Published in final edited form as:
Free Radic Biol Med. 2013 December ; 65: . doi:10.1016/j.freeradbiomed.2013.07.012.

Selenium and diabetes - evidence from animal studies

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Abstract

Whereas selenium was found to act as an insulin-mimic and to be anti-diabetic in earlier studies, recent animal experiments and human trials have shown unexpected risk of prolonged high Se intake in potentiating insulin resistance and type 2 diabetes. Elevating dietary Se intakes (0.4 to 3.0 mg/kg of diet) above the nutrient requirements, similar to overproduction of selenoproteins, led to insulin resistance and(or) diabetes-like phenotypes in mice, rats, and pigs. Although its diabetogenic mechanism remains unclear, the high Se intake elevated activity or production of selenoproteins including GPx1, MsrB1, SelS, and SelP. This up-regulation diminished intracellular reactive oxygen species (ROS) and then dys-regulated key regulators of β cells and insulin synthesis and secretion, leading to chronic hyperinsulinaemia. Over-scavenging intracellular H_2O_2 also attenuated oxidative inhibition of protein tyrosine phosphatases and suppressed insulin signaling. High Se intake might affect expression and(or) function of key regulators for glycolysis, gluconeogenesis, and lipogenesis. Future research is needed to find out if certain forms of Se metabolites in addition to selenoproteins and if mechanisms other than intracellular redox control mediate the diabetogenic effect of high Se intakes. Furthermore, a potential interactive role of high Se intakes in the interphase of carcinogenesis and diabetogenesis should be explored to make the optimal use of Se in human nutrition and health.

Keywords

Diabetes; Insulin; Reactive oxygen species; Selenium; Selenoprotein

Introduction

Selenium (Se) was discovered in 1817 and reported in 1818 by Jöns Jacob Berzelius [1]. It was initially found as a toxic element because of Se poisoning in animals and humans [2]. However, Se deficiency was later shown to be more practically problematic and deleterious or fatal in animals [3,4] and humans [5]. In 1957, Se was recognized as an essential nutrient for animals [6] and 15 years later cellular glutathione peroxidase (GPx1) became the first identified Se-dependent enzyme [7,8]. Another landmark of Se biology was seen in 1996

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

when Clark and colleagues reported a striking effect of Se supranutrition on decreasing mortality of three types of human cancers [9].

Diabetes mellitus is one of the most costly chronic diseases, with an estimated worldwide prevalence of 366 million in 2011 and an expected rise to 552 million by 2030 [10]. In 2007, the prevalence of diabetes in the USA was 7.8% [11]. Meanwhile, China has the largest diabetic population in the world, accounting for 92.4 million adults in 2007–2008 [12]. There are four types of diabetes: Type 1 diabetes, Type 2 diabetes, gestational diabetes, and maturity onset diabetes of the young (MODY). Type 2 diabetes accounts for 90% of all diabetes and is characterized by peripheral insulin resistance, with an insulin-secretory defect that varies in severity. Although mechanisms for insulin resistance and diabetes are not fully understood, a growing body of evidence suggests that oxidative stress plays an important role in both of their onset and progress [13,14]. While there was a high hope for using antioxidants including Se to prevent and treat diabetes and its complications, a number of recent human trials have actually shown an alarming correlation between high Se intake or body Se status and diabetic risks [15–21]. Before this revealing, overexpression of GPx1, the “oldest” and most abundant Se-dependent protein, was shown to induce type 2 diabetes-like phenotypes in mice [22–24]. After this initial linking of selenoprotein to glucose and lipid metabolism, several new animal studies have provided compelling evidence and mechanism for the pro-diabetic potential of prolonged high Se intakes in different species.

Two tales of Se on diabetes

Se as an insulin mimic

Early studies indicated that inorganic Se acted as an insulin-mimic [25]. High doses of sodium selenate (0.1 to10 mM for 10 or 20 min) stimulated glucose uptake in isolated rat adipocytes through enhancing translocation of glucose transporters to plasma membrane, and activating serine/threonine kinases including p70 S6 kinase [26, 27]. Moreover, sodium selenate also produced dose-dependent stimulation of glucose uptake in dissected skeletal muscle of rats with the maximal response reached at 100 mM (60 min) [28]. Intraperitoneal injection or oral administration of sodium selenate improved glucose homeostasis in Type 1 and Type 2 diabetic animals [29–33]. Similarly, the insulin-like and anti-diabetic effects of sodium selenite and selenomethionine were also observed in diabetic animals [34–39], although their effects were shown to be weaker than sodium selenate. Mechanisms underlying differentiated effects of various selenium compounds have been reviewed [40]. However, all these insulin-like effects were mainly observed at high Se doses (0.9–4.5 mg/kg body weight) [29–39].

