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Prioritized brain selenium retention and selenoprotein expression: Nutritional insights into Parkinson's disease

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ABSTRACT

Selenium (Se), an essential trace mineral, confers its physiological functions mainly through selenoproteins, most of which are oxidoreductases. Results from animal, epidemiological, and human genetic studies link Parkinson's disease to Se and certain selenoproteins. Parkinson's disease is characterized by multiple motor and non-motor symptoms that are difficult to diagnose at early stages of the pathogenesis. While irreversible, degenerative and age-related, the onset of Parkinson's disease may be delayed through proper dietary and environmental controls. One particular attribute of Se biology is that brain has the highest priority to receive and retain this nutrient even in Se deficiency. Thus, brain Se deficiency is rare; however, a strong body of recent evidence implicates selenoprotein dysfunction in Parkinson's disease. Direct and indirect evidence from mouse models implicate selenoprotein T, glutathione peroxidase 1, selenoprotein P and glutathione peroxidase 4 in counteracting Parkinson's disease through Se transportation to the brain and reduced oxidative stress. It is of future interest to further characterize the full selenoproteomes in various types of brain cells and elucidate the mechanism of their actions in Parkinson's disease.

1. Introduction

Selenium (Se) was long considered toxic until 1957 when this element was identified to account for the protection of a preparation known as "Factor 3" against liver necrosis in vitamin E-deficient rats (Schwarz and Foltz, 1957). In 1972, the first Se-dependent biochemical reaction was demonstrated with the use of erythrocyte hemolyzates for analyses of chromatographic fractions, showing co-existence of the enzymatic activity of glutathione peroxidase 1 (GPX1) and Se in rats injected with ^{75}Se-labeled sodium selenite (Flohe et al., 1973; Rotruck et al., 1973). Prior to 2003, a total of 18 human selenoprotein genes were individually discovered employing traditional molecular biology methods (Hatfield and Gladyshev, 2002). The completion of the historic Human Genome Project in 2003 enables genome-wide searches for 1) selenocysteine insertion sequence (SECIS) conserved among previously identified selenoproteins and 2) cysteine-containing homologs to verdict the total number of selenoproteins as 25 in humans and 24 in mice (Kryukov et al., 2003).

Selenoproteins specifically incorporate Se into nascent polypeptides from selenocysteine-tRNA that recodes the otherwise stop codon UGA as selenocysteine. The genes known as *Trsp* in rodents or *TRU-TCA1-1* in humans encode tRNA$^{[Ser]Sec}$, which is sequentially modified by seryl-tRNA synthetase (*SARS*), phosphoseryl-tRNA kinase (*PSTK*) and selenocysteine synthase (*SEPSECS*) for eukaryotic selenocysteine-tRNA biosynthesis. Synthesis of selenophosphate, the Se donor for selenocysteine synthase, is made through selenophosphate synthetase (*SPS*). These events are prerequisites for selenocysteine insertion, which requires the SECIS at 3′-untranslated region of selenoprotein mRNAs, selenocysteine-specific eukaryotic elongation factor (*EFSec*), and SECIS-binding protein 2 (*SECISBP2*) (Labunskyy et al., 2014; Xu et al., 2007). These *cis*-acting element and *trans*-acting factors are necessary and sufficient for eukaryotic selenoprotein expression (Gupta et al., 2013).

Body Se is distributed primarily to proteins in three forms and, to a much less extent, as compounds (Fig. 1). At nutritional levels of intake, Se is mainly incorporated into selenoproteins to exert its biological functions. In Se deficiency, selenoproteins are downregulated in a tissue- and selenoprotein-specific manner. While selenoproteins exist in all three domains of life, they do not exist in all species and their numbers vary, ranging from zero in the yeast Saccharomyces cerevisiae to 59 in the pelagophyte *Aureococcus anophagefferens* (Labunskyy et al.,

Abbreviations: GPX1, glutathione peroxidase 1; GPX4, glutathione peroxidase 4; Se, selenium; SECIS, selenocysteine insertion sequence; SELENOP, selenoprotein P

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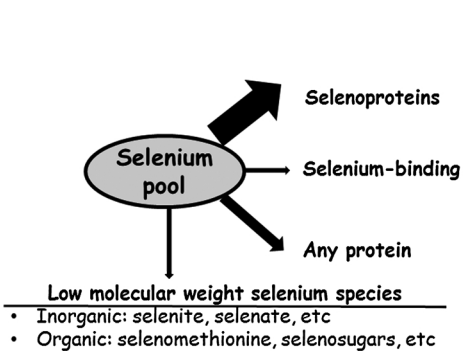

Fig. 1. Categories of selenium in biological forms. In forms of proteins, selenium can be 1) specifically incorporated into nascent polypeptides of selenoproteins by recoding UGA as selenocysteine; 2) specifically bound with a group of proteins known as selenium-binding proteins possibly through structural compatibility; 3) nonspecifically added to any proteins by replacement of sulfur on methionine and cysteine residues most often when selenium status is in excess. In addition, a small portion of selenium exists as selenium-containing chemicals either in inorganic or in organic forms.

