

Review article

Selenoprotein P and glucose metabolism: The involvement of redox signaling.

Yoshiro Saito

Laboratory of Molecular and Biochemical Toxicology, Graduate School of Pharmaceutical Sciences,
Tohoku University, Sendai, Japan

Abstract

Selenoprotein P (SeP; encoded by *SELENOP*) is a major selenium-containing protein in human plasma and plays a pivotal role in the metabolism of selenium, an essential trace element. SeP possesses selenium as a selenocysteine (Sec) which is an analog of cysteine containing selenium instead of sulfur. SeP has 10 Sec residues which are important for the function of SeP; namely, the 1st Sec in the N-terminal region forms the active site of phosphatidylcholine hydroperoxide reducing activity, while nine Sec residues in the C-terminal region functions as a selenium transporter to maintain antioxidative seleno-enzymes. Thus, SeP is a multifunctional protein which plays a significant role in the antioxidative defense. However, recent evidence indicates that excess SeP worsens glucose metabolism and advances type 2 diabetes. In this review, the biochemical character and biological function of SeP are described. Further, the recent evidence related to the undesired effects of excess SeP on glucose metabolism is summarized. Finally, the molecular mechanisms of excess SeP-induced impairment effects on glucose metabolism, particularly the involvement of redox signaling, are discussed.

KEY WORDS: selenoprotein P, selenium, type 2 diabetes, insulin resistance, exercise resistance, insulin secretion

Introduction

Selenium (Se) is an essential trace element, and its deficiency has been associated with complications including increased risk of mortality, poor immune function, and cognitive decline¹⁾. Whereas Se has a high toxicity, and the optimum range of Se between excess and deficiency is quite narrow. The essential biological role of Se is mediated by Se-containing proteins called selenoproteins²⁾. Selenoprotein P (SeP; encoded by *SELENOP*) is a major selenoprotein in plasma and functions as a Se transporter to deliver Se to several tissues³⁾. The function of SeP is important for the maintenance of tissue selenoproteins; however, recent evidence indicates that SeP levels are increased in type 2 diabetes (T2DM) patients and excess SeP impairs glucose metabolism⁴⁻⁶⁾. In this review, the worse effects of excess SeP on glucose metabolism are summarized, and the molecular mechanisms of excess SeP-induced impairment effects on glucose metabolism, particularly the relation of redox signaling, are discussed.

Selenoprotein P

SeP is a major selenoprotein in plasma, possessing almost half of plasma Se⁷⁾. SeP is mainly synthesized in the liver and secreted into the plasma. SeP has a Se as selenocysteine (Sec; a cysteine analog contained Se instead of sulfur), which is encoded by UGA stop codon⁸⁾. Sec-containing protein is termed selenoprotein, and now 25 types of selenoproteins have been identified²⁾. The “P” in SeP means plasma. SeP possesses 10 Sec residues which are important for SeP function. The gross structure of SeP is shown in [Fig. 1](#). The 1st Sec residue in the N-terminal region forms an active site of enzyme activity to reduce phospholipid hydroperoxide using glutathione as a reductant^{9,10)}. The C-terminal region of SeP is rich in Sec and functions as a Se transporter to supply Se to the cells effectively^{7,10)}. Cellular selenoproteins such as glutathione peroxidase (GPx) and thioredoxin reductase (TrxR) play a significant role in removing reactive oxygen species (ROS) and in redox regulation. Thus, SeP is a pivotal antioxidative protein not only to reduce lipid hydroperoxide directly but also to maintain the cellular antioxidative system ([Fig. 1](#)).

Correspondence to:
Laboratory of Molecular and Biochemical Toxicology,
Graduate School of Pharmaceutical Sciences, Tohoku University
Sendai, 980-8578, Japan
TEL: +81-22-795-6870
e-mail: yoshiro.saito.a8@tohoku.ac.jp

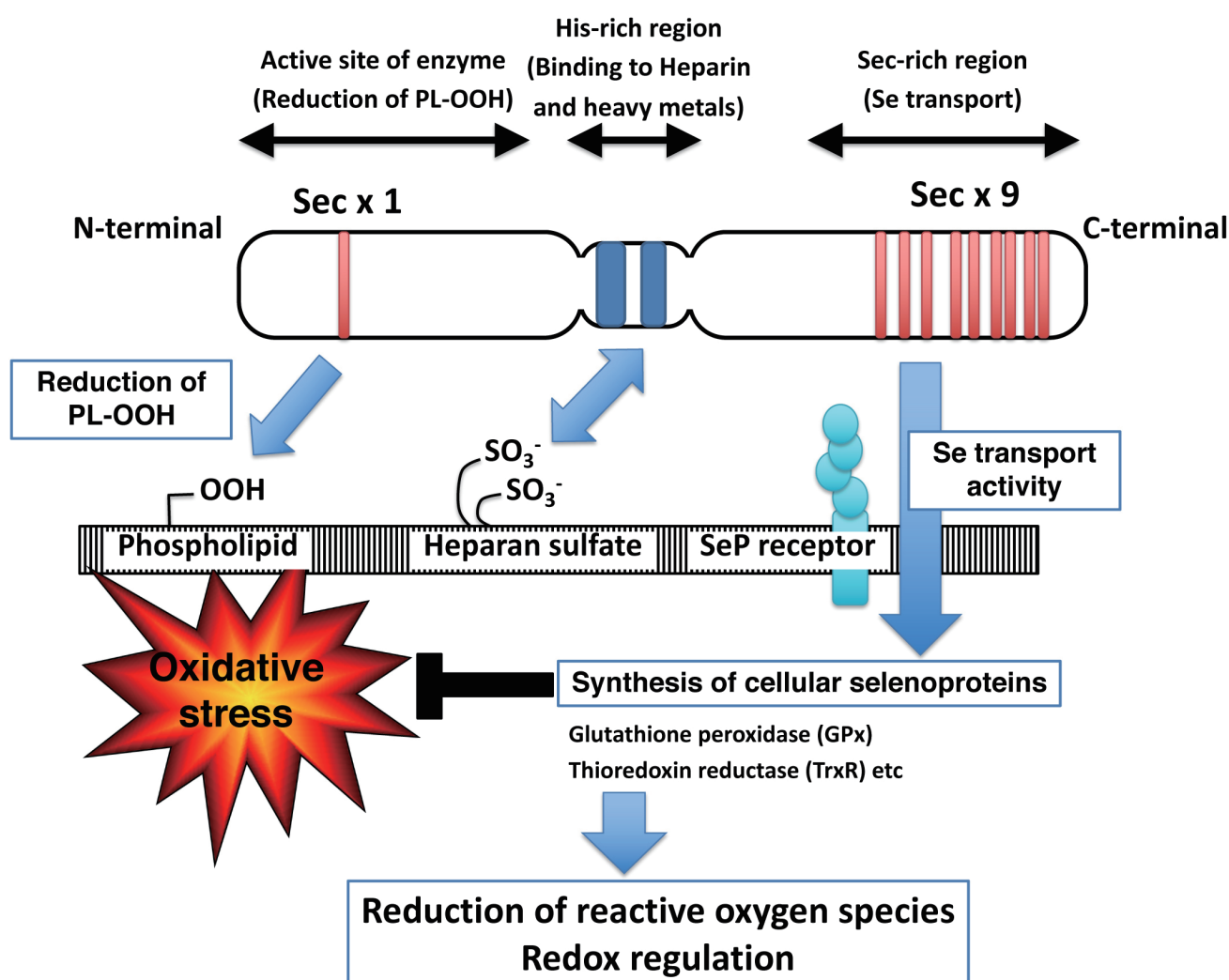


Fig. 1. Gross structure and function of selenoprotein P.

PL-OOH, Phospholipid hydroperoxide; Sec, Selenocysteine; SeP, selenoprotein P.

The increase of selenoprotein P in type 2 diabetes patients and model animals

Transcriptome analysis of liver biopsy samples from T2DM patients revealed an increase of SeP mRNA in these patients ⁴⁾. This analysis was conducted to identify “Hepatokine,” a liver secretion protein influencing the pathophysiology of diabetes. The mRNA levels of SeP in the liver significantly correlated with blood glucose levels at 120 min after glucose ingestion ⁴⁾. SeP protein levels in serum are also positively correlated with fasting plasma glucose, indicating the increase of SeP in T2DM ⁴⁾. To explore the role of increased SeP in the pathophysiology of diabetes, the effects of excess SeP was investigated. Several *in vivo* and *in vitro* experiments indicate that increased SeP worsens glucose metabolism and precedes diabetes ⁴⁾. The treatment of hepatocytes with high glucose resulted in the increase of SeP mRNA and protein levels. Similar to this observation, SeP levels in plasma increased in animal models of T2DM.