Deficiencies of Se and selenoprotein on diabetes

Data from earlier epidemiologic investigations showed correlations between abnormal glucose or lipid metabolism and decreased plasma Se concentrations or selenoperoxidase activity in diabetic subjects [41–48]. Likewise, there were also similar correlations or associations in animals. Thompson et al [49] reported that feeding chicks with Se-deficient diet (< 0.02 mg Se/kg of diet) for 3–5 weeks resulted in poor growth, poor feathering, atrophy of the pancreas, and impaired lipid absorption, compared with Se-supplemented controls. Souness et al [50] showed that rats fed a Se-deficient diet (Se content was too low to be detected) for 7–8 weeks had lower insulin-stimulated glucose oxidation in adipocytes compared with that of control rats fed the same diet supplemented with 0.5 mg Se/kg of diet as sodium selenite. Asayama et al [51] reported that Se deficiency impaired islet function and free radical scavenging systems in rats, resulting in decreased insulin secretory reserve. Furthermore, feeding both normal and diabetic rats [52] with a Se-deficient diet (< 0.025 mg Se/kg of diet) for 10 weeks elevated their plasma glucose concentrations and induced

albuminuria and glomerular sclerosis, compared with those fed 0.27 or 0.78 mg Se/kg of diet. While Se deficiency caused renal oxidative stress, Se supplementation to diabetic rats prevented not only oxidative stress but also renal structural injury. Thus, supplementing Se was perceived as an effective strategy to prevent and treat diabetes.

Likewise, two groups have recently suggested that selenoprotein deficiency in mice was closely associated with diabetes or metabolic syndrome. Labunskyy et al [53] reported that reducing selenoprotein synthesis by overexpressing an i(6)A(−) mutant selenocysteine tRNA promoted glucose intolerance and led to a type 2 diabetes-like phenotype in mice. Seale et al [54] showed that knockout (KO) of selenocysteine lyase (Scly) in mice affected hepatic glucose and lipid homeostasis. Mice lacking Scly and raised on a Se-adequate diet exhibited hyperinsulinemia, hyperleptinemia, glucose intolerance, hepatic steatosis, and increased hepatic oxidative stress, but maintained selenoprotein levels and circulating Se status. Upon dietary Se deficiency, Scly KO animals developed several characteristics of metabolic syndrome, such as obesity, fatty liver, and hypercholesterolemia, with aggravated hyperleptinemia, hyperinsulinemia, and glucose intolerance. Altogether, these findings suggest a dependence of glucose and lipid homeostasis on Scly activity.

Elevations of Se intake and selenoprotein expression on diabetes

As mentioned above, a number of animal studies have been conducted to determine impacts of high Se intakes or overexpression of selenoprotein on glucose and lipid metabolism in mice, rats, and pigs. The main findings are summarized in Table 1.

Mice—The GPx1 overexpressing (OE) mice became obese at 6 months of age, and developed hyperglycemia, hyperinsulinemia, hyperlipidemia, and insulin resistance, along with elevated pancreatic β cell mass, islet insulin secretion, plasma leptin concentration, and hepatic lipogenesis [22–24]. Diet restriction (3 vs. 5 g of feed/day) of OE mice from 2 to 6 months of age [55] prevented all their phenotypes except for fasting hyperinsulinemia and hyper-secretion of insulin after glucose stimulation [55]. While dietary Se deficiency [23] did not rescue these two primary phenotypes of GPx1 overproduction in the feed-restricted OE mice, it exerted a strong effect on mRNA and(or) protein levels of 14 molecules involved in islet insulin synthesis and secretion and hepatic lipogenesis [23]. Dietary Se deficiency exhibited a hypoinsulinemic trend in OE mice and a strong hypolipidemic effect in the liver of WT mice. Because the overwhelming metabolic effect of diet restriction and the relatively short length of Se deficiency might preclude further benefit of dietary Se depletion in this study [23], a consecutive study [56] was conducted by Yan et al to explore whether dietary Se deficiency in the full-fed OE mice could completely rescue their phenotypes. While dietary Se deficiency (<0.02 mg of Se/kg of diet from 1 to 5 months of age) indeed precluded the GPx1 overproduction in the full-fed OE mice, 3 of their phenotypes, including hyperglycemia, insulin resistance, and elevated hepatic lipid profiles [22], were nearly rescued. Meanwhile, their hyperinsulinemia and aggravated glucose stimulated insulin secretion (GSIS) were also improved by dietary Se deficiency [56]. Mechanistically, this alleviation resulted from modulating the expression and/or function of proinsulin genes, lipogenesis rate-limiting enzyme genes, and key glycolysis and gluconeogenesis enzymes in islets, liver, and muscle. Taken together, these findings suggest that GPx1 was an important regulator of energy metabolism and insulin synthesis, secretion, and function. The C57BL/6 J mice fed a Torula yeast-based diet supplemented with Se at 0.4 mg/kg of diet for 3 months developed hyperinsulinemia and had decreased insulin sensitivity, compared with those fed a Se-deficient diet and the diet supplemented with 0.1 mg of Se/kg of diet [53].

Rats—Rasekh et al. [57] showed that acute intraperitoneal administration of sodium selenite to the rats (1.6 mg/kg of body weight or more) caused hyperglycemia in a time- and dose-dependent manner. While sodium selenite did not change plasma insulin levels in either fasted or fed animals, increases in corticosterone levels of the rats suggested the involvement of gluconeogenesis in this hyperglycemic response. In contrast to the nearly toxic doses of Se used in the above-mentioned study, Mueller et al [58] reported that rats received diets supplemented with sodium selenate to obtain final Se concentrations of 75 or 150 μg Se/kg of diet for 8 weeks had markedly elevated body weight, higher liver protein tyrosine phosphatase 1b (PTP1b) activity and higher liver triglyceride concentrations than the control group fed a Se-deficient diet. It is now well recognized that protein tyrosine phosphatases (PTPases) counteract insulin signaling and that maintaining the reduced state of PTPases supports this effect. They [59] also found that rats fed diets containing Se as selenite or selenate (final Se concentrations of 0.2, 1 and 2 mg/kg diet) for 8 weeks featured a higher body weight compared to their Se-deficient controls. In another recent study [60], female Wistar rats were fed a Se-deficient (0.01 mg/kg of diet) corn–soy basal diet (BD) or BD+Se (as Se-yeast) at 0.3 or 3.0 mg/kg of diet from 5 weeks before breeding to day 14 postpartum, and offspring of the 0.3 and 3.0 mg Se/kg of diet dams were fed with the same respective diet until age 112 days. Compared with the 0.3 mg Se/kg of diet, the 3.0 mg Se/kg of diet induced hyperinsulinemia, insulin resistance, and glucose intolerance in the dams at late gestation and/or day 14 postpartum and in the offspring at age of 112 days. Furthermore, plasma triglyceride levels in the dams were increased by the high dietary Se intake on day 19 of gestation. This hyperlipidemic effect of the high-Se diet in the gestating dams was also similar to the data from the above studies by Mueller et al [58,59].

Pigs—As a better model than rodents for human nutrition and medicine, pigs share with humans a greater metabolic similarity and disease susceptibility to develop type 2 diabetes or metabolic syndrome [61]. Feeding pigs with 3.0 mg of Se/kg of diet for 16 weeks induced hyperinsulinemia compared with those fed 0.3 mg of Se/kg of diet [62]. More specifically, the Se-overdosed pigs had >50% plasma insulin levels than the Se-adequate pigs to maintain similar plasma glucose concentrations, indicating an early sign of insulin resistance. Unlike rats [58–60], pigs fed the high-Se diet (3 mg of Se/kg of diet) did not develop hyperlipidemia compared with those fed 0.3 mg of Se/kg of diet. Meanwhile, Pinto et al [63] reported that after 16 weeks of intervention, fasting plasma insulin and cholesterol levels were increased in pigs fed 0.50 mg of Se/kg of diet (as Se-yeast) compared with those fed 0.17 mg of Se/kg of diet, although fasting glucose concentrations did not differ between the two groups.

Other models—Past studies using high Se intakes not designed for diabetes research, but for cancer chemoprevention or selenium toxicity research, have often overlooked or ignored glucose homeostasis or energy metabolism. However, there was at least one study illustrating such link. That study was aimed at characterizing Se action on normal rat heart function [64] and showed that sodium selenite administration to the normal rats (5 μmol or 0.86 mg/kg of body weight per day) for 4 weeks caused a slight but significant increase in blood glucose level, and a significant decrease in plasma insulin level.

Putative mechanisms of high Se on diabetes

ROS on islet insulin synthesis and secretion

Compared with liver, islets contain only 1% catalase, 2% GPx1, and 29% SOD1 activities [65–67]. Accordingly, β cells are considered to be low in antioxidant defense and susceptible to oxidative stress. In diabetic subjects, the β cell apoptosis seems to be a more deciding factor than replication in controlling the cell mass compared with control subjects

[68]. Thus, maintaining pancreatic islet β cell mass is recognized as a pivotal prevention from pathogenesis of both types 1 and 2 diabetes [69]. The β cell apoptosis can be triggered by high glucose [70] and cytokines that elevate ROS production [71]. Furthermore, the key regulators of β cells and insulin synthesis are responsive to ROS, such as mitochondrial uncoupling protein 2 (UCP2), and the transcriptional factors, pancreatic duodenal homebox 1 (PDX1) and forkhead box A2 (FOXA2). In general, elevated ROS contribute to β cell apoptosis and defective insulin synthesis via affecting expression and function of these transcriptional factors. Although being considered to be wasteful and deleterious, ROS, especially H_2O_2, function as important factors in normal cellular signal transduction [72, 73], although contradictory results have been published regarding their impacts on acute glucose exposure and roles in GSIS. While numerous studies have described the negative effects of ROS generation in β cells including attenuation of GSIS [74], emerging evidence indicates that ROS derived from glucose metabolism, in particular H_2O_2, serve as additional metabolic signals to elicit GSIS [75–78]. This view has been reviewed elsewhere [79, 80].

ROS on insulin sensitivity

In insulin-responsive tissues, actual roles of ROS in insulin signaling depend on the balance of ROS production and antioxidant defense. Excessive ROS is involved in the multifactorial etiology of insulin resistance, and the subsequent development of type 2 diabetes [13,14]. Meanwhile, elevating ROS may activate a variety of serine/threonine kinases that in turn phosphorylate multiple targets, including the insulin receptor (IR) and the insulin receptor substrate (IRS) proteins [81]. In consequence, increased serine phosphorylation of IRS-1 decreases insulin-stimulated tyrosine phosphorylation of the protein, leading to insulin resistance. On the other hand, H_2O_2 may prolong phosphorylation of key proteins in the insulin signaling cascade by an oxidative inhibition of PTP1b [82–85].

Selenoproteins and antioxidant enzymes on tissue ROS tone and related signaling

Overexpression or knockout of GPx1 altered intracellular ROS status and subsequent redox regulation of key events in insulin synthesis, secretion, and function, resulting in dys-regulated glucose and lipid metabolism [22, 24]. More specifically, GPx1 overproduction up-regulated PDX1 mRNA and protein levels and attenuated degradation of PDX1 protein in islets [55]. The decrease in phosphorylated PDX1 protein was likely due to a reductive environment in islets, and the decreased phosphorylation of AKT at Thr 308 [86, 87], in line with the idea that phosphorylation of PDX1 is required for degradation by the proteasome machinery. An elevated functional PDX1 protein in islets resulted in hypertrophy of β cell mass, and subsequent increased pancreatic and plasma insulin concentrations [88–90]. In contrast, the reverse was induced by the GPx1 knockout [24]. Furthermore, GPx1 overexpression resulted in hyperacetylation of histone 3 and 4 (H3 and H4) in the PDX1 gene promoter [55] that may help explain in part the increased islet PDX1 mRNA levels. However, GPx1 overproduction had no significant effect on islet FOXA2 mRNA levels. Unlike the GPx1 overproduction, the GPx1 knockout did not affect islet PDX1 mRNA and H3 and H4 acetylation [24]. GPx1 overproduction down-regulated islet UCP2 protein and elevated mitochondrial membrane potential, contributing to the accelerated GSIS and hyperinsulinemia [55]. In contrast, knockout of GPx1 alone or together with SOD1 up-regulated UCP2 protein in pancreas and decreased islet ATP content [24]. Both changes could contribute to the attenuated GSIS in these mice. In the GPx1 overexpressing mice, insulin resistance was associated with an attenuated insulin-stimulated phosphorylation of IR β subunit and AKT at Ser 473 and Thr 308 in liver and muscle [22]. These decreased phosphorylations were presumably caused by the diminished intracellular H_2O_2, which lifted the oxidative inhibition of protein tyrosine phosphatases. In contrast, knockout of GPx1 resulted in enhanced phosphorylation of AKT in muscle [24], and rendered mice

resistant to a high fat diet induced-insulin resistance via an enhanced oxidation of phosphatase with tensin homology (PTEN) selectively in muscle tissue [91].

SelP (in humans encoded by the *Sepp1* gene), a secretory protein primarily produced by the liver [92, 93], contains ten selenocysteine residues and functions as a Se transporter [94]. A pioneer study by Walter et al [95] reported the stimulation of the *Sepp1* promoter activity by the forkhead box transcriptional factor FoxO1a in hepatoma cells and its attenuation by insulin. Moreover, the production of SelP was regulated similarly to that of the gluconeogenic enzyme glucose-6-phosphatase, by concerted action of peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α) and the transcriptional factors FoxO1a and hepatocyte nuclear factor-4α (HNF-4α) [96]. They also found that treatment of rat hepatocytes with high glucose resulted in increased *Sepp1* mRNA expression and secretion. Furthermore, the treatment with metformin induced dose-dependent down-regulation of *Sepp1* mRNA expression and secretion, and suppressed glucocorticoid-stimulated production of SelP [97]. Recently, Misu et al [98] found a positive correlation between hepatic *Sepp1* mRNA levels and insulin resistance in humans, along with a positive correlation between serum SelP levels and both fasting plasma glucose and hemoglobin A_{1c} (HbA_{1c}) levels. Administration of purified SelP impaired insulin signaling and dysregulated glucose metabolism both *in vitro* and *in vivo*. In contrast, genetic deletion and RNA interference-mediated knockdown of SelP improved systemic insulin sensitivity and glucose tolerance in mice. The metabolic actions of SelP were mediated, at least partly, by inactivation of adenosine monophosphate-activated protein kinase (AMPK). Accordingly, the metabolic effect of SelP on insulin sensitivity was similar to that of GPx1. However, SelP did not show effect on β cell mass or insulin synthesis and secretion.

Walder and colleagues showed that Tanis (in humans encoded by the *Sels* gene) was regulated by glucose and altered in the diabetic state [99,100]. Furthermore, Tanis overexpression in H4IIE cells reduced glucose uptake, basal and insulin-stimulated glycogen synthesis, and glycogen content, attenuated the suppression of phosphoenolpyruvate carboxykinase (PEPCK) gene expression by insulin, and had no effect on insulin-stimulated IR phosphorylation or triglyceride synthesis [101]. These results suggested that Tanis might be involved in the regulation of glucose metabolism, and increased expression of Tanis could contribute to insulin resistance in the liver. Furthermore, emerging evidences suggest that elevations of *Sels* [102–105] or *Sepp1* [106,107] mRNA and protein expression were observed in type 2 diabetic patients.

It has been widely accepted that catalase, GPx, and SOD represent the three most important intracellular antioxidant enzymes. SOD1 (Cu,Zn-SOD) comprises over 90% of the total cellular SOD activity, and functions upstream of GPx1 in catalyzing dismutation of superoxide ion into H_2O_2. Catalase shares a common substrate of H_2O_2 with GPx1, but with a lower affinity for H_2O_2. Altered expressions of SOD1 and catalase have produced variable metabolic outcomes. Whereas β cell-specific or global overexpression of SOD1 enhanced mouse resistance to alloxan-induced diabetes [108, 109], β cell-specific overexpression of catalase aggravated onset of type 1 diabetes in nonobese diabetic mice [110]. It seems that the role of catalase in glucose metabolism is similar to that of GPx1, but different from that of SOD1. A comprehensive review of this topic can be found elsewhere [48].

High Se intake on tissue redox status and selenoprotein expression

High dietary Se intake may induce the generation of superoxide radicals and/or other ROS [33,111–115]. This type of ROS elevation is implicated in the molecular mechanisms for the insulin-like effects of Se, as elevated H_2O_2 may activate insulin signaling by an oxidative inhibition of PTP-1b [82–85]. Meanwhile, a high selenite diet (1.0–2.0 mg of Se/kg of diet) [59] resulted in a lower GSSG/GSH ratio in the rat liver, compared with a Se adequate diet

(0.2 mg of Se/kg of diet). This antioxidant effect was in accordance with increased plasma GPx3 activity by high Se over adequate Se supplements, although the high selenite diet had no effect on the activities of GPx1 and SOD in the liver, and even decreased catalase activity. Using the Se-enriched yeast [116], Zhou et al. have demonstrated that 3.0 mg of Se/kg of diet enhanced (43–88%) GPx activity among four tissues of pigs (liver, testis, thyroid, and pituitary) compared to those fed 0.3 mg of Se/kg of diet. However, the high Se diet did not affect activities of plasma GPx3 and other three antioxidant enzymes in any of the four tissues. The increased GPx activity was in accordance with data from another pig study [63]. Moreover, similar increases in hepatic or erythrocyte GPx activity by high Se diets over adequate Se supplements have also been seen in mice [117], rats [118], and fish [119]. Thus, the increases in liver and erythrocyte GPx activity seem to be a plausible mediator for the high Se intake to disturb glucose and lipid metabolism.

While Zhou et al [116] found little effect of dietary Se concentrations (0.02, 0.3, and 3.0 mg/kg diet) on mRNA levels of 12 selenoprotein genes in thyroid, pituitary, liver, or muscle, Liu et al [62] reported that mRNA expression of the remaining 13 selenoproteins in 10 tissues of pigs responded to dietary Se in three patterns. But, there was no common regulation for any given gene across all tissues or for any given tissue across all genes [62]. Dietary Se affected 2, 3, 3, 5, 6, 7, 7, and 8 selenoprotein genes in muscle, hypothalamus, liver, kidney, heart, spleen, thyroid, and pituitary, respectively. Protein abundance of GPx1, Sepp1, Selh, and Sels in 6 tissues was also regulated by dietary Se concentrations in three ways. The high Se diet (3.0 mg of Se/kg of diet) resulted in greater protein levels of GPx1 in heart and testis, Sepp1 in thyroid and testis, Selh in liver and kidney, and Sels in thyroid compared with Se adequate diet (0.3 mg of Se/kg of diet). As reported previously, these selenoproteins have the biochemical potential to be involved in glucose metabolism. In the rat study [60], dietary Se produced dose-dependent increases in GPx1 mRNA or GPx activity in pancreas, liver, and erythrocytes of dams. The 3.0 mg of Se/kg of diet decreased Selh, Sepp1, and Sepw1, but increased Sels mRNA levels in the liver of the offspring, compared with the 0.3 mg of Se/kg of diet. Expression of 6 selenoprotein genes, in particular Gpx1, was linked to gestational diabetes and insulin resistance. Likewise, Labunskyy et al showed that high-Se diet (0.4 mg/kg of diet), compared with the diet containing 0.1 mg of Se/kg of diet, resulted in slight elevation of GPx1 and MsrB1 protein levels in mice [53]. In contrast, protein expression of mitochondrial thioredoxin reductase 3 (TrxR3) in livers and kidneys was less responsive to changes in dietary Se levels. Moreover, Pinto et al [63] observed an increase in GPx activity in the skeletal muscle of pigs fed a high Se diet compared with the controls. However, the protein expression of GPx1 and thioredoxin reductase 1 (TrxR1) was not altered by Se supplementation. No significant changes in mRNA levels of any of the selenoproteins assayed in liver, skeletal muscle or visceral adipose tissue (VAT) were found in the pigs fed the high Se diet over the Se-adequate diet.

High Se intake on key regulators of beta cells and insulin

Given the positive effect of GPx1 overproduction on beta cell mass and insulin synthesis and secretion [22–24], the above-mentioned elevated tissue GPx activity by the high Se diets compared with the Se-adequate diets in various species might represent one of the pathways for the high Se intake regulation of insulin levels. While the elevated tissue GPx activity could attenuate insulin sensitivity by diminishing oxidative inhibition of PTP1b, Mueller et al [59] reported a high Se diet (1.0–2.0 mg of Se/kg of diet as selenite or selenate) markedly elevated liver PTP1b activity in rats through reduction of glutathionylation of PTP1b, compared with the Se adequate diet (0.2 mg of Se/kg of diet). Apparently, this elevation of PTP1b activity attenuated insulin-stimulated tyrosine phosphorylation of IRS, resulting in impairment of insulin signaling. Moreover, insulin resistance induced by the high Se diet in

the dams and offspring of rats was associated with down-regulation of mRNA levels of hepatic *Insr*, *Irs1*, and *Akt2* genes and/or hepatic IR and AKT protein levels [60]. The high Se intake also reduced mRNA levels of hepatic *Irs2* in the dams as well as those of muscle *Irs2* in the offspring. Because these genes code for key insulin signal proteins [120], downregulation of their mRNA expression or protein production may compromise insulin sensitivity. The high Se diet-induced porcine hyperinsulinemia was concurrent with Akt protein decreases in liver and other tissues [62].

High Se intake on key regulators of glucose and lipid metabolism

The altered expression and function of key enzymes and factors for glucose and lipid metabolism is also implicated in the mechanisms for the pro-diabetic potential of high Se intake. This notion is supported by the finding that high Se diets increased gene expression of forkhead box O1 and PGC-1α, and reduced gene expression of the glycolytic enzyme pyruvate kinase in skeletal muscle of pigs [63]. Moreover, high Se diets enhanced mRNA expression of sterol regulatory element-binding transcription factor 1 and lipoprotein lipase (LPL) (1.90 fold, $P = 0.17$), decreased mRNA levels of PGC-13 (55%, $P = 0.27$), and affected the phosphorylation of AMPK and mitogen-activated protein kinases in visceral adipose tissue [63]. The elevated expression of SREBP-1c was in accordance with data from a rat study in which high Se diet elevated liver PTP1b activity, possibly by activating lipogenic mechanisms involving the activation of SREBP-1c [59]. Likewise, high Se intake reduced mRNA levels of hepatic *FoxO1* and muscle *Pgc-1* in the rat offspring [60].

Perspective and conclusion

Feeding mice, rats, and pigs with high Se diets containing 0.4 to 3.0 mg of Se/kg of diet for extended periods of time induced hyperinsulinemia, hyperglycemia, insulin resistance, glucose intolerance, and altered lipid metabolism. This type of effect seems to be independent of different forms of Se sources, compositions of basal diets, and physiological stages. Thus, it is hard to deny a causative relationship between prolonged high Se intakes and pro-diabetic potential.

As illustrated in Fig. 1, high Se intake may lead to elevated activity or production of GPx1 and other selenoproteins including MsrB1, SelS, ad SelP. This type of up-regulation diminishes intracellular ROS and dys-regulates key regulators of β cells and insulin synthesis and secretion, leading to chronic hyperinsulinaemia. Over-scavenging intracellular H_2O_2 also attenuates oxidative inhibition of protein tyrosine phosphatases including PTP1b or PTEN, suppressing insulin-stimulated IR/IRS/PI3-K/Akt signaling. At the same time, un-inhibited PTP1b stimulates the lipogenic pathway [121–124], promoting lipogenesis and further aggravating insulin resistance. High Se intake may affect expression and(or) function of the key regulators for glycolysis, gluconeogenesis, and lipogenesis. These pathways might contribute to the pro-diabetic potential of high Se intake cooperatively or independently [40, 48, 125–127]. Although expression and activity of many selenoproteins are saturated at the adequate Se intake, several selenoproteins or their mRNA levels are affected by higher Se intake [128–130]. Because the low molecular weight Se metabolites require a higher dietary selenium intake for their saturation [131–134], it is tempting to test if those metabolites [135] mediate the pro-diabetic potential of high Se intake.

There are at least three reasons for the discrepancy on dietary Se role in diabetes between the past and present experiments. First, many of the past animal studies used diabetic animals [29–39], but the present studies have been conducted in normal animals [53,57–60, 62–63]. Second, the past experiments used high or nearly toxic doses of Se (0.9–4.5 mg/kg body weight) [29–39], while recent experiments used Se levels not exceeding their maximal tolerable limits (≤33.0 mg Se/kg diet). Finally, many of the past animal studies lasted only 2

to 8 weeks, whereas in most of recent animal studies the duration of Se supplementation has been 12 weeks or longer [53,57–60, 62–63].

The causative relationship between prolonged high Se intake and pro-diabetic potential in different animal species was consistent with findings from several major human trials including the Nutritional Prevention of Cancer (NPC) [15] and the Selenium and Vitamin E Cancer Prevention Trial (SELECT) [16] trials. Most striking, Faghihi et al [136] have recently conducted a randomized, double-blind placebo-controlled trial and assessed the effects of supplemental Se (200 μg/day or placebo was administered orally for 3 months) on blood glucose, lipid profile, and oxidative stress in 60 patients with type 2 diabetes. At endpoint, plasma Se concentration reached to 71.98 (45.08) μg/L in Se recipients compared with 45.38 (46.45) μg/L in placebo recipients ($P < 0.01$). Between-group comparison showed that fasting plasma glucose, glycosylated hemoglobin A1c, and high-density lipoprotein cholesterol were higher in the Se recipient arm. Apparently, the Se supplementation in patients with type 2 diabetes was associated with adverse effects on blood glucose homeostasis, although plasma Se concentration was raised from deficient status to the optimal concentration of antioxidant activity. They suggested that until results of further studies became available, indiscriminate use of Se supplements in patients with type 2 diabetes should warrant caution. Caution should also be given to relate the animal responses to high Se intake to human cases because many factors such as genetic variation, living style, and environment could affect onset and development of diabetes and the potential role of Se in this regard. At the mechanist level, many challenging questions remain to be answered. It is important to find out if certain forms of Se metabolites or selenoproteins mediate the diabetogenic effect of high Se intake. It is also imperative to reveal if biochemical or molecular mechanisms other than modulating intracellular redox status are also involved in the diabetogenic action of high Se intake. Lastly, it is most important to elucidate the metabolic significance and mechanistic basis for a potential interactive role of high Se intakes in the interphase of carcinogenesis and diabetogenesis. This is because prolonged high Se diet induces hyperinsulinemia and insulin resistance in insulin-responsive tissues, and insulin signaling is recognized for being pro-carcinogenic [137,138]. Thus, it is tempting to speculate that high Se intake may suppress carcinogenesis by inhibiting insulin signaling. However, several human cancer trials including the NPC [9,15,139] and SELECT [16] have yielded inconsistent results in that regard. Seemingly, a U-shaped relation exists between the dietary Se intake/body Se status and cancer risk. If the body Se status reaches or rises above a threshold, higher Se intake may turn into potentiating the cancer risk. Prudently, indiscriminant Se supplementation to healthy subjects with adequate Se intake should not be recommended to avoid the possible double risks of diabetogenic and pro-carcinogenic potential of excessive Se.

Acknowledgments

The research conducted by the authors was supported in part by NIH grant DK53018 (X.G.L.), the National Natural Science Foundation of China (J. Z., No 21001045 and 31270870), and the Fundamental Research Funds for the Central Universities, HUST: No 2012QN145 (J. Z.).

List of Abbreviations

ACC	Acetyl-CoA carboxylase
AMPK	adenosine monophosphate-activated protein kinase
BD	basal diet
FOXA2	forkhead box A2

FoxO1	forkhead box O1
GPx1	glutathione peroxidase 1
GSIS	glucose stimulated insulin secretion
HbA_{1c}	hemoglobin A_{1c}
HNF-4α	hepatocyte nuclear factor-4α
H_2O_2	hydrogen peroxide
H3	histone 3
H4	histone 4
Insr	insulin receptor
IR	insulin receptor
IRS	insulin receptor substrate
JNK	c-Jun N-terminal kinase
KO	knockout
LPL	lipoprotein lipase
MAPK	mitogen-activated protein kinase
MODY	maturity onset diabetes of the young
MsrB1	methionine-R-sulfoxide reductase 1
mTOR	mammalian target of rapamycin
NPC	Nutritional Prevention of Cancer
OE	overexpressing
PDX1	pancreatic duodenal homebox 1
PEPCK	phosphoenolpyruvate carboxykinase
PGC-1α	peroxisomal proliferator-activated receptor-γ coactivator 1α
PI3-K	phosphatidylinositol 3-kinase
PTEN	phosphatase with tensin homology
PTPase	phosphotyrosine phosphatase
PTP1b	protein tyrosine phosphatase 1b
ROS	reactive oxygen species
Scly	selenocysteine lyase
Se	selenium
SELECT	Selenium and Vitamin E Cancer Prevention Trial
SelP	selenoprotein P
SelS	selenoprotein S
SelT	selenoprotein T
SOD	superoxide dismutase
SREBP-1c	sterol regulatory element binding protein-1c

TrxR1	thioredoxin reductase 1
UCP2	uncoupling protein 2
VAT	visceral adipose tissue
WT	wild type

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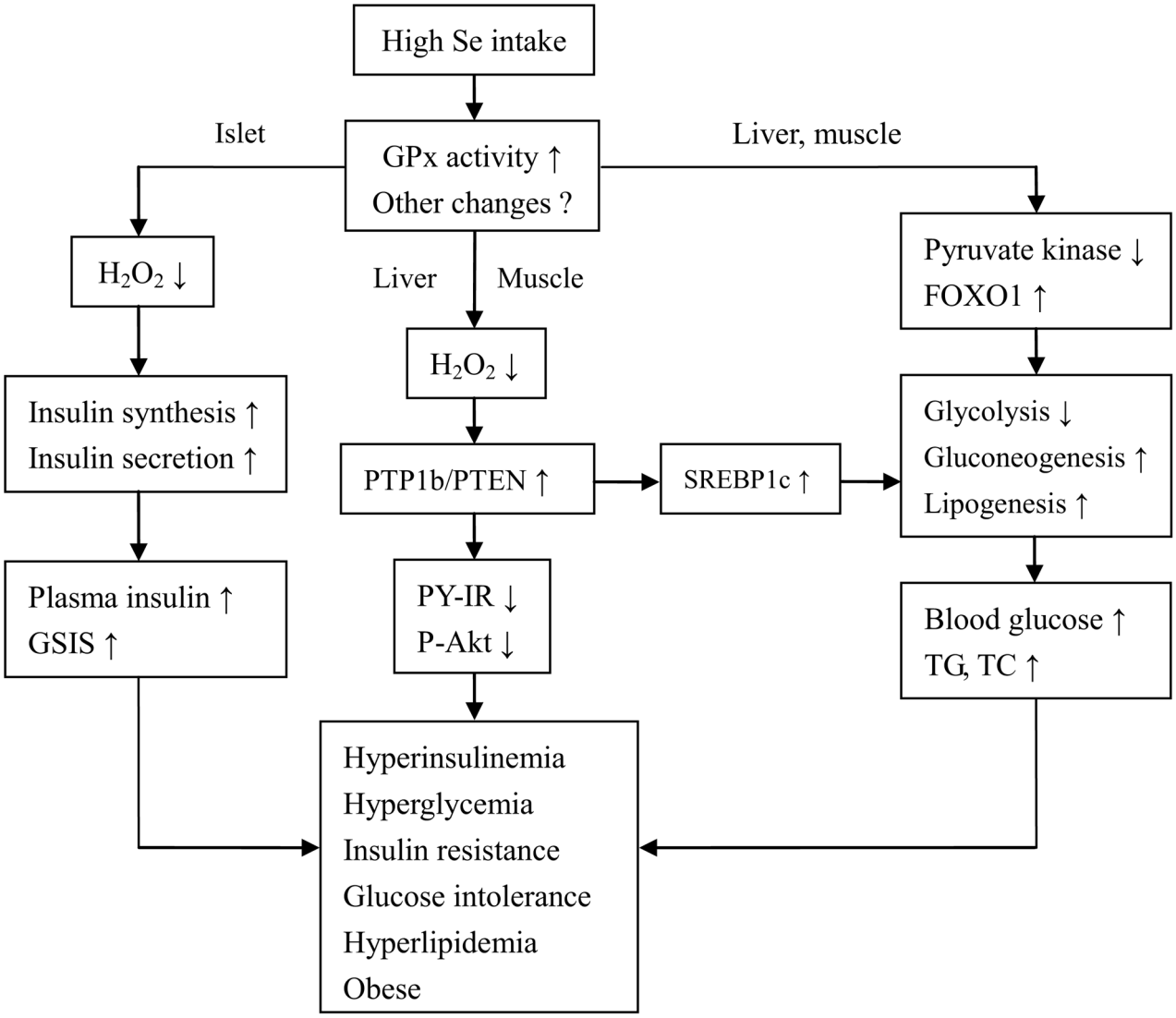

Figure 1.

Scheme of potential regulatory pathways and mechanisms for the diabetogenic potential of high Se intake. ↑, Activation or increase; ↓, inhibition or decrease; Akt, protein kinase B; FOXO1, forkhead box O1; GPx1, glutathione peroxidase-1; GSIS, glucose-stimulated insulin secretion; H_2O_2, hydrogen peroxide; IR, insulin receptor; P, phosphorylation; PY, tyrosine phosphorylation; PTEN, phosphatase with tensin homology; PTP1b, protein tyrosine phosphatase 1b; SREBP1c, sterol regulatory element binding protein-1c; TC, total cholesterol; TG, triglyceride.

Table 1

Diabetogenic potential of elevated Se intakes or selenoprotein expression in animals

Treatment	Finding	Reference
The GPX1-overexpressing (OE) and wild type (WT) male mice (n = 80) were fed a Se-adequate diet (0.4 mg/kg) from 8 to 24 weeks of age	Compared with the WT, the OE mice developed hyperglycemia, hyperinsulinemia, increased β-cell mass, hyper-secretion of insulin, insulin resistance, and obesity	22, 55
C57BL/6J mice (n = 6–7 per group) were fed either Se-deficient Torula yeast-based diet or diets supplemented with Se at 0.1 and 0.4 mg (sodium selenite)/kg of diet for 3 months	Mice in the 0.4 mg Se/kg group showed decreased insulin sensitivity and hyperinsulinemia compared to those fed the Se-deficient diet and 0.1 mg of Se/kg of diet	53
Three groups of rats (n = 10) were fed either a Se-deficient diet or diets supplemented with Se at 75 or 150 μg/kg of diet for 8 weeks	Rats in groups of 75 and 150 μg Se/kg diet had greater body weight, liver PTP1b activity, and liver triglyceride concentrations than the control group fed the Se-deficient diet	58
Seven groups of rats (n = 7) were fed either a Se-deficient diet or diets contained Se (as selenite or selenite) at 0.20, 1.0, and 2.0 mg/kg of diet for 8 weeks	All Se-supplemented animals featured a higher body weight, elevated liver GPx1 expression and activity, increased liver PTP1b activity, and reduced PTP1b glutathionylation, compared to their Se-deficient controls	59
Female Wistar rats were fed a Se-deficient (0.01 mg/kg of diet) corn–soy basal diet (BD) or BD+Se (as Se-yeast) at 0.3 or 3.0 mg/kg of diet from 5 weeks before breeding to day 14 postpartum. Offspring (n = 8/diet) born to dams fed 0.3 and 3.0 mg of Se/kg were fed with the same respective diet until age 112 days	Compared with the 0.3 mg of Se/kg of diet, the 3.0 mg of Se/kg of diet induced hyperinsulinemia, insulin resistance, and glucose intolerance in the dams at late gestation and/or day 14 postpartum and in the offspring at age 112 days	60
Weanling male pigs (n = 24) were fed a Se-deficient (< 0.02 mg of Se/kg of diet) corn-soy basal diet supplemented with 0, 0.3, or 3.0 mg of Se/kg of diet as Se-enriched yeast for 16 weeks	Compared with those fed 0.3 mg of Se/kg of diet, pigs fed 3.0 mg of Se/kg of diet became hyperinsulinemic and had lower tissue levels of serine/threonine protein kinase (Akt)	62
Male pigs were fed either a Se-adequate (0.17 mg of Se/kg of diet) or a high Se (0.50 mg of Se/kg of diet) diet for 16 weeks	The fasting plasma insulin and cholesterol levels were non-significantly increased in the pigs fed the high-Se diet, whereas fasting glucose concentrations did not differ between the two groups. Dietary Se oversupply affected expression and activity of proteins involved in energy metabolism in major was probably not sufficient to induce diabetes	63
Rats were intraperitoneally injected with saline (control) or 1.3, 1.6 and 3.8 mg of Se/kg of body weight as sodium selenite	Sodium selenite administration caused hyperglycemia in rats and elevated plasma corticosterone levels, but did not change plasma insulin levels	57