct selenocysteine insertion sequence structures of selenoprotein transcripts, ii) expression of apolipoprotein E receptor 2 (ApoER2) in the testes, kidney, and brain, and iii) the local expression of abundant selenoproteins, including glutathione peroxidase 1 (GPX1), that retain Se at their active sites [7]. ApoER2, which is the membrane transport protein that is involved in the cellular uptake of the Se transport and storage protein selenoprotein P (SEPP1) [8], is expressed at low levels in the thyroid. The thyroid has the highest Se content in mice and humans and expresses most known selenoproteins [9]. It may be speculated that the functional role of endocrine tissues to actively secrete hormones throughout life requires a highly efficient Se-related redox system that regulates both the regeneration of the cell machinery involved in hormone secretion and the function of the quality control system for secreted peptides, proteins, and glycoproteins [10] acting as hormones on target tissues and cells. Several selenoproteins reside in the endoplasmic reticulum (ER) and are involved in protein biosynthesis [10]. Many of these functions can be adequately covered by various selenoproteins in endocrine tissues (for review see [3]). In addition, thyroid as well as steroid hormone-producing glands, such as gonads and adrenals, experience high and life-long exposure to H_2O_2 and reactive oxygen species (ROS), which are required for hormone synthesis. Several selenoprotein families are perfectly suited to provide adequate antioxidative function, along with the cellular redox control that is required to quench any excessively produced H_2O_2-derived ROS and to protect endocrine cells for their integrative function in development, growth, and metabolism. At the same time, most endocrine tissues have very low proliferation rates and may thus accumulate and deposit insoluble heavy metal selenides.

33.2 Hypothalamus–Pituitary-Feedback Axis, Selenium, and the Hormonal Regulation of Energy Metabolism

Various groups of hypothalamic neurons, called nuclei, are involved in the central coordination of hormone secretion by integrating sensory input from the central nervous system and metabolic signals from peripheral tissues. These nuclei translate such

information into the production of various 'releasing hormones', which instruct anterior pituitary cells to secrete their glandotropic hormones. Various selenoproteins and high Se content have been found in both endocrine structures. Of special interest is the role of the thioredoxin (TXN)-like ER-resident, selenoprotein M, whose genetic inactivation in mice alters body composition and increases white adipose tissue mass [11]. This likely occurs by decreasing the leptin sensitivity of hypothalamic centers regulating satiety. Leptin, which is produced in white adipose tissue, is a main regulator of energy expenditure, satiety, and food intake. It is unclear whether this observation is related to the anorexic effect of diphenyl diselenide [$(PhSe)_2$] and p-chloro-diphenyl diselenide [$(p\text{-}ClPhSe)_2$]. These agents decrease satiety, food intake, fat mass, and body weight after pharmacological or dietary administration [12, 13].

The TXN-like selenoprotein T (SELT) is another selenoprotein that is expressed in the anterior pituitary, as well as in several other endocrine tissues (e.g., thyroid, pancreas, and testicular Leydig cells). SELT is also involved in the hormonal regulation of energy metabolism [14]. The pituitary adenylate cyclase-activating polypeptide (PACAP) represents a main activator of SELT expression, especially in the β and δ cells of the pancreatic islets of Langerhans. In these Langerhans islets, PACAP mobilizes intracellular Ca^{2+} secretion and significantly contributes to the enhanced secretion of insulin and somatostatin in β cells and δ cells, respectively [15, 16]. The genetic inactivation of *Selt* in β cells impairs glucose tolerance, and the number and size of these Langerhans islets are decreased compared to those in wild type mice [16].

The paraventricular nucleus of the hypothalamus is a key structure in the regulation of energy metabolism and contains thyrotropin-releasing hormone (TRH)-producing neurons. TRH stimulates the production of anterior pituitary thyrotropin (TSH), which is the main stimulator of thyroid hormone (TH) formation [17]. Both TRH and TSH feedback regulation are negatively controlled by the active TH 3,3′,5-triiodo-L-thyronine (T_3), which binds nuclear T_3 receptors. Local production of T_3 from the prohormone L-thyroxine (T_4) occurs by 5′-deiodinases (DIO1, DIO2), which are selenoproteins ([3] and Chap. 41). In the hypothalamus, T_4 and T_3 may also be inactivated to TH metabolites, which do not modulate the function of cellular T_3 receptors. This reaction is catalyzed by the selenoenzyme deiodinase 3 (DIO3). DIO2 is mainly expressed in tanycytes, which are specialized ependymal cells that are located in the third ventricle and use their extensions to bridge the distance between the ventricular floor and the mediobasal hypothalamus. These tanycytes convey signals, such as locally produced T_3, to hypothalamic TRH neurons [17]. Neurons exhibit low DIO2 activity but express T_3-inactivating DIO3. A complex pattern of TH transporters expressed in neurons, astrocytes, and other brain cells contributes to local TH bioavailability [18]. In contrast to other tissues, hypothalamic DIO2 is less sensitive to T_4-induced, ubiquitination-dependent inactivation, which may explain the high sensitivity of the hypothalamus to T_4 feedback inhibition [19]. Whether nutritional variations in Se status can significantly alter hypothalamic and pituitary DIO activity remains unclear. However, severe Se depletion has been shown to affect DIO-regulated TRH and TSH feedback [2, 20]. Interestingly, the strong inhibitory action of proinflammatory cytokines on both DIO2 and DIO3 function results in an inappropriate TH-dependent feedback regulation of the TH axis in severe non-thyroidal illness and starvation [21].

33.3 Selenium in the Thyroid Gland and Thyroid Hormone Synthesis, Metabolism, and Action

The effects of Se status on TH homeostasis have been demonstrated. The pathogenesis of cretinism is associated with Se and iodine deficiency [3, 22], and several investigator teams have concomitantly discovered DIO as the second family of selenoenzymes [23–25]. Adequate Se status is required for proper TH synthesis, which depends on the life-long production of H_2O_2 by dual oxidase inside the functional angiofollicular units of the thyroid gland [26]. The thyrocytes express several selenoproteins that contribute to continuous cellular redox control and antioxidative defense [9] to protect the ROS-exposed gland. In females, the thyroid gland is highly affected by the development of autoimmune thyroiditis [27–29] and thyroid cancer [30, 31], which is the most frequent endocrine tissue-related malignancy. Both diseases might be linked to the continuous exposure of the gland to H_2O_2 and ROS [32–34]. In terms of TH metabolism and action, it is important to know that all three DIOs are selenoproteins, and that severe nutritional Se deficiency in experimental animal models impairs their function, mainly resulting in the decreased enzymatic formation of the active TH T_3 [3, 29]. However, even under severe systemic Se deficiency induced by genetic inactivation of the *Sepp1* gene in mice, tissue DIO function is maintained close-to-normal levels [35]. Furthermore, serum TH concentrations, including TSH feedback regulation, remain at normal status. A remarkably mild phenotype with respect to the TH axis and metabolic function is observed in mice exhibiting liver-specific or complete knockout of *Dio1* or *Dio2* [36]. Similar phenotypes are observed in mice exhibiting knockdown of all three *Dio* isoenzymes. A major phenotype is only observed with the inactivation of *Dio3*, an imprinted gene. This inactivation alters the setpoint of the hypothalamus-pituitary-thyroid (HPT) axis, thus leading to impaired growth, development, metabolic function, and transient hypothyroidism [37].

Surprisingly, the thyroid-specific genetic inactivation of $tRNA^{[Ser]Sec}$, which depletes all functional selenoproteins in thyrocytes, had only minor effects on thyroid morphology and function in mice [38]. This was the case even after experimental challenge by iodine deficiency, which did not destroy this 'unprotected gland'. In fact, the gland continued to produce close-to-normal levels of serum TH, albeit being exposed to increased oxidative stress. These results suggest that the expression of selenoproteins is not essential for thyroid function and/or other components of cellular redox control. Antioxidative defense might adequately handle follicular exposure to H_2O_2 and ROS, even under stimulatory conditions of iodine deficiency. This finding in mice contrasts with current clinical observations showing that Se supplementation and adequate Se status, especially under conditions of combined iodine deficiency, might i) protect against benign and malignant thyroid disease, ii) improve thyroid function, iii) reduce thyroid volume and goiter size, and iv) decrease the titer of circulating anti-thyroid peroxidase (TPO) antibodies in autoimmune thyroiditis (see recent reviews [28, 29, 38, 39]). However, with few exceptions [27, 40–42], such intermediate conclusions were mainly drawn from small and controversial studies,

which provided only low-grade evidence for clinical guidelines and the code of daily practice [43–47]. Currently, several prospective and adequately powered Se interventional studies are being conducted to clarify these open questions [48–50].

