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Review Article

Role of glutathione peroxidase 1 in glucose and lipid metabolism-related diseases

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ABSTRACT

Glutathione peroxidase 1 (GPX1) is a selenium-dependent enzyme that reduces intracellular hydrogen peroxide and lipid peroxides. While past research explored regulations of gene expression and biochemical function of this selenoperoxidase, GPX1 has recently been implicated in the onset and development of chronic diseases. Clinical data have shown associations of human *GPX1* gene variants with elevated risks of diabetes. Knockout and overexpression of *Gpx1* in mice may induce types 1 and 2 diabetes-like phenotypes, respectively. This review assembles the latest advances in this new field of selenium biology, and attempts to postulate signal and molecular mechanisms mediating the role of GPX1 in glucose and lipid metabolism-related diseases. Potential therapies by harnessing the beneficial effects of this ubiquitous redox-modulating enzyme are briefly discussed.

1. Introduction

Diabetes resulted in a total of 1.6 million deaths in 2015 [1], and is projected to be the seventh leading cause of death by 2030 [2]. The prevalence of diabetes is rapidly rising not only in developed countries but also in middle- and low-income nations [3]. Overdosing or deprivation of dietary selenium (Se) is associated with increased risks of type 2 diabetes (T2D), following a U-shaped curve [4–6]. Although nutritional essentiality of Se and cellular glutathione peroxidase 1 (GPX1) were both identified in 1957 [7–9], GPX1 had not been known until 1972 as the very first selenoprotein and selenoperoxidase to help link these two important discoveries [7,10–12]. However, a virtually exclusive focus on the redox-modulating functions of GPX1 and the "undoubted" belief in its benefit, similar to that of other antioxidants, to insulin sensitivity and function have made the novel finding of T2D-like phenotypes in the *Gpx1*-overexpressing mice initially counterintuitive [13–16]. Nevertheless, that metabolic paradox has prompted interests in potential roles of the redox enzymes such as GPX1 in glucose and lipid metabolism [10,17–19]. Subsequently, a new research field has been created during the past decade or so [20–23] to explore the role and mechanism of GPX1 in regulating insulin synthesis, secretion, and sensitivity, glucose homeostasis, lipogenesis, and lipolysis and in the onset and progression of diabetes.

2. Diet-mediated *GPX1* expression on glucose and lipid metabolism

2.1. Selenium deficiency

Dietary Se deficiency decreased *GPX1* gene and protein expression in different tissues of several mammalian species [24–35]. While the deficiency did not affect body weights of mice [36], it decreased blood glucose concentration and hepatic concentrations of total cholesterol (TC), triglyceride (TG), and nonesterified free fatty acid (NEFA) in 5-month old mice [13,15,37], compared with the Se-adequate controls. Dietary Se deficiency decreased hepatic mRNA abundances of lipogenesis-related genes such as cytochrome P450, family 7, subfamily a, polypeptide 1 (*Cyp7a1*), sterol regulatory element binding transcription

Abbreviations: ACC1, acetylcoenzyme A carboxylase 1; ASIP, agouti signaling protein; BETA2, transcription factor Beta 2; CYP7a1, cytochrome P450, family 7, subfamily a, polypeptide 1; cFOS, transcription factor C-fos; FASN, fatty acid synthase; FOXA2, forkhead box protein A2; GK1, glucokinase; GPX1, glutathione peroxidase 1; GPX1(OE), GPX1 overexpression; GSIS, glucose-stimulated insulin secretion; INSR, insulin receptor; LDL, low-density lipoprotein; NEFA, nonesterified free fatty acid; PAT, perirenal adipose tissue; PDX1, pancreatic and duodenal homeobox 1; PEPCK, phosphoenolpyruvate carboxykinase; PI3K, phosphoinositide 3-kinase; ROS, reactive oxygen species; SAT, subcutaneous adipose tissue; Se, selenium; SLC2A2, solute carrier family 2 member 2; SNPs, single nucleotide polymorphisms; SOD, superoxide dismutase; SREBPs, sterol regulatory element-binding proteins; SUR1, sulfonylurea receptor 1; T1D, type 1 diabetes; T2D, type 2 diabetes; TC, total cholesterol, TG, triglyceride; Trp53, transformation related protein 53; UCPs, uncoupling proteins

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factor 1a (*Srebp1a*) and 2 (*Srebp2*), and hepatic activities of glucokinase (Gk) and phosphoenolpyruvate carboxykinase (Pepck) in the muscle of mice [14,15,37]. Meanwhile, dietary Se deficiency enhanced pancreatic islet mRNA abundances of catalase (*Cat*), transcription factor C-fos (*Cfos*), hepatic nuclear factor 4, alpha (*Hnf4α*), forkhead box o1 (*Foxo1*), glucokinase (*Gk1*), insulin 1 (*Ins1*), and transformation related protein 53 (*Trp53*) in the 5-month old mice. In rats, dietary Se deficiency decreased Gpx activity in erythrocytes of dams on day 19 of gestation and in the liver of dams on day 14 postpartum, but elevated mRNA abundances of insulin receptor substrate 2 (*Irs2*) in the liver of dams on day 14 postpartum. In pigs, dietary Se deficiency did not affect plasma glucose or insulin concentration, but decreased plasma concentration of TC [34,38].

Because broiler chicks are fast growing and susceptible to dietary Se deficiency [25,26,39], and also contain much higher blood glucose concentrations than mammalian species, they may serve as a unique model to study roles of Se and GPX1 in glucose and insulin metabolism. Feeding chicks an Se-deficient diet for 15 weeks decreased TC and TG, but elevated insulin and glucose concentrations in their plasma [39]. While the Se deficiency enhanced mRNA abundances of forkhead box a 2 (*FOXA2*), glucagon (*GCG*), and insulin receptor substrate 1 (*IRS1*) in the liver [39], it decreased transcript numbers of 16 insulin-related genes in three tissues. These genes include *IRS2,* insulin (*INS*), pancreatic and duodenal homeobox factor 1 *(PDX1),* protein tyrosine phosphatase, non-receptor type 1 (*PTPN1*), and solute carrier family 2, facilitated glucose transporter member 2 (*SLC2A2*) in the liver; AKT serine/threonine kinase 1 (*AKT1*), B-Raf proto-oncogene, serine/threonine kinase (*BRAF*), *FOXO1, FOXA2,* insulin receptor (*INSR*), *IRS1, IRS2, INS,* neuronal differentiation 1 (*NEUROD1*), *PTPN1*, phosphoinositide 3-kinase (*PI3K*), *SLC2A2,* and uncoupling protein (*UCP*) in the muscle, and *AKT1, FOXA2*, Hnf1 homeobox a (*HNF1A*), *HNF4α, INSR,* and *PDX1* in the pancreas. In summary, dietary Se deficiency dysregulated glucose homeostasis and altered expression of many insulin- and lipogenesis-related genes in the liver, muscle, and pancreas of both mammalian and avian species.

2.2. Selenium supranutrition

Rats: Compared with those fed 0.3 mg Se/kg diet [33], dams of rats fed 3.0 mg Se/kg diet had greater Gpx activities in the erythrocytes on day 19 of gestation and in the liver on day 14 postpartum. Supranutritional Se induced hyperinsulinemia, insulin resistance, and glucose intolerance in the dams at late gestation and/or day 14 postpartum as well as in the offspring at the age of 112 days old. These impairments concurred with decreased transcript and/or protein levels of insulin signaling proteins in the liver and muscle of dams and/or pups. Compared with the 0.3 mg Se/kg diet, the 3.0 mg Se/kg diet resulted in 50% decreases in transcripts of *Akt2*, *Insr*, and *Irs1* and 36% decrease in the transcript of *Foxo1* in the liver of the offspring. The decreased hepatic transcripts of *Insr* and *Akt2* were verified by approximately 60% decreases in the respective proteins Insr and Akt. Although the transcripts of these genes in the muscle was not significantly altered by the high-Se diet, the treatment decreased the expression of *Irs2* and phosphatidylglycerol phospholipase (*Pgc1*) in the muscle of dams on day 14 postpartum. Meanwhile, *Foxo1* expression was decreased by both Se depletion and supranutrition.

Pigs: Compared with those fed 0.3 mg Se/kg diet [40], pigs fed 3.0 mg Se/kg diet had GPX activities in the liver and muscle enhanced by 21% and 57%, respectively. However, there were no significant differences in the transcript levels of *GPX1* in the two tissues between the two diets. Pigs fed 1.0 mg Se/kg had 23–28% lower plasma TG and (or) TC concentrations than did those fed 0.3 mg Se/kg. Pigs fed 3.0 mg Se/kg diet had doubled plasma insulin concentration at week 11 than pigs fed 0.3 mg Se/kg diet. Their TC and TG concentrations in the adipose tissue were 2.4-fold and 41% greater, respectively, than those fed 0.3 mg Se/kg. Likewise, hepatic concentrations of TC, TG, and NEFA in pigs fed 3.0 mg Se/kg diet were 40%, 2.3-fold, and 63% greater, respectively, than those fed 0.3 mg Se/kg. However, no such differences in the lipid profiles of the muscle tissue were seen between these two levels of dietary Se. Compared with those fed the 0.3 mg Se/kg diet, pig fed 3.0 mg Se/kg diet showed up-regulations of *SREBP1* (59%) and fatty acid synthase (*FASN*) (doubled) in the liver and peroxisome proliferator-activated receptor gamma (*PPARG*) and *TRP53* (42–48%) in the muscle, and down-regulations of *CYP7A1* (88%) in the liver and *acetylcoenzyme A carboxylase 1 ACC1* (51%) and *FASN* (57%) in the muscle, respectively.