2014). Interestingly, the fungal phyla was previously considered to be completely lack of selenoprotein, but recent evidence identifies selenoproteins in nine early-branching fungi and suggests an alternative SECIS-like RNA structure for selenocysteine incorporation (Mariotti et al., 2019). The second group of Se-containing proteins encompasses those that bind Se plausibly through structural compatibility but contain no selenocysteine residue. There are two such proteins known to exist, namely Se-binding protein-1 and 14-kDa fatty acid binding protein (Bansal et al., 1989a, b). Levels of these two nonselenoproteins do not change in response to fluctuations in body Se status. The third route of Se integration takes place on essentially all proteins post-translationally. Above nutritional needs, selenoprotein expression gradually reaches a plateau such that a good portion of Se replaces sulfur on methionine and cysteine residues of albumin in the plasma and, to a larger extent, any proteins in the body. Last but not least, a small portion of Se exists as low molecular weight species in forms of inorganic or organic chemicals, levels of which are believed to remain consistent regardless of Se status (Combs, 2015).

Brain is at the apex of the tissue hierarchy of Se and expresses all selenoproteins (Burk and Hill, 2015; Zhang et al., 2008). Results from rat studies on a Se-deficient diet show that while most organs lose up to 90% of Se, brain is phenomenally managed to retain > 75% of Se (Burk and Hill, 2015). This is consistent with the notion, to the best of our knowledge, that no neurological symptoms in humans are ascribed to Se insufficiency or found in patients of Keshan disease, a classic Se deficiency disorder. Nonetheless, it is noteworthy that while whole blood Se concentrations were reduced by as much as 83% in men diagnosed with Keshan disease at an average age of 27.6 (n = 22) in a Chinese cohort (Xia et al., 1989), it remains indefinable as to whether chronic Se deficiency predisposes them to neurodegenerative disorders later in life. In a comparative study analyzing selenotranscriptomes of adult mice, all 24 selenoprotein mRNAs were identified in all the 159 brain regions, with the expression of selenoprotein P (SELENOP), SELENOM, SELENOK, SELENOF, SELENOW and glutathione peroxidase 4 (GPX4) being the highest (Zhang et al., 2008). In particular, brain selenoproteins are expressed mainly in neurons and their roles in the prevention of seizures and neurodegeneration are considered to be particularly prominent (Wirth et al., 2010; Zhang et al., 2008). Thus, it was proposed that altered expression of and mutations in selenoproteins might be associated with certain forms of neuronal degeneration such as Parkinson's disease. As discussed below, such a perception has been increasingly supported by recent selenoprotein studies of human genetic mutations and with the use of novel knockout and knockin mouse models. This review discusses Se and key selenoprotein functions as they relate to the pathophysiology of Parkinson's disease.

2. Selenium and brain

An intuitive and interesting question is: Why and how is body Se prioritized to the brain? In 1991, the Burk Lab demonstrated prioritized delivery of Se to the brain in Se deficiency (Burk et al., 1991). SELENOP contains ten selenocysteine residues in humans and can be secreted to extracellular fluids, rendering this selenoprotein an ideal transporter of Se. From the functional perspective, SELENOP is the only selenoprotein carrying more than one selenocysteine residues (Labunskyy et al., 2014). While the second UGA of iodothyronine deiodinase 2 mRNA in humans has been reported to function either as a selenocysteine or a stop codon, only the upstream selenocysteine is essential for its enzymatic activity (Salvatore et al., 1999). There are also tissue-specific receptors of SELENOP at the blood-brain barrier that enable brain to be ranked the highest in the tissue hierarchy of Se (Burk and Hill, 2015). SELENOP accounts for 73% of total Se in plasma and is the major carrier of Se to the brain (Burk and Hill, 2015; Olson et al., 2010).

Dietary Se is stored in the liver as GPX1 and distributed to other tissues mainly through SELENOP. SELENOP enters peripheral tissues via endocytosis by binding to 1) low density lipoprotein-related protein 2, commonly known as LRP2 or megalin, at the blood-brain barrier and kidneys; 2) apolipoprotein E receptor 2 at the blood-brain barrier, Sertoli cells forming the blood-testis barrier, and brain neurons (Burk et al., 2007; Chiu-Ugalde et al., 2010; Hill et al., 2012; Olson et al., 2008, 2007). In the brain, SELENOP supplies Se for the expression of other selenoproteins in various areas, including Parvalbumin-positive interneurons that express high levels of selenophosphate synthetase 2 and are markedly sensitive to reduced selenoprotein function (Pitts et al., 2015). In particular, levels of SELENOP are not greatly reduced in response to Se deficiency because it ranks high in selenoprotein hierarchy; furthermore, SELENOP receptors are not selenoproteins such that their expression is independent of Se status (Fig. 2). As a consequence, SELENOP continues to effectively deliver Se to organs such as brain and testes highly expressing its receptors at the expense of others when Se status is suboptimal or even deficient. The brain and testes further compete for Se, as castration in *Selenop*$^{-/-}$ mice increases brain Se content and alleviates their neurological phenotypes (Pitts et al., 2015). In mice, GPX4, SELENOF, SELENOM, SELENOW and SELENOP are abundant selenoproteins across cerebellum, substantia nigra, cortex, pons and hippocampus through a selenotranscriptomic analysis (Zhang et al., 2016). Altogether, Se retention is prioritized to the brain under Se-deficient conditions through apolipoprotein E receptor 2- and megalin-mediated endocytosis of SELENOP.

Mutations in selenoprotein genes and those for selenoprotein biosynthesis have been discovered in patients with neurodegenerative and other disorders in recent years. Frameshift and truncation mutations in *GPX4* cause Sedaghatian type of spondylometaphyseal chondrodysplasia, an autosomal disorder displaying an array of neurological and other phenotypes (Smith et al., 2014). An inactivating point mutation of *TXNRD1* (Pro190Leu) reduces its enzymatic activity and the patients display genetic generalized epilepsy (Kudin et al., 2017). Because mice null in *Gpx4* or *Txnrd1* die as embryos (Bondareva et al., 2007; Imai et al., 2003; Jakupoglu et al., 2005; Yant et al., 2003), hypomorphic mutations in these two genes in humans are invaluable for understanding their physiological functions. Likewise, deletion of any of the genes for selenocysteine biosynthesis in principle influences the

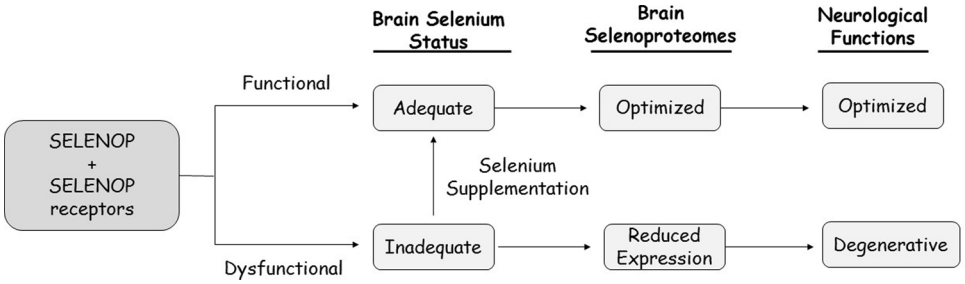

Fig. 2. A diagram of impacts of selenium status, SELENOP and its receptors on Parkinson's and other neurodegenerative diseases. Optimized neurological functions can generally be maintained irrespective of adequate or marginally inadequate intakes of dietary selenium. If SELENOP, apolipoprotein E receptor 2, or megalin manifests reduced expression or functional abnormality, brain selenium status is reduced due to a hampered selenium delivery to cross the blood-brain barrier and enter neurons with the brain. Under such circumstances, selenium supplementation at levels exceeding nutritional needs could improve selenium status to an adequate level in the brain. Otherwise, there is insufficient selenium to support full expression of selenoproteoms such that the brain eventually is prone to early onset of neurodegeneration. As elaborated in Section 4.2, knockouts of SELENOT or GPX1 render the mice hypersensitive to neurotoxins that induce loss of dopaminergic neurons, a hallmark of Parkinson's disease.

expression of all selenoproteins and thus is detrimental. For instance, knockout of $tRNA^{[Ser]Sec}$ (Bosl et al., 1997) or SECIS-binding protein 2 (Seeher et al., 2014a) in mice leads to embryonic death. However, hypomorphic mutations in these genes are not lethal and result in partial loss of selenoproteome and a spectrum of disorders. In patients carrying a missense or a Thr325Ser mutations in *SEPSECS*, they have reduced expression of brain GPX1, GPX4, TXNRD1, and TXNRD2 and display neurological symptoms including cerebellocerebral atrophy and seizures (Anttonen et al., 2015). In contrast, a homozygous C65G mutation in *TRU-TCA1-1* reduces the expression of SELENOW and GPX1, but not GPX4 or TXNRD1, and the patient was not reported to display discernible neurological symptoms (Schoenmakers et al., 2016). These results further support critical neurological roles of GPX4 and TXNRD1. It is of future interest to determine whether other selenoproteins participate in neurological maintenance. An array of human mutations in selenoprotein genes and others for selenocysteine biosynthesis, together with their neurological and other phenotypes, can be found in recent reviews (Labunskyy et al., 2014; Schweizer and Fradejas-Villar, 2016).

Comparative gene expression analyses of selenoproteins and related factors point to neurons as the most important cells for Se function in the brain (Zhang et al., 2008). While elimination of Se in the brain or whole body is technically impossible and consequently lethal, there are experimental approaches to remove essential selenoprotein or even all selenoproteins in a tissue-specific manner. Either $Trsp^{-/-}$, $Secisbp2^{-/-}$, or $Gpx4^{-/-}$ mice die as embryos (Imai et al., 2003; Seeher et al., 2014a; Yant et al., 2003). However, neuron-specific $Trsp^{-/-}$ mice are normal at birth, followed by appearance of such phenotypes as growth retardation and neurological symptoms including seizures, ataxia and loss of parvalbumin-positive interneurons (Wirth et al., 2010). These results suggest that Se confers one of its essential roles to neuronal protection by selenoproteins. Because whole-body and neuron-specific $Gpx4^{-/-}$ mice phenotypically recapitulate those of $Trsp^{-/-}$ mice, GPX4 was proposed as a pivotal, if not the most important, selenoprotein in the brain (Wirth et al., 2010). Moreover, neuron-specific $Secisbp2^{-/-}$ mice express reduced levels of brain selenoprotein and display neurological symptoms including seizures and increased loss of parvalbumin-positive interneurons (Seeher et al., 2014b). These results further support essential roles of selenoproteins in the maintenance of neurological integrity. Altogether, retention of Se in the brain enables optimized selenoprotein expression and neurological functions (Fig. 2). This review focuses on recent advances in studies employing mouse models to explore functions of selenoproteins in the pathophysiology of Parkinson's disease. Selenoproteins that are involved in other neurological symptoms have been reviewed elsewhere (Gong et al., 2018; Pitts et al., 2014).

3. Parkinson's disease

Parkinson's disease, the second-most common neurodegenerative disorder progressively affecting 2–3% of the population ≥65 years of age, is characterized by multiple motor and non-motor symptoms. Motor features include loss of dopaminergic neurons and accumulation of the α-synuclein-containing Lewy bodies in substantia nigra pars compacta (Kalia and Lang, 2015). Non-motor symptoms, including cognitive impairment, psychiatric signs and autonomic dysfunction, usually occur at advanced stage. While there is no specific biomarker available, Parkinson's disease is routinely diagnosed according to clinical characteristics such as resting tremor, rigidity, bradykinesia, abnormal gait, and postural instability. Therefore, correct diagnosis of Parkinson's disease relies greatly on clinical experience of the physician in these physical examinations, although imaging and blood tests can be performed as auxiliary tools to rule out other diseases that share common symptoms. While loss of dopaminergic neurons and accumulation of Lewy bodies are hallmarks of Parkinson's disease, they are largely immature or inapplicable for clinical diagnosis. For instance, although single-photon emission computed tomography has been used to track the activity of dopamine transporter as a marker of the loss of dopaminergic neurons in striatum, there are concerns on the radioactive nature, cost, and even accuracy (Saari et al., 2017). Another diagnostic concern is that Parkinson's disease patients are usually classified as advanced stages during their initial visits of a neurologist when they already lose > 50% of total dopaminergic neurons in the substantia nigra. Thus, there is an urgent need to develop reliable biomarkers for Parkinson's disease targeting early stages. Meanwhile, medications such as those that increase dopamine levels or inhibit its breakdown can be administrated to alleviate symptoms of Parkinson's disease. Individuals with advanced Parkinson's disease may be considered for surgical procedures by deep brain stimulation. From a biochemical perspective, increased oxidative stress and mitochondrial dysfunction usually occur during the pathogenesis of Parkinson's disease (Hauser and Hastings, 2013). As such, the link between selenoproteins and Parkinson's disease is rationalized considering that most selenoproteins are demonstrated or predicted to be oxidoreductases and some are located in the mitochondria or can modulate mitochondrial functions (Labunskyy et al., 2014).

Many molecular and biochemical changes are known to contribute to or be associated with the progression of Parkinson's disease. More than 20 disease-causing mutations have been found in inheritable Parkinson's disease, some of which are listