เซเลเนียมและบทบาททางชีวภาพของเซเลโนโปรตีนต่อสุขภาพและโรคต่างๆ

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บทคัดย่อ

เซเลเนียมเป็นหนึ่งในแร่ธาตุที่มีความจำเป็นต่อร่างกายแต่มีความต้องการในปริมาณน้อย ซึ่งการทำงานในร่างกายจะเกี่ยวข้องกับเซเลโนโปรตีนที่มีมากกว่า 30 ชนิดในกลุ่มสัตว์เลี้ยงลูกด้วยนม แหล่งอาหารที่สำคัญของเซเลเนียมได้แก่ ขนมปัง ธัญพืช เนื้อสัตว์ ปลา ไข่ นม ผลิตภัณฑ์จากนมและเครื่องดื่ม ผักและผลไม้ ปัจจัยที่มีผลต่อปริมาณของเซเลเนียมในอาหารทั้งจากพืชและสัตว์ ได้แก่ สภาพภูมิประเทศที่มีการปลูกผักและผลไม้ ตลอดจนการเลี้ยงสัตว์ ปัจจัยทางด้านสิ่งแวดล้อม ปริมาณเซเลเนียมในปุ๋ยสำหรับใช้ในเกษตรกรรมและอาหารสัตว์ ปริมาณการบริโภคเซเลเนียมในกลุ่มประชากรแต่ละประเทศจะแตกต่างกัน และปริมาณการบริโภคที่ต่างกันนี้จะบ่งบอกได้ถึงสถานะของเซเลเนียมในร่างกายและประสิทธิภาพของการทำหน้าที่ของเซเลเนียมในร่างกาย เซเลโนโปรตีนประกอบด้วยกลูต้าไธโอนเพอร์อกซิเดส (glutathione peroxidases), ไอโอโดไธโรนีนดีไอโอดิเนส (iodothyronine deiodinases), ไธโอรีดอกซินรีดักเตส (thioredoxin reductases) และ เซเลโนฟอสเฟสซินเทเตส (selenophosphate synthetase) ซึ่งโปรตีนเหล่านี้ทำหน้าที่ในเรื่องของระบบการป้องกันหรือชะลอกระบวนการเกิดออกซิเดชั่น ปฏิกิริยารีดอกซ์ กระบวนการเมตาบอลิสมของไทรอย์ฮอร์โมน และการตอบสนองของระบบภูมิคุ้มกันในร่างกาย ภาวะที่ร่างกายมีเซเลเนียมในปริมาณต่ำ อาจจะนำไปสู่การเกิดโรคต่างๆ เช่นโรคหลอดเลือดและหัวใจ โรคมะเร็งและการทำงานของระบบภูมิคุมกันที่ผิดปกติ จากข้อมูลที่กล่าวมาข้างต้นจึงนำไปสู่การเพิ่มความพยายามและงานวิจัยที่สามารถนำเสนอวิธีการประเมินการบริโภคเซเลเนียม ภาวะของเซเลเนียมในร่างกายและกลไกที่เกี่ยวข้องกับการเกิดโรค เพื่อจะนำไปสู่ประโยชน์ต่อการดูแลสุขภาพ

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***ผู้รับผิดชอบบทความ**

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Selenium and Biological Function of Selenoprotein in Health and Diseases

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Abstract

Selenium is one of the important trace elements with its biological function in human health through over 30 mammalian selenoproteins. Food sources of selenium are bread and cereals, meat, fish and eggs, milk, dairy products and beverage, fruit and vegetables. There are some factors that may regulate selenium contents in food (plants and animals) such as geological conditions, environmental factors, fertilizer with selenium and animal feedstuffs. Individual selenium intakes among populations in different countries are also varied and quantity of human intake reflects selenium status as well as efficacy of biological functions. Selenoproteins include in glutathione peroxidases, iodothyronine deiodinases, thioredoxin reductases, and selenophosphate synthetase. These proteins mostly function in antioxidant system, redox reaction, thyroid hormone metabolism and immune response. Low selenium status can lead to a large number of diseases, including cardiovascular disease, cancer and immune dysfunction. From these evidence, more attempts and researches have been proposed to assess selenium intake, selenium status and related mechanism for health benefit effects.

Keywords : Glutathione peroxidases, Iodothyronine deiodinases, Keshan disease, Selenium, Selenoprotein, Thioredoxin reductases

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Introduction

Nowadays, scientific data and clinical evidences has been supported the important role of selenium and selenoproteins in health and diseases[1-4]. The quantification of selenium intake, the identification of selenoproteins and the investigation of selenium deficiency-induced disorders are crucial in multidisciplinary research, including biology, nutrition, clinical chemistry and toxicology. Selenium from food is major source for general population and for selenium contents in plant, this level is related to its protein content. There were geographic differences in the content and availability of selenium from soils to food crops and animal products with influencing the selenium status of entire communities. However, in some area where crops were grown in soil with low selenium, the suggestive strategies have been followed in order to supply the population with sufficient selenium; for example, use of selenium-enriched fertilizers and supplementation in animals. Factors affecting selenium and selenoproteins requirement are also important issues and the assessment of selenium status with current techniques has been investigated. Selenoproteins with known functions have been identified as five glutathione peroxidases, two deiodinases, several thioredoxin reductases, and selenophosphate synthetase[5]. The main purposes of this articles focus on food source and dietary selenium intake, selenium bioavailability, selenoproteins and biological functions.

Food source and dietary selenium intake

Dietary selenium has been reported with a variety of chemical forms and many biological actions may result from their chemical forms that were consumed. Numerous food sources of selenium have been reported both in animal and plant-based foods. Selenium content in food is determined by various factors, including geographical origin, seasonal cultivation, animal feed from crops grown in soil, protein content in edible meat product and type of food processing. The important groups of selenium rich food are fish and seafood; meat, poultry and egg; legume, nut and cereal; milk and dairy products; and vegetables and fruits (Table 1). For fish and seafood, the selenium contents in different locations were between 27.3 and 88.1 µg/100 g. Marro, et al. (1996) reported that selenium levels in salmon (from Australia) ranged from 27.3 to 36.8 µg/100 g and mean levels in sardines and oysters were 57.0 and 77.0 µg/100 g, respectively[6]. In Thailand, mean selenium contents were 47.3 µg/100 g for catfish, 88.1 µg/100 g for mackerel, 29.3 µg/100 g for oyster and 35.4 µg/100 g for prawn[7].

Table 1 Selenium content in different food items from various countries

Food item	Countries	Selenium content (µg/100g)	Reference
Fish and seafood			
Salmon	Australia	27.3-36.8	Marro (1996)
Tuna (in oil)	Egypt	81.0	Fardy et al. (1994)
Sardines	Australia	57.0	Akl et al. (2006)
Batrachian walking catfish (raw)	Thailand	47.3	Sirichakwal et al. (2005)
Short-bodies mackerel (raw)	Thailand	88.1	Sirichakwal et al. (2005)
Oyster (Pacific)	Thailand	29.3	Sirichakwal et al. (2005)
Oyster	Australia	77.0	Marro (1996)
Prawn, green tiger (raw)	Thailand	35.4	Sirichakwal et al. (2005)
Meat and poultry			
Beef, streak	Australia	8.0-20.0	Tinggi (1999)
Beef, lean (raw)	Thailand	15.8	Sirichakwal et al. (2005)
Pork	USA	14.4-45.0	USDA (1999)
Pork, kidney	Spain	84.9-154.3	Diaz-Alarcon, et al (1996)
Pork, lean (raw)	Thailand	17.2	Sirichakwal et al. (2005)
Chicken, breast (raw)	Thailand	22.3	Sirichakwal et al. (2005)
Egg	Australia	0.07-1.42	Marro (1996)
Egg, hen (whole)	Thailand	32.7	Sirichakwal et al. (2005)
Milk and dairy products			
Cow's milk	Greece	1.31-2.19	Pappa et al. (2006)
Condensed milk	Spain	7.50	Cabrera et al. (1996)
Milk, Whole, UHT (natural)	Thailand	2.8	Sirichakwal et al. (2005)
Milk, powder, full cream	Thailand	6.4	Sirichakwal et al. (2005)
Vegetables and fruits			
Celery	Australia	0.93-1.42	Marro (1996)
Celery	Thailand	0.3	Sirichakwal et al. (2005)
Lettuce	Australia	0.3-2.28	Marro (1996)
Lettuce	Thailand	0.3	Sirichakwal et al. (2005)
Onion	India	12.7	Singh and Garg (2006)
Onion, bulbs	Thailand	1.1	Sirichakwal et al. (2005)
Acacia pennata (Cha-om)	Thailand	12.7	Sirichakwal et al. (2005)
Grapes	Australia	4.0-7.6	Marro (1996)
Grapes, red	Thailand	0.2	Sirichakwal et al. (2005)
Ly chee, Jom-jai-jakkapat varieties	Thailand	2.8	Sirichakwal et al. (2005)
Legumes, nuts, and cereals			
Lentils	USA	2.8	USDA (1999)
Peanuts	USA	7.5	USDA (1999)
Peanut/groundnut, seeds, dried	Thailand	11.1	Sirichakwal et al. (2005)
Rice bean, seeds, dried	Thailand	15.7	Sirichakwal et al. (2005)
Rice	Greece	1.91	Pappa et al. (2006)
Rice, polished raw	Thailand	5.4	Sirichakwal et al. (2005)

Meat, especially offal, also contained high levels of selenium. In Spain, the selenium level of kidney from pork was 84.9-154.3 µg/100 g[8] which was higher than those in lean pork (17.2 µg/100 g from Thailand)[7] and beef (15.8 µg/100 g from Thailand, and 8.0-20.2 µg/100 g from Australia)[7,9]. The selenium contents of hens' eggs showed slight differences; 32.7 and 0.07-1.42 µg selenium per whole egg in Thailand[7] and Australia[6], respectively. Milk and dairy products were also other source of selenium and its level varies widely between 0.01-0.03 mg/kg in the UK and the prominent selenium species in cows' milk were seleno-cysteine and selenite[10]. In Thailand, Sirichakwal et al. (2005) reported selenium content in whole milk and milk powder (2.8 and 6.4 µg/100 g, respectively)[7].

For legume, nut and cereal, some studied demonstrated that unshelled nuts provided in high selenium content than those with shelled. Especially, Brazil nuts (*Bertholletia excelsa*, family Lecythidaceae) were widely known as one of the richest selenium sources with reported level between 8-83 µg of Se/g. The selenium content in nuts was highly dependent on the soil selenium concentration and this issue was supported by data of Brazil nuts originating from the western part of Brazil contained less ten time selenium than those from the central part[11-13]. Moreover, one single Brazil nut exceeded the US RDA for selenium and it was also high in sulphur-containing amino acids that enhanced the absorption of selenium and other minerals in the nuts[14]. There were variations of selenium content in this nut with reported influences of moisture content, maturity of the tree and root system, soil type, and pH. Other nuts from USA[15] and Thailand[7] were reported of 7.5 and 11.1 µg/100 g, respectively. Dumont et al. (2006) showed that selenium level in cereals ranged from 10.0-550.0 ng/g[6] and Marrow (1996) reported this element in white bread of 80.0-109.0 ng/g[6]. For rice, differences in selenium levels were found in Thailand (5.4 µg/100 g) [7]and Greece (1.91 µg/100 g)[16].

Basically, most of vegetables and fruits contained low levels of selenium. Fresh vegetables from Australia such as celery and lettuce were found with 0.93-1.42 µg/100 g selenium and 0.3-2.28 µg/100 g[6] whereas from Thailand, selenium levels in both vegetables were 0.3 µg/100 g[7]. However, *Acacia pennata* (Cha-om) which is local Thai vegetable contains 12.7 µg/100 g[7] (Sirichakwal et al., 2005), comparable with onion from India (12.7 µg/100 g of selenium)[17]. In addition, the main selenium species in onions were 63% of γ-glutamyl-Se-methylselenocysteine, 10% of selenite and 5% of selenomethionine and other species[18]. For fruits, there were different

levels of selenium in grape from different countries; 4.0-7.6 µg/100 g of selenium from Australia[6] and 0.2 µg/100 g of selenium from Thailand[7]. However, one of Thai fruits reported by Sirichakwal et al. (2005)[7] as Ly Chee, Jom-jai-jakkapat varieties showed slightly higher selenium content (2.8 µg/100 g) than others.

Selenium intake

The Food and Nutrition Board at the Institute of Medicine of the National Academies, US, has recommended selenium intake for 19–50-year-old men and women in three reference values; 45 micrograms (µg) of Se/day as the estimated average requirement (EAR), 55 µg of Se/day as the recommended dietary allowance (RDA) and 400 µg of Se/day as the tolerable upper intake level (UL)[19-20] (Sunde, 2001 and Food and Nutrition Board-USA Institute of Medicine, 2000). This RDA level has been recommended from the amount needed to maximize synthesis of the selenoprotein glutathione peroxidase (GPx) that was assessed by the plateau in the activity of the plasma isoform of this enzyme. For USA, most population seemed to consume adequate amounts of selenium as seen by data from National Health and Nutrition Examination Survey (NHANES) 2003–2004 with mean 105.3 µg (n = 1,159, and mean age 56.8 years) from both food and supplements[21]. Based on selenium total dietary intake, data from various researchers have been proposed. At least 40 µg/day of selenium was an adequate intake for adult to support the maximum expression of selenium enzymes and a high selenium levels as 300 µg/day was mentioned to reduce cancer risk[22]. In addition, three selenium levels of biological activity were level for normal growth and development (as trace concentrations), for selenium body storage and maintenance of homeostatic functions (as moderate concentrations) and for toxic effects (as elevated concentrations)[23].