Chicks: In broiler chicks [41], a high Se (3.0 mg Se/kg) diet elevated plasma GPX activity by 37% at week 4 and muscle GPX activities by about 1.8-, 2.2- and 2.8-fold at week 2, 4, and 6, respectively, compared with the 0.3 mg Se/kg diet. Meanwhile, the high Se diet resulted in 38% higher GPX activity in the pancreas compared with that in the 0.3 mg Se/kg group at week 2 [41]. Broilers fed 3.0 mg Se/kg exhibited a lower fasting plasma glucose concentration, but higher plasma insulin concentration compared with those fed the 0.3 mg Se/kg at week 2. Plasma concentrations of TC and TG were also higher in broilers fed 3.0 mg Se/kg than those fed 0.3 mg Se/kg. The 3.0 mg Se/kg diet increased muscle transcripts of *FOXO1*, *HNF4α*, *IRS2*, and *PI3K*, hepatic transcripts of *GCG, HNF4α, and SLC2A2*, and pancreatic transcripts of *HNF4α and IRS2* at week 6. In contrast, the 3.0 mg Se/kg diet downregulated insulin signaling-related genes of *AKT1*, *FOXA2*, *INS*, *PI3K*, and *UCP* in the pancreas and *AKT1*, *GCG*, and *INSR* in the muscle at the same time. Meanwhile, hepatic transcripts of *GCG* were elevated by the Se supranutrition and deficiency in broiler chicks. Pancreatic transcripts of *AKT1* and *FOXA2* and muscle transcripts of *AKT1* and *INSR* in the chicks were downregulated by the Se supranutrition and deficiency in the same direction. In contrast, muscle transcripts of *FOXO1* and *IRS2*, hepatic transcript of *SLC2A2*, and pancreatic transcript of *HNF4α* were affected by the Se supranutrition and deficiency in opposite ways. Organic sources of Se from 2-hydroxy-4-methylselenobutanoic acid and Se-enriched yeast seemed to be more effective in restoring hepatic *GPX1* transcript and GPX activity in tissues than sodium selenite in broiler chicks [42]. However, differences of these Se forms in affecting glucose and lipid metabolism remain unclear.

Humans: Blood or plasma Se, instead of GPX(1) activity, has often been measure to assess body Se status in human population studies. A recent review [43] indicated that five out of eight cross-sectional studies had shown positive associations between serum/plasma Se and T2D or fasting circulating glucose. Among the five randomized controlled trials (RCTs) with Se supplementation, three trials, including the well-known Se and Vitamin E Cancer Prevention Trial [44], showed no effect, one showed lower fasting serum insulin and homeostasis model assessment of insulin resistance, and only one, the Nutritional Prevention of Cancer study conducted in the dermatology outpatients, showed an increased incidence of T2D [45]. But, Algotar et al. [46]failed to observe the same positive effect of Se on diabetes prevention at a later time. The Selenium and Celecoxib Trial for the prevention of colorectal adenoma recurrence suggested that Se supplementation might increase the risk of T2D in older participants following removal of adenomas [47]. A recent case control study reported that high serum Se concentrations were associated with increased risks for diabetes mellitus, independent of central obesity and insulin resistance [48].

Higher risks of dyslipidemia were associated with higher circulating Se concentrations in the observation trials from all the three times of National Health and Nutrition Examination Survey conducted between 1988 and 2012 in US [49–51], as well as from the populations of Lebanon [52], Taiwan [53], Britain [54], Finland [55], and Spain [56,57]. But results from the Se supplementation trials were inconsistent, similar to those for the glucose metabolism. Supplementing Se at 100 μg/day for 6 months increased the cord blood concentrations of TG in a small group of pregnant women (n = 34 for supplementation vs 32 for placebo) [58]. While supplementing antioxidants including Se increased for > 7 years the risk of dyslipidemia in women [59]. However,