Although the biological significance of the increase of SeP in high glucose conditions is not understood, the increase of SeP in diabetes is common between human and model animals.

It has been reported that the risk of diabetes increases from Se supplements ^{11, 12)}; however, this observation is limited to the population with high Se content in plasma ^{13, 14)}. In addition, it is considered to be unlikely that high Se intake alone could induce diabetes condition. Actually, CE2, usual fed to mice, contains 0.4 mg Se/kg, which is enough quantity to maintain maximum levels of selenoproteins, while it could not induce diabetes ¹⁵⁾. On the other hand, a high fat and high sucrose diet containing 0.2 mg Se/kg can induce diabetes. It appears that the high glucose and high lipid stimulus is important to induce SeP expression under diabetic conditions. Of course, Se is essential to synthesis SeP protein. It is, therefore, considered that high Se is not a sufficient condition but the necessary condition to achieve high SeP levels in diabetes patients. To induce SeP expression, the inhibition of

AMP-activated kinase (AMPK) activity and sterol regulatory element-binding protein-1c (SREBP-1c) transcriptional activity in hepatocytes are important, and these are known as a target of therapeutics of diabetes and metabolic syndrome^{16,17}. Metformin, an AMPK activator, suppressed the expression of SeP, via the decreased binding of FoxO3a, a direct target of AMPK, to the SELENOP promoter¹⁶. While eicosapentaenoic acid (EPA) suppressed SeP expression by the decrease of SREBP-1c binding of SELENOP promoter in AMPK-independent manner¹⁷. These results indicate the regulation of SeP expression by several transcriptional factors related to metabolism, suggesting the importance of developing the therapeutic reagents targeting SeP expression.

The effects of excess selenoprotein P on insulin and exercise resistance

An increasing volume of evidence has demonstrated that increased SeP impairs insulin resistance and secretion, indicating the involvement of the onset as well as the

procession of T2DM (Fig.2)⁴⁻⁶. It has been reported that low levels of reactive oxygen species (ROS) positively work for the insulin signal¹⁸. Several factors related to the signal transduction of insulin are regulated by ROS. AMPK, one of the important regulators of energy metabolism, is regulated not only by AMP but also by several factors including ROS^{19,20}. It has also been known that ROS regulates the activity of protein tyrosine phosphatase 1b (PTP1B) via the oxidation of the reactive cysteine, and its phosphatase activity is related to insulin signaling²¹. The increase of insulin resistance has been reported in transgenic (TG) mice of selenoenzyme GPx1, suggesting the physiological role of ROS in the insulin signal²². In the case of diabetes model mice with excess SeP, insulin signal transduction was disturbed, and the negative effect of SeP was diminished by the inhibitor of glutathione synthesis, buthionine sulfoximine (BSO), suggesting the relation of antioxidant effects on the increase of insulin resistance was induced by excess SeP⁴. On the other hand, exercise is commonly used as a leading cure to improve insulin resistance. In this beneficial effect of exercise, the significant role of ROS has been discussed²³. It has been reported that positive intake of antioxidants counteracts the

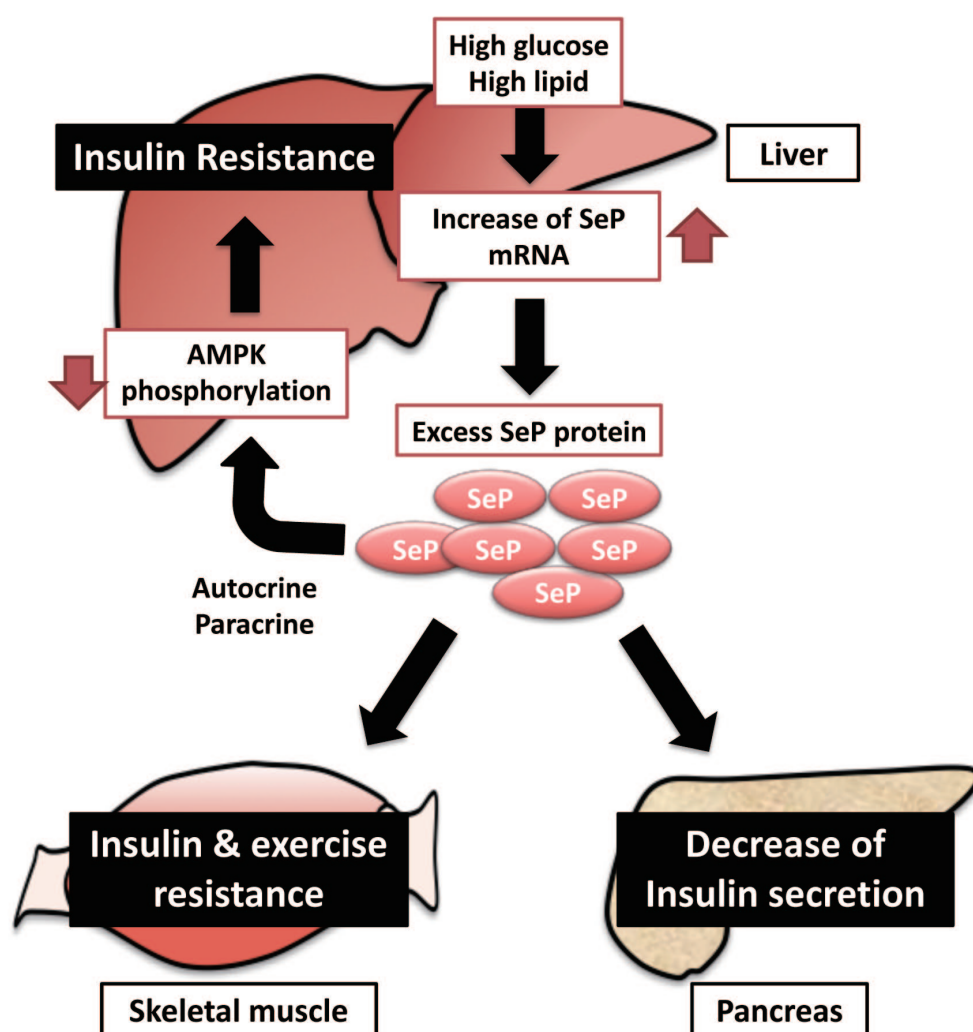


Fig. 2. Effects of excess selenoprotein P on glucose metabolism.

AMPK, AMP-activated kinase; SeP, selenoprotein P.

health-promoting effects of exercise, namely increasing the exercise resistance. Increased SeP induced exercise resistance through its muscle receptor low-density lipoprotein receptor-related protein 1 (LRP1)⁵⁾. Interestingly, SeP-deficient mice showed a 'super-endurance' phenotype after exercise training, enhanced ROS production, and AMPK phosphorylation. Human studies also showed a significant correlation between SeP levels and the ineffectiveness of training on endurance capacity, suggesting the increased amounts of circulating SeP as a predictor of exercise resistance⁵⁾.

The effects of excess selenoprotein P on insulin secretion

Recent evidence indicates that excess SeP inhibits secretion of insulin from pancreatic β cells (Fig. 2)⁶⁾. The addition of excess SeP to MIN6 cells, a model of pancreatic β cells, and rat primary pancreatic islets significantly decreased cellular insulin levels and high glucose-induced

insulin secretion. Selenocystine, an equal amount to excess SeP, showed similar inhibitory effects on insulin secretion, suggesting the relation with Se-transport activity of SeP. The impairment effects of excess SeP were observed *in vivo* experiments, and the injection of purified SeP protein resulted in the decrease of pancreatic insulin levels, the area of islets, and glucose-induced insulin secretion (Fig. 3)⁶⁾. Interestingly, SeP injection resulted in a decrease of both α - and β -cells in the pancreas, accompanied by the rearrangement of the position of these cells in the pancreatic island (Fig. 3). The rearrangement and decrease of both α - and β -cells have been observed in the diabetes model of animals and human cases²⁴⁾. The details of molecular mechanisms of the change in the pancreas of SeP-injected mice are still unknown, and further research is necessary to elucidate these molecular mechanisms. In the diabetic model animals, such as KKAY mice and high-fat and high-sucrose (HFHS) fed mice, neutralizing the SeP antibody effectively improved the insulin secretion, suggesting the impairment effects of excess SeP on pancreatic function⁶⁾.

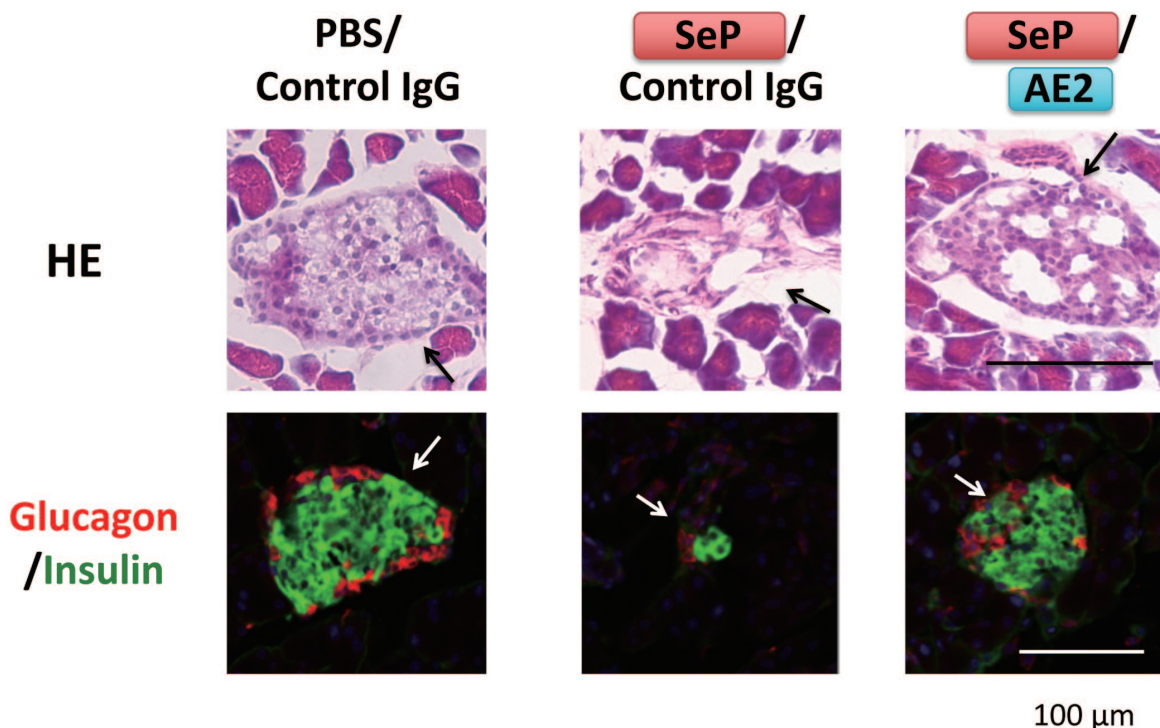


Fig. 3. Effects of excess selenoprotein P on pancreatic islets: Immunohistochemical analysis.

After administration of purified SeP protein and its neutralizing antibody AE2 to C57BL/6J mice, a histochemical analysis was conducted on pancreas tissues using HE stain, anti-insulin Ab (green) and Glucagon (red, indicative of α -cells). Scale bars = 100 μ m. HE, haematoxylin and eosin; Ab, antibody; SeP, selenoprotein P. Adapted from Mita et al., (2017, ref 6) with permission.

Conclusion

SeP is a powerful antioxidant protein to control cellular redox status; however, the excess quantity of circulating SeP is quite bad for our health, causing insulin and exercise resistance and impaired insulin secretion. However, its detail molecular mechanism is still not cleared, and the relationship between selenoproteins and glycative stress is also currently unknown. Further studies are necessary to elucidate the mechanisms of the undesired action of excess SeP. The development of SeP-targeting therapeutic agents is necessary to realize the effective treatment of diabetic individuals with high SeP ([Fig. 4](#)).

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Conflict of Interest Statement

The author claims no conflict of interest in this manuscript.

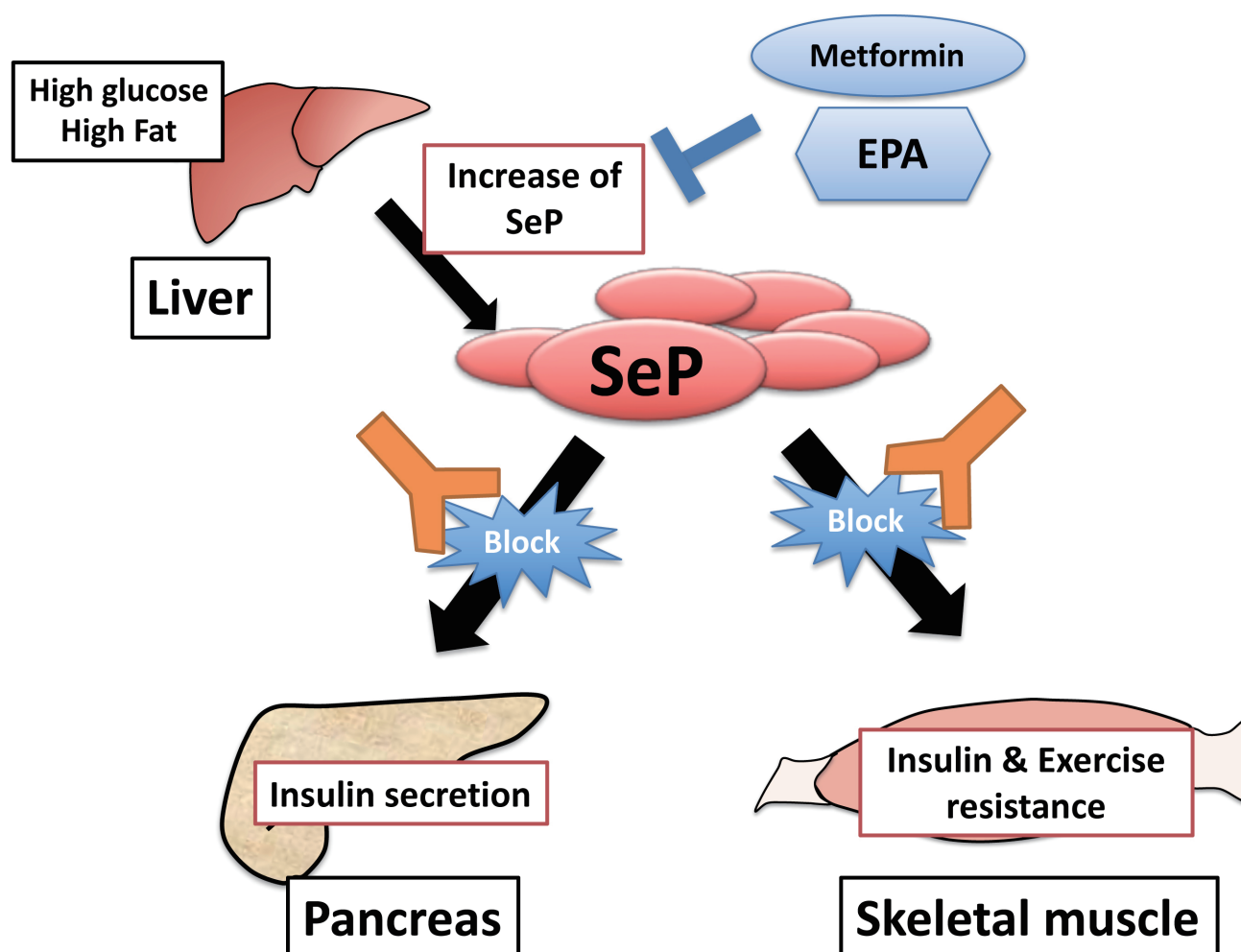


Fig. 4. Possible therapeutic strategies for metabolic disorder induced by excess selenoprotein P.

EPA, eicosapentaenoic acid; SeP, selenoprotein P.

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