Figure 1 shows means of human selenium intakes from various countries without supplementations. In Europe, the daily selenium intakes ranged from 30.0-89.22 µg[3, 4, 13, 16, 24-33]. The highest level of selenium intake was reported from population from United Kingdom (UK) with above the recommended reference nutrient intake (RNI) of 60 µg/day for adult women and of 75 µg/day for lactating women and adult men[24]. Recently, the European Food Safety Authority (EFSA), in the European Union (EU), reported a daily adequate intake for Se at 70 µg[25]. In Asia, means selenium intake of Korean was 43.51 µg/day[26] and 46 µg/day for Thais[27] with lower than Thai Recommended Daily Intake (70 µg/day)[28]. In Africa, Benemariya et al. revealed that the daily dietary intake was 17 µg and concluded that rural population were

in high potential risk for selenium deficiency[29]. These data demonstrated the wide variability between countries. However, in the present time, the optimal selenium intake for health benefits and achievements is not definitely conclusive. Additional researches focus on selenium intake related to dietary surveys, dietary supplements and factors affecting selenium bioavailability are very important and may lead to refine selenium dietary recommendation and to develop effectively public health policies.

To our knowledge, studies on the selenium intake and status in Thai population is very limited. Krittaphol, et al. have reported selenium intake of 515 northeast Thai children aged 6-10 years with mean dietary selenium intake 46 µg/day. Males tended to have higher mean selenium intake than female (51 vs 41 µg/day[27]. It was noted that children with high serum selenium concentrations had a greater mean selenium intake than those with low serum selenium concentrations. However, this study population were not at risk of selenium deficiency. Based on selenium content in Thai food, seafood and fish (especially short-bodies mackerel) are considered rich sources of selenium (~45 µg/100g). Pork, beef, legumes and seeds contain moderate levels of selenium. For vegetables and fruits, selenium content present in low to negligible amount. Thus, it is practically to promote selenium intake from these food items for reduction of selenium deficiency among Thai population.

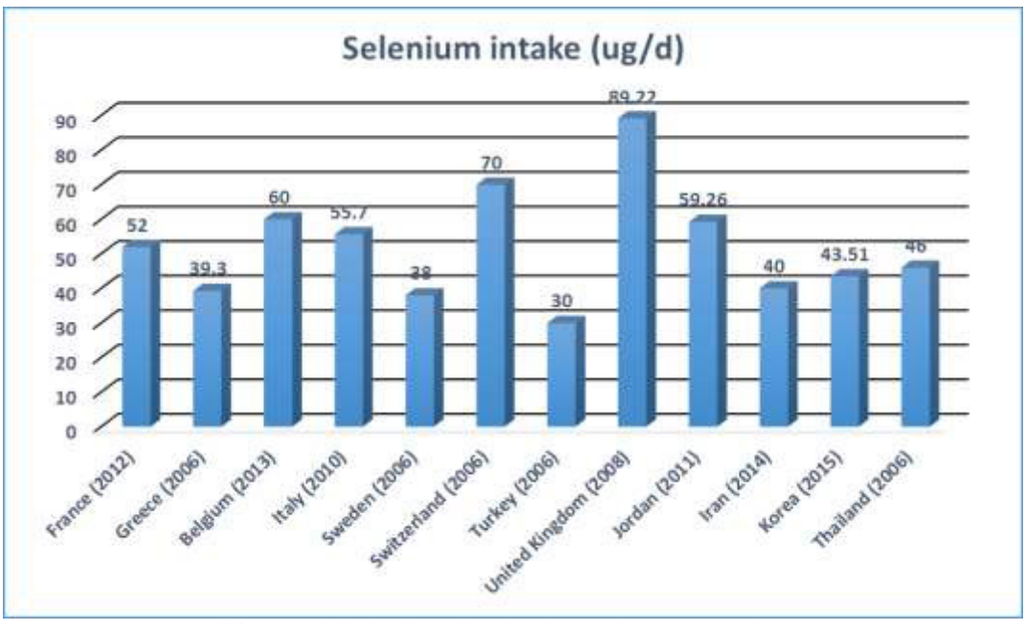
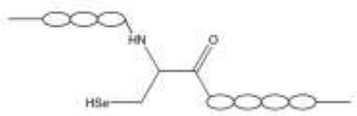
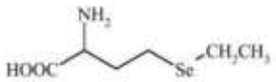
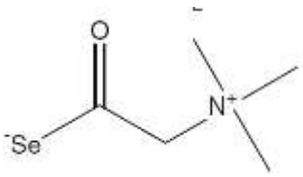
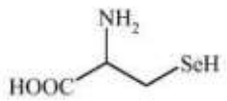
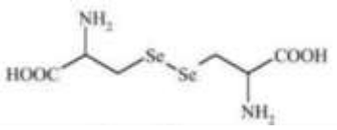
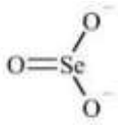
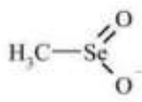
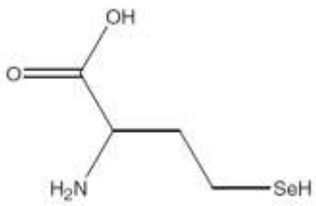
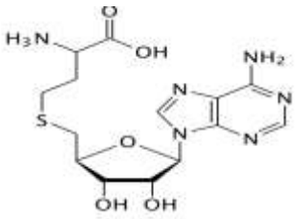
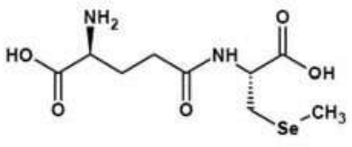
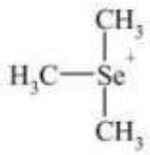


Figure 1 Selenium intake in various countries

Selenium bioavailability

The bioavailability of selenium is very important due to different species both in animal and plant sources. Up-to-date literatures on selenium speciation analysis are illustrating the identification of selenium compounds in plant-based food and the results reveal various chemical forms such as selenite, selenate, selenomethionine, selenocystine, selenohomocysteine, seleno-methylselenocysteine, γ-glutamyl-selenocy-stathionine, Se-Met, selenoxide, γ-glutamyl-Se-methylselenocysteine, selenocysteine, selenic acid, selenoxide, Se-methyl-selenomethionine, selenocystathionine, dimethyl diselenide, selenosinigrin and selenopeptide. However, analysis in animal-based foods showed Se-Cys, selenotrisulfides of cystine, selenate and selenite[34]. Some selenium compounds and theirs structural formulas have been demonstrated in Table 2. The report of the US Food and Nutrition Board[19] mentioned that the most dietary selenium was highly available and selenomethionine from plant and animal accounted for half of the dietary selenium with a bioavailability of more than 90%. For selenocysteine from animal source, it might be absorbed very well. As inorganic form, approximately 100% of selenate was absorbed with loss of some fractions in urine whereas more than 50% of selenite was absorbed and less excretion in urine than selenate. However, other dietary components and some heavy metals have been described as influencing factor on selenium bioavailability and function. According to role of enzyme glutathione peroxidase, selenium could interact with other nutrients affecting imbalance between free radical generation and antioxidant system in cells. In particular, prevention of lipid peroxidation will occur in high effectiveness with sufficient vitamin E and selenium because of synergistic antioxidant properties. Interactions of selenium with heavy metals such as cadmium, and mercury can lead to decreased toxicity of these metals by formation complex as inert metal selenide. On the other hand, these bindings of selenium and metals may reduce the bioavailability of selenium from foods[35]. For selenium supplementation, degree of bioavailability is influenced by some factors, including dose, physicochemical form, time of taking the supplements in fasting or meal conditions, interaction with other drugs and nutrients. Lacour et al. (2004) also proposed dietary factors resulting in abnormal selenium bioavailability in supplements such as types and quantity of amino acid, protein, polysaccharides, fiber, oxalate, and phytate[36]. In summary, factors affecting selenium bioavailability in human include chemical properties, interaction with some heavy metals and nutrients, as well as health status (such as inflammation, and abnormal

Table 2 Various structures of selenium compounds

Type	Structure	Type	Structure
Selenoprotein		Se-methionine	
Selenobetaine		Se-cysteine	
Selenate		Se-cystine	
Selenite		Methylselenite	
Se-homocysteine		Se-adenosyl-homocysteine	
γ-glutamyl-Se-methylselenocysteine		Trimethylselenium ion	

of nutritional metabolism). Based on these relevant data, the identification and/or quantification of selenium species and evaluation of factors affecting selenium requirements will increase knowledge and supporting relevant issues of this element in nutrition, toxicology and clinical disciplines.

Selenoproteins and biological functions in health and disease

It has been recognized that selenium is a component of selenoproteins with various biological functions. Glutathione peroxidase (GPx) is selenium-dependent enzyme with selenocysteine at the active site. This enzyme plays an important role in protection of oxidative stress via the detoxification of hydrogen peroxide, specifically by catalyzing the reduction of hydrogen peroxide into water. The different

isoforms are expression in various sites and least four isoforms have currently been identified as GPx1 in erythrocyte and cytosolic, GPx2 in gastrointestinal tract, GPx3 in plasma and GPx4 in intracellular fluid. For GPx1-3, theirs functions mostly are related to scavenging of hydrogen peroxide and organic hydroperoxide whereas GPx4 function directly to detoxify phospholipid hydroperoxides and cholesterol hydroperoxides[1]. Moreover, these peroxidases have potential influence on immune system which related to neutrophil function. Study of neutrophils from animals with selenium-deficiency found that neutrophils could ingest pathogens *in vitro* but less than those with selenium-sufficiency. Dysfunction has been associated with decreased cytosolic GPx1 activity in the neutrophils, which cause excess reactive oxygen metabolites (superoxide, O_2-and hydrogen peroxide, H_2O_2) produced in the respiratory burst to kill neutrophils themselves[37]. Bierl et al. (2004), suggested that GPx3 acts as one of the key antioxidant enzymes in plasma and could be used as a functional parameter in assessment of selenium status and its deficiency has been linked to CVD and stroke[2]. Measurement of activity or expression of GPx is accepted for selenium status assessment in research and clinical issues. Increasing attention in genetic polymorphism of GPx are observed with risks of diseases, including metabolic disease, CVD and cancers.

For thioredoxin reductase (TrxR), it is also classified as Se-dependent enzyme and three isoforms found in human; TrxR1 in cytosolic, TrxR2 in mitochondria and TrxR3 (or thioredoxin glutathione reductase) in testis. In addition, thioredoxin and NADPH are important components of thioredoxin system which is a major cellular redox system and responsible for detoxifying ROS in human[38]. In addition, TrxR is the only enzyme known to catalyze the reduction of thioredoxin which reduced Trx providing electrons to ribonucleotide reductase, essential for DNA synthesis, by converting ribonucleotide to deoxyribonucleotides. TrxR also takes part in various cellular signaling pathways which involves in regulation of transcription factors including NF-kB, activator protein-1 (AP-1), p53, and the glucocorticoid receptor[39]. Another enzyme is iodothyronine deiodinases (IDIs) that mainly catalyze the removal of an iodine residue from the pro-hormone thyroxine (T4) molecule, thus producing either the active form triiodothyronine (T3; activation) or inactive metabolites (reverse T3; inactivation)[40]. Three types of IDIs have different physiological activities. Type I is mainly expressed in liver and kidney and responsible for T3 levels in the blood stream. Cytokines, nutritional status, sex

steroids, and other factors also regulate D1 activity, although different organs often show different responses. For stage of stimulated thyroid gland, the transformation of T4 to T3 is done by activity of IDI type II. The IDI type III found in fetal tissue and placenta and also present throughout the brain. This isoform catalyzes the inner-ring deiodination of T(4) to reverse T(3) and T(3) to 3, 3'-diiodothyronine, both of which are biologically inactive. Considering serum thyroid hormone profile, it is partly determined by genetic background. Single nucleotide polymorphisms (SNPs) in the deiodinase genes can lead to the alteration of the phenotypic expression of these enzymes influencing the levels of thyroid hormone[41].

Based on antioxidant activities of selenoproteins, they indicated one potential mechanism of the beneficial health effects of selenium. The selenoprotein P (SelP) contains ten selenocysteine residues and functions as a Se transporter and it is mainly derived from hepatic sources. The mRNA can be detected in almost all tissues (kidney, heart, lung, brain, skeletal muscle, and testis)[42]. SelP constitutes more than 60% of plasma Se and this level can reflect selenium status because its alteration related to dietary selenium. For selenoprotein W (SelW), it has a selenocysteine residue at the active site and partly expression determined by selenium diet. Previous study reported that SelWwas required for epidermal growth factor (EGF) receptor (EGFR) that played important roles in modulate a complex network of intracellular signaling pathways controlling growth, proliferation, differentiation, and motility[43]. Selenoprotein N (SelN) is a 65-kDa transmembrane glycoprotein localized within the endoplasmic reticulum. Moreover, SelN is the only selenoprotein directly associated with a human genetic disease which mutations of this gene lead to SEPN1-related myopathy, a particular early-onset muscle disorder. Recent studies have identified SelN as a key protein in cell protection against oxidative stress and redox-related calcium homeostasis[44]. The selenoprotein S (SelS) is a thioredoxin-dependent reductase that can reduce its substrate hydrogen peroxide (H_2O_2) or other peroxidases and detoxify ROS-produced during the oxidative stress reaction. It is widely expressed in various tissues, including liver, skeletal muscle, adipose tissue, pancreatic islets, kidney and blood vessels. In addition, association between SelS and mechanisms-induced diseases have been purposed such as inflammation (by regulating the production of inflammatory factors such as IL-1β and IL-6), oxidative stress and endoplasmic stress[45]. From the mentioned data suggested that it might play roles in the pathogenesis and development of diabetes mellitus and atherosclerosis. Yu et al. (2016) also mentioned that SelS

expression in the liver, adipose tissue, and skeletal muscle promoted the pathogenesis and development of DM and insulin resistance, whereas overexpression of SelS in pancreatic islets protected pancreatic islet β cells from oxidative stress-induced injury[46].

Focusing on updated evidences suggests that low selenium intakes are involved in the high potential health risks related to inflammation response because of antioxidant and anti-inflammatory properties of selenium and selenoproteins. In signaling pathway related to the nuclear factor kappa-B (NF-κB), there has been observed that enhanced inflammatory response and its activation was significantly associated with interleukin-6 and TNF-α production. These conditions involved selenium metabolism because selenium may inhibit the activation of NF-κB by modulating selenoprotein genes expression. In addition, Se supplementation in chronic inflammation can restore the depleted hepatic and serum Se levels by increasing selenoprotein biosynthesis leading to suppressed CRP production thereby attenuating the inflammatory process. Moreover, high c-reactive protein levels in acute and chronic inflammatory stages have been reported with decreased selenium levels[47]. It is well known that GPx plays a major role in antioxidant system, especially in 3 mechanistic pathways; 1) reduction of hydrogen peroxides, lipid and phospholipid hydroperoxides and leading to inhibit the propagation of free radicals and ROS; 2) reduction in generation of hydroperoxide intermediates in the cyclo-oxygenase and lipoxygenase pathways and resulting in downregulate the production of inflammatory prostaglandins and leukotrienes; and 3) modulation of the respiratory burst, by removal of hydrogen peroxide and reduction of superoxide production[48]. In the human population, low selenium status has been associated with Keshan disease, a cardiomyopathy found in rural areas of China, and Kashin-Beck disease, a chronic endemic osteochondropathy found primarily in northeastern to southwestern China[49]. For selenium toxicity, an outbreak of acute selenium poisoning (~200 cases in USA) from a liquid dietary supplement with containing 200 times the labeled concentration of selenium has been reported. The median estimated dose of selenium consumed was 41,749 μg/d (recommended dietary allowance is 55 μg/d). Frequently reported symptoms included diarrhea (78%), fatigue (75%), hair loss (72%), joint pain (70%), nail discoloration or brittleness (61%), and nausea (58%). For more than three months after acute stage, some symptoms have also persisted such as

fingernail discoloration and loss (52%), fatigue (35%), and hair loss (29%)[50].

Conclusion

Selenium is a critical component of a number of selenoenzymes with antioxidative and anti-inflammatory properties, i.e. glutathione peroxidases or selenoprotein P, and thus may be important in preventing cancer and other chronic diseases. Based on various functions in human health, a greater challenge to more clarify the biological roles of the mammalian selenoproteins is mentioned. Another important issue is further investigation of the regulatory mechanisms responsible for selenium distribution, homeostasis and protective effects of additional selenium supplementation. Data from this point of view can lead to the optimal selenium intake for achieving the most beneficial effects. Moreover, genetic variability in selenoenzymes are associated with enzyme activity and a subsequent risk of diseases. Results from genetic studies both in animal and human will improve our understanding of the role of selenium in disease development and of the molecular mechanisms that underlie selenium effects.

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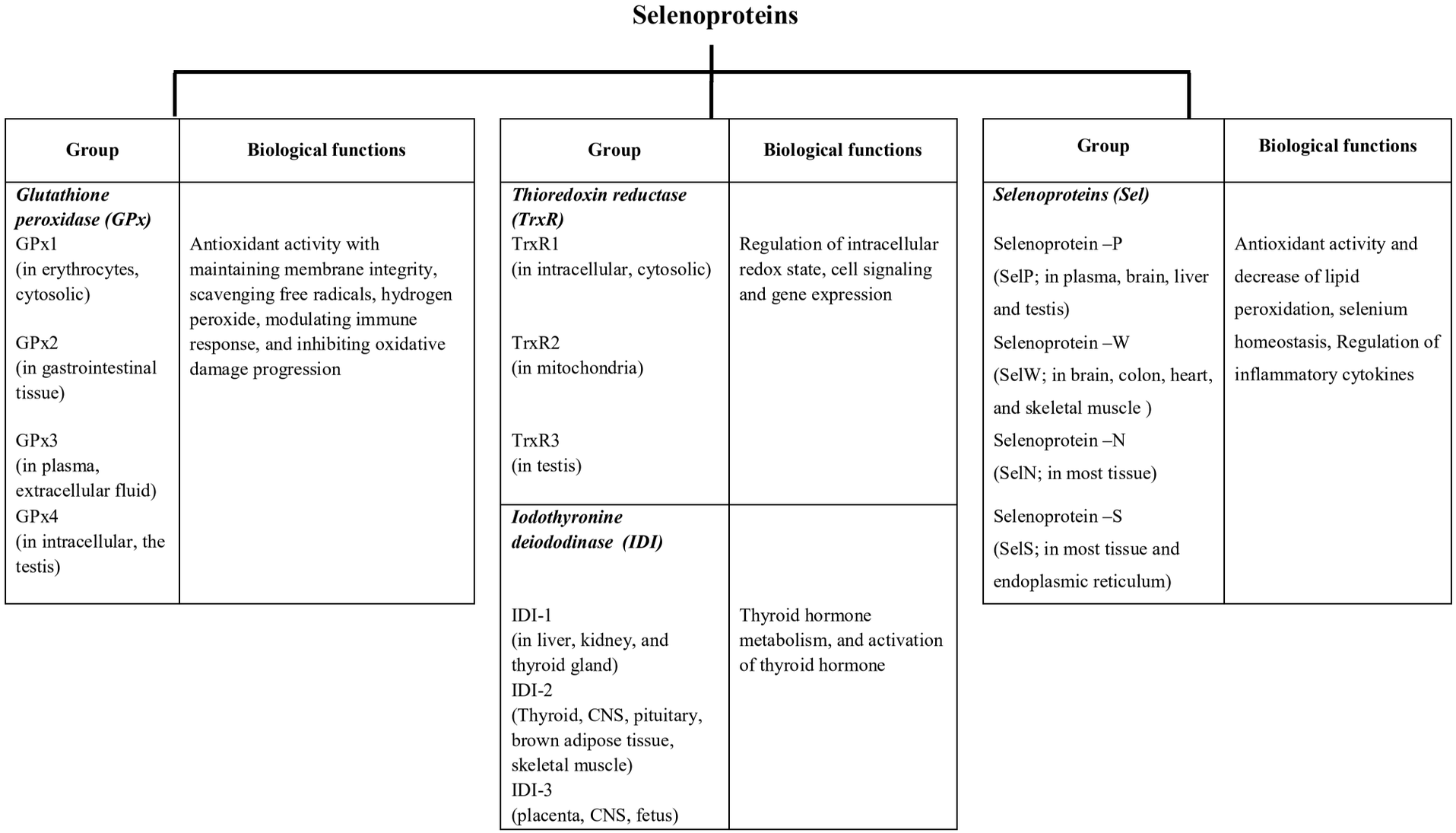

Group	Biological functions
Glutathione peroxidase (GPx)	
GPx1 (in erythrocytes, cytosolic)	Antioxidant activity with maintaining membrane integrity, scavenging free radicals, hydrogen peroxide, modulating immune response, and inhibiting oxidative damage progression
GPx2 (in gastrointestinal tissue)	
GPx3 (in plasma, extracellular fluid)	
GPx4 (in intracellular, the testis)	

Group	Biological functions
Thioredoxin reductase (TrxR)	
TrxR1 (in intracellular, cytosolic)	Regulation of intracellular redox state, cell signaling and gene expression
TrxR2 (in mitochondria)	
TrxR3 (in testis)	
Iodothyronine deiodinase (IDI)	
IDI-1 (in liver, kidney, and thyroid gland)	Thyroid hormone metabolism, and activation of thyroid hormone
IDI-2 (Thyroid, CNS, pituitary, brown adipose tissue, skeletal muscle)	
IDI-3 (placenta, CNS, fetus)	

Group	Biological functions
Selenoproteins (Sel)	
Selenoprotein –P (SelP; in plasma, brain, liver and testis)	Antioxidant activity and decrease of lipid peroxidation, selenium homeostasis, Regulation of inflammatory cytokines
Selenoprotein –W (SelW; in brain, colon, heart, and skeletal muscle)	
Selenoprotein –N (SelN; in most tissue)	
Selenoprotein –S (SelS; in most tissue and endoplasmic reticulum)	

Figure 2 Several human selenoproteins and biological functions