Proposed links between low Se status and thyroid cancer incidence have not been confirmed [45, 46, 51, 52]. At this point, it is not clear whether low Se status, which is observed under various conditions of inadequate thyroid function and autoimmune disease, is a cause or effect of this condition. An altered thyroid status has been shown to affect the homeostasis of trace elements, such as Se, copper, zinc, and iron [46, 53–56]. Currently, there are divergent opinions concerning the chemical form, duration, and dose of Se to be administered in the prevention and treatment of thyroid-related (autoimmune) diseases. Effects were mainly observed if doses higher than 100 μg/day and longer than 3 months were used, whereas selenite, selenomethionine, and other organic forms appeared to be effective in patients with inadequate Se status. Some studies have suggested a gender-specific action of supplementation with Se compounds [28, 29, 43].

There is evidence that the rate-limiting step in iodide uptake by thyrocytes is sensitive to Se status, as Se increases the expression and function of the sodium-iodide symporter (NIS) that is localized in the basolateral membrane of angiofollicular units. Se-dependent TXN/thioredoxin reductase and an altered cellular redox state have also been shown to enhance the binding of the redox-sensitive transcription factor Pax8, which is essential for TSH-dependent NIS transcription [57].

Although Se compounds might enhance tissue-specific DIO activity [58], they may also interfere with or inhibit TH metabolism [59, 60]. DIO expression is affected by proinflammatory cytokines, both at the transcriptional and posttranscriptional levels. Typically, *Dio1* and *Dio2* are decreased, and *Dio3* may be increased under such circumstances in cell cultures in vitro or in appropriate animal models ex vivo [61–63]. However, Se supplementation does not fully rescue cytokine-impaired DIO activity in various cell lines in vitro [64].

Recently, a study in Portugal reported a twofold elevation in the risk for carriers of the 105 GA and AA SNPs in *SEPS1* and autoimmune thyroiditis [65]. Carriers of the GG phenotype might be more efficient in antioxidant selenoprotein synthesis, as indicated by their higher GPX activity [66], and their SEPS expression might be less impaired under the influence of proinflammatory cytokines [67]. The effects of Se on various components of the humoral and cellular immune system have been described [68]. Selenomethionine treatment (80 or 160 μg/day) for 6 or 12 months had no effect on TPO autoantibody titers and thyroid morphology in patients with autoimmune thyroiditis. However, decreases in serum interferon-γ-dependent chemokines were observed, which suggests that these chemokines might serve as Se-responsive biomarkers for autoimmune thyroiditis [69]. In an experimental autoimmune thyroiditis female rat model, high Se intake (2 μg Se/kg body weight) improved thyroid morphology, decreased circulating thyroid-related autoantibody titers, increased the TH_1/TH_2 cytokine ratio, and mitigated inflammatory response [70].

SNPs of selenoprotein genes and several components of the HPT axis have an impact on TH and Se status, as indicated for several SNPs of the *DIO* genes (see also Chap. 13). There is evidence that such SNPs alter Se bioavailability and incorporation

into selenoproteins, as indicated by Se biomarkers [71–73]. SNPs in the promotors and (non-) coding regions of *DIO* genes impair their expression, correct posttranslational handling in the ER and Golgi apparatus (e.g., Thr92Ala-DIO), and affect the efficiency of TH deiodination [74–76]. Such SNPs have been linked to a susceptibility to type 2 diabetes mellitus (T2DM), age-related disorders, neurocognitive function, and neurodegenerative diseases. Most of the currently available data are limited to animal experiments or underpowered human studies and thus require confirmation in replicate cohorts by independent groups to strengthen the claims of cause-effect relationship levels. None of the SNPs in the *DIO* genes directly affect the Se-dependent reaction mechanism, and no major gene defects in human *DIO* genes linked to severe disease have been reported [56, 74]. The Ala variant of Thr92Ala-DIO2 appears to have a longer half-life and might accumulate in the Golgi apparatus and disturb proper Golgi function, as observed in transfected human embryonic kidney cells [76].

Several factors are known to modify both TH status and Se-related parameters and biomarkers, but these might again reflect associations rather than cause-effect relationships. In particular, chronic kidney disease and hemodialysis interfere with Se homeostasis, and impaired renal function and advanced chronic kidney disease are associated with increases and decreases in serum SEPP1 and T_4 levels, respectively [77]. Seasonal variations in serum TH concentrations have also been reported to be related to alterations in nutritional Se intake under extreme climatic living conditions [78]. In a small observational study, nutritional Se intake was analyzed in relation to anthropomorphic parameters, and high serum Se levels were positively correlated with body mass index, waist circumference, and the T_3/T_4 ratio [79]. Several other studies, however, did not observe such direct 'simple' associations [3, 30, 73].

Se supplementation alone or in combination with other trace elements has been studied in euthyroid and (subclinically) hypo- or hyperthyroid patients at various doses and with different Se compounds resulting in rather variable outcomes on the serum parameters of thyroid function [39, 50, 80]. These studies have not provided any conclusions for interventions for the purpose of normalizing thyroid function. Recently, a systematic, dose-related (100–300 μg Se-enriched yeast), randomized, controlled, double-blinded trial that was designated the Danish PREvention of Cancer by Intervention with Selenium pilot study (DK-PRECISE) was performed [50]. Of 491 subjects aged 60–74 years old, 361 subjects completed the 5-year intervention period. No changes in free T_3 levels or T_3/T_4 ratios were found, but Se dose-relatedly reduced serum TSH and free T_4 concentrations. Until further studies can show a therapeutic benefit of Se compounds in thyroid disorders, iodide supplementation should be used for prevention of goiter and T_4 alone or in combination with iodide should continue to be prescribed to treat hypothyroidism. Administration of antithyroid drugs is the first choice in therapy of hyperthyroidism. Se compounds in supplementation doses (100–200 mg/day in adults) appear to have adjuvant benefit in these disorders without adverse effects.

Compared to healthy pregnant controls, lower serum TSH and Se concentrations and higher TH levels have been observed in pregnant women with hyperthyroidism [81, 82]. However, no cause-effect relationships between pregnancy and Se or TH are known [47]. Whether altered maternal Se status during pregnancy impacts on

fetal and postnatal child development (either directly or via Se-dependent TH status of the maternal-fetal unit) requires further long-term and follow-up studies. An alteration in Se status has been observed during pregnancy and might affect placental DIO activity and fetal supply with maternal TH [3]. The limited number of studies in experimental animals and human (term) placenta do not support a direct effect of nutritional Se status on altered placental DIO activity, especially DIO3, even under conditions of preeclampsia [83, 84].

Combined nutritional Se and iodine deficiency has been proposed as a mechanism underlying the development of cretinism caused by inadequate TH availability and action during fetal and postnatal (brain) development [22]. While "neurological cretinism" might rise from maternal and fetal Se and TH deficiency during pregnancy, myxedematous cretinism appears to develop postnatally by combined Se and iodine deficiency [3, 22, 29, 85]. Elevated TSH-stimulated H_2O_2 production under the latter condition leads to fibrotic changes irreversibly destroying functional thyroid tissue. Considering that more than 700 publications on human and animal experimental studies addressing the relationship between Se status and thyroid function in context of iodine intake have been published during the last three decades, it is surprising that the exact molecular mechanisms causing the devastating but preventable disease cretinism, which affects more than five million individuals and may be associated with Kashin-Beck disease [85], are still unknown.

33.4 Selenium, Bone, and Calcium-Regulating Hormones

Se is an organic component of bone but not a constituent of the mineral hydroxyapatite deposit. Severe Se deficiency strongly impairs chondrocyte differentiation, bone development, and calcification, as indicated by the classical Kashin-Beck disease phenotype [85]. However, no clear effects of Se status on hormones regulating Ca^{2+} and phosphate homeostasis have been reported, albeit several mouse selenoprotein knockout models exhibit marked bone phenotypes [86]. Bone is clearly a target for SEPP1-mediated Se delivery via ApoER2, as indicated by the decreased Se content in bones in *Sepp1* knockout mice and the restoration of normal Se status after transgenic expression of human *SEPP1* in this model [87]. Hormones regulate several selenoproteins in bone. For example, estradiol stimulates *Gpx1* expression in osteoclasts, and 1α,25-dihydroxyvitamin D_3 rapidly induces *Txnrd1* in osteoblasts along with their differentiation [88, 89]. Similarly, local expression of the selenoprotein Dio2 generates T_3 which binds to the T_3 receptor, thus initiating steps that are essential for proper bone development [90]. Adequate Se supply is also essential for the development and function of bone marrow stromal cells during their differentiation into bone cells [91].

Interestingly, supplementation of adult Saudi T2DM patients with vitamin D_3 tablets (2000 IU/day) for 6 months decreased serum parathyroid hormone concentrations but also increased serum Se and magnesium concentrations; this

intervention was accompanied by several gender-specific changes in metabolic serum parameters [92]. The mechanisms underlying these observations for positive links between vitamin D and Se status remain unclear. In a 6-year, prospective, European Osteoporosis and Ultrasound Study (OPUS) evaluating fracture-related factors in 2374 postmenopausal euthyroid women associations between parameters of Se status and bone were observed [93]. A positive association between SEPP1 concentration and hip and lumbar spine bone mineral density (BMD) was observed and accompanied by decreased serum markers of bone formation (osteocalcin) and bone resorption (C- and N-telopeptide). Investigators have concluded that adequate Se status positively and inversely correlates with parameters of BMD and bone turnover, respectively, in elderly, euthyroid women. However, hormonal links among Se, vitamin D, Ca^{2+}, and metabolic parameters need to be studied in more detail. Furthermore, it has not been elucidated whether Se status affects fibroblast growth factor 23 (FGF23). This is the main phosphatonine hormone secreted by osteocytes which regulates phosphate homeostasis and its renal excretion [94].

33.5 The Effect of Se on Renal and Adrenal Hormones, Hypertension, and Steroid Biosynthesis

Recently, a homozygous inactivating mutation of thioredoxin reductase 2 (TXNRD2) was shown to result in familial glucocorticoid deficiency and impaired adrenal cell redox-homeostasis, thus linking another selenoprotein gene defect to the endocrine system [95]. The authors proposed that an impaired mitochondrial antioxidant defense has a marked impact on adrenal steroid hormonal biosynthesis. Lack of functional TXNRD2 fails to reduce mitochondrial TXN2, which inactivates H_2O_2 together with glutaredoxin 2. The regeneration of glutaredoxin 2 by glutathione reductase and GSH may initiate a compensatory pathway involving TXN2. Furthermore, accumulation of H_2O_2 might harm adrenal function and cause impaired angiofollicular TH biosynthesis.

No convincing data have associated Se status with hormones that regulate blood pressure and salt homeostasis, such as renal (renin-angiotensin-aldosterone system), adrenal (catecholamines, mineralocorticoids), cardiac (natriuretic peptides), and pituitary (antidiuretic hormone/vasopressin) hormones. In addition, a close relationship between Se status and hypertension has not yet been demonstrated, even in epidemiological studies with sufficient sample sizes [96]. However, clinical conditions related to obesity, diabetes, metabolic syndrome, hyperlipidemia, PCOS, and other cardiovascular diseases might indirectly affect Se status in the context of their proinflammatory effects and thus also change hormonal parameters and actions [97]. In particular, low Se status during pregnancy might represent a risk factor with adverse impacts on hypertension, preeclampsia, and cardiovascular complications [98]. Whether Se status modifies endothelin production and endothelin receptor function is unclear, but Se might protect the endothelium against exposure to heavy metals.

33.6 Selenium, Glucoregulatory Hormones, and Diabetes

Several selenoproteins are expressed in the islets of Langerhans in the pancreas [99], and Se status has been linked to insulin secretion [3]. Controversially, high Se intake has also been suggested to increase the prevalence of T2DM [100–102]. H_2O_2 and ROS-related oxidative stress, as well as the hyperglycemia-induced damage to β cells, might contribute to β cell failure. These cells exhibit low expression of the antioxidative enzymes (catalase and GPX) but show high expression of SEPP1, which may protect β cells and α cells under exposure to high glucose [103]. Apart from GPX isoforms, TXNRD family members are expressed in pancreatic islets, and SEPW1 strongly responds to Se exposure in parallel to selenocysteyl-$tRNA^{[Ser]Sec}$ synthase (SEPSECS) but not selenophosphate synthetase 1 (SEPHS1) in the bird pancreas [104]. In another study investigating the response of the selenoprotein transcripts to Se status in the bird pancreas, one group of genes (*Txrnd1*, *SelS*, *SelU*, *SepX1*, and *Sps2*) was highly expressed under Se-deficient conditions. Another gene set was strongly decreased under these same conditions (*Txnrd2*, *Gpx1*, *Gpx3*, *SelI*, *Dio1*, *Sepp1*, *SepW1*, *SelO*, *SelT*, *SelM*, *SepX1*, *Sps2*); this was partly associated with nitric oxide (NO) synthase activity and NO content [99].

A major role in the regulation of insulin secretion has been attributed to the PACAP-regulated selenoprotein, SEPS1, which is induced by high glucose [16]. In mice, the conditional inactivation of SEPS1 in β cells impairs glucose tolerance and glucose-induced insulin secretion. These mice have smaller and fewer islets. The role of SEPS1 for PACAP-stimulated somatostatin secretion by δ cells has not yet been clarified.

Similar to other tissues, the development of the pancreas and β cells requires the timely expression of DIO3 to protect against inappropriate T_3 exposure. Knockout of *Dio3*, which is maternally inherited in mouse islets, results in smaller islets with fewer β cells, decreased glucose-induced insulin secretion, and glucose intolerance [105, 106].

The expression and secretion of the hepatokine Sepp1 is stimulated by high glucose and inhibits pancreatic insulin secretion [101]. This mutual dependency might represent part of an endocrine feedback loop, but this might have been overinterpreted that high serum Se would favor T2DM. In contrast, elevated Sepp1 appears to be the result and not the cause of high glucose concentrations [107]. Epidemiological studies have also shown associations between SEPP1 SNPs and insulin resistance in a Spanish cohort [108], as well as associations between Se status and (gestational) T2DM or other aspects of metabolic diseases, such as lipid status [109]. Several other studies suggest that adequate Se status improves glucose regulation and might be beneficial or without effect [110]. Observations on impaired glucose regulation in a Gpx1-overexpressing mouse model clearly indicate that the regulation of H_2O_2 and ROS signaling and redox control by selenoproteins in β cells is essential for normal glucose-regulated insulin secretion [100, 101, 111].

Various groups have investigated whether high Se supply might improve β-cell function while decreasing insulin sensitivity in target tissues, such as the liver, muscle, and adipose tissues. These studies used several animal models (e.g., mouse, rat, chicken) under conditions of compromised energy or lipid metabolism

and implemented different Se intervention protocols [101, 111]. Although high Se might improve β-cell function and insulin secretion [102, 112], it might also induce steatosis via the increased exposure of liver to fatty acids released by adipose tissue and higher hepatic oxidative stress resulting therefrom [102, 111, 113].

The first randomized controlled trial involving moderate doses of Se (60 μg/d) during pregnancy revealed no adverse effects on glucose metabolism or insulin resistance, as assessed by adiponectin [114]. Furthermore, a larger epidemiological study in the elderly population revealed no association between Se status and T2DM [110].

In patients with diabetes and hyperglycemia, a decreased activity of GPX4 and higher concentrations of oxidative stress markers were observed in heart tissue [115]. These observations match cardiometabolic impairments in mice haploinsufficient in *Gpx4* and exposed to high fat and high sucrose diet, which results in elevated lipid peroxides. This situation differs from lower expression of *Gpx1* in mice, where impaired insulin secretion is found albeit they are protected from insulin resistance and steatosis [115].

33.7 Concluding Remarks

Phenotypes with disturbed thyroid or endocrine functions are only observed in a small number of knockout or transgenic mouse models for various selenoproteins. This might convey the impression that the endocrine system is capable of adaptation to alterations that are caused by the systemic or tissue-specific loss of selenoprotein gene function. Alternatively, such phenotypes might have been overlooked during the initial characterization of these mouse models due to the lack of attention to hormonal changes. Furthermore, investigators may not have considered the prominent role of several selenoproteins, such as Dio3, in the development of endocrine tissue function and hormonal regulation.

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References

1. D Behne et al 1988 *Biochim Biophys Acta* 966:12
2. JM Bates et al 2000 *Endocrinology* 141:2490
3. J Köhrle et al 2005 *Endocr Rev* 26:944
4. G Drasch et al 2000 *Biol Trace Elem Res* 77:219
5. I Falnoga et al 2006 *Biometals* 19:283
6. V Ralston, LJ Raymond 2010 *Toxicology* 278:112
7. RF Burk, KE Hill 2015 *Annu Rev Nutr* 35:109
8. GE Olson et al 2007 *J Biol Chem* 282:12290
9. U Schweizer et al 2008 *Antioxid Redox Signal* 10:1577
10. VA Shchedrina 2010 *Antioxid Redox Signal* 12:839
11. MW Pitts et al 2013 *J Biol Chem* 288:26121

12. CF Bortolatto et al 2015 *Psychopharmacology (Berl)* 232:2239
13. CF Bortolatto et al 2015 *Physiol Behav* 151:298
14. Y Tanguy et al 2011 *Endocrinology* 152:4322
15. L Grumolato 2008 *FASEB J* 22:1756
16. G Prevost et al 2013 *Endocrinology* 154:3796
17. TL Fonseca et al 2013 *J Clin Invest* 123:1492
18. EK Wirth et al 2014 *Front Endocrinol (Lausanne)* 5:98
19. JP Werneck de Castro 2015 *J Clin Invest* 125:769
20. SE Chadio et al 2006 *Biol Trace Elem Res* 109:145
21. EM de Vries et al 2015 *J Endocrinol* 225:R67
22. JB Vanderpas et al 1990 *Am J Clin Nutr* 52:1087
23. JR Arthur et al 1990 *Biochem J* 272:537
24. D Behne et al 1990 *Biochem Biophys Res Commun* 173:1143
25. MJ Berry et al 1991 *Nature* 349:438
26. F Miot et al 2015 in *Thyroid Hormone Synthesis and Secretion, Endotext [MDText.com],* LJ De Groot et al Eds (South Dartmouth MA)
27. Q Wu et al 2015 *J Clin Endocrinol Metab* 100:4037
28. L Schomburg 2011 *Nat Rev Endocrinol* 18:160
29. J Köhrle 2015 *Curr Opin Endocrinol Diabetes Obes* 22:392
30. MP Rayman 2012 *Lancet* 379:1256
31. M Derwahl, D Nicula 2014 *Endocr Relat Cancer* 21:T273
32. H Li, J Li 2015 *Minerva Med* 106:109
33. A Hasham, Y Tomer 2012 *Immunol Res* 54:204
34. RS Fortunato et al 2014 *J Endocrinol* 221:R31
35. L Schomburg et al 2006 *Endocrinology* 147:1306
36. VA Galton et al 2014 *Endocrinology* 155:4081
37. ME Martinez et al 2014 *Mol Endocrinol* 28:1875
38. J Chiu-Ugalde et al 2012 *Antioxid Redox Signal* 17:902
39. LH Duntas, S Benvenga 2015 *Endocrine* 48:756
40. LB Rasmussen et al 2011 *Eur J Endocrinol* 164:585
41. I Bülow Pedersen et al 2013 *Clin Endocrinol (Oxf)* 79:584
42. KH Winther et al 2015 *Eur J Endocrinol* 172:657
43. EJ van Zuuren et al 2014 *Eur Thyroid J* 3:25
44. Y Liu et al 2013 *PMC Public Health* 13:1153
45. E Glattre et al 2012 *J Trace Elem Med Biol* 26:168
46. F Shen et al 2015 *Biol Trace Elem Res* 167:225
47. J Mao et al 2016 *Eur J Nutr* 55:55
48. KH Winther et al 2014 *Trials* 15:115
49. T Watt et al 2013 *Trials* 14:119
50. KH Winther et al 2015 *Eur J Endocrinol* 172:657
51. TJ O'Grady et al 2014 *PLoS One* 9:e110886
52. Y Ren et al 2014 *Asian Pac J Cancer Prev* 15:5187
53. J Mittag et al 2012 *Biochem J* 443:103
54. RB Jain 2014 *Biol Trace Elem Res* 159:87
55. RB Jain, YS Choi 2016 *Int J Environ Health Res* 26:75
56. C Zevenbergen et al 2016 *Eur J Endocrinol* 174:425
57. SG Leoni et al 2015 *Antioxid Redox Signal* doi:10.1089/ars.2014.6228
58. M Stoedter et al 2015 *Metallomics* 7:347
59. K Raja, G Mugesh 2015 *Angew Chem Int Ed Engl* 54:7674
60. E Rijntjes et al 2013 *Eur Thyroid J* 2:252
61. J Martitz et al 2015 *Metallomics* 7:1515
62. A Boelen et al 2011 *Endocr Rev* 32:670
63. TC Jakobs et al 2002 *Eur J Endocrinol* 146:559

64. SM Wajner et al 2015 *Redox Biol* 6:436
65. LR Santos et al 2014 *J Clin Endocrinol Metab* 99:E719
66. N Karunasinghe et al 2012 *Genes Nutr* 7:179
67. Y Gao et al 2006 *Cytokine* 33:246
68. Z Huang et al 2012 *Antioxid Redox Signal* 16:705
69. T Pilli et al 2015 *Eur Thyroid J* 4:226
70. L Tan et al 2013 *Biomed Environ Sci* 26:920
71. C Méplan 2015 *Nutrients* 7:3621
72. JN Hellwege et al 2014 *Gene* 534:33
73. GF Combs Jr 2015 *Nutrients* 7:2209
74. M Medici et al 2015 *Endocr Rev* 36:214
75. H Verloop et al 2014 *Eur J Endocrinol* 171:R123
76. EA McAninch et al 2015 *J Clin Endocrinol Metab* 100:920
77. W Reinhardt et al 2015 *Thyroid* 25:1091
78. O Parshukova et al 2014 *Int Arch Occup Environ Health* 87:607
79. RF Carvalho et al 2015 *Nutr Hosp* 31:1832
80. S Mahmoodianfard et al 2015 *J Am Coll Nutr* 34:391
81. TA Arikan 2015 *Biol Trace Elem Res* 167:194
82. C Marcocci, L Bartalena 2013 *J Endocrinol Invest* 36:15
83. LO Kurlak et al 2013 *Placenta* 34:395
84. M Akturk et al 2013 *Biol Trace Elem Res* 154:338
85. R Moreno-Reyes 1998 *N Engl J Med* 339:1112
86. Z Zhang et al 2014 *Biochim Biophys Acta* 1840:3246
87. N Pietschmann et al 2014 *Metallomics* 6:1043
88. N Schütze et al 1998 *Biofactors* 7:299
89. F Jakob et al 2002 *Methods Enzymol* 347:168
90. CH Gouveia et al 2005 *Endocrinology* 146:195
91. R Ebert et al 2006 *Stem Cells* 24:1226
92. NM Al-Daghri et al 2014 *Int J Vitam Nutr Res* 84:27
93. A Hoeg et al 2012 *J Clin Endocrinol Metab* 97:4061
94. CP Kovesdy, LD Quarles 2016 *Am J Physiol Renal Physiol* doi:10.1152/ajprenal.00606.2015
95. R Prasad et al 2014 *J Clin Endocrinol Metab* 99:E1556
96. D Kuruppu et al 2014 *Public Health Nutr* 17:1342
97. HK Berthold et al 2012 *J Hypertens* 30:1328
98. MP Rayman et al 2015 *Br J Nutr* 113:249
99. X Zhao et al 2014 *Biol Trace Elem Res* 161:341
100. J Zhou et al 2013 *Free Radic Biol Med* 65:1548
101. H Steinbrenner 2013 *Free Radic Biol Med* 65:1538
102. X Wang et al 2014 *Toxicol Lett* 224:16
103. H Steinbrenner et al 2012 *J Mol Endocrinol* 50:31
104. R Wang et al 2011 *J Inorg Biochem* 105:1156
105. MC Medina et al 2011 *Endocrinology* 152:3717
106. MC Medina et al 2014 *Endocrinology* 155:3160
107. J Mao, W Teng 2013 *Nutrients* 29:1937
108. JN Hellwege et al 2014 *Gene* 534:33
109. K Christensen et al 2015 *Environ Res* 140:76
110. H Gao et al 2014 *Diabet Med* 31:787
111. J Zhou et al 2015 *Toxicol Appl Pharmacol* 289:409
112. H Ueno et al 2014 *Biol Pharm Bull* 37:1569
113. C Wang et al 2014 *PLoS One* 9:e101315
114. J Mao et al 2016 *Br J Nutr* 115:32
115. LA Katunga et al 2015 *Mol Metab* 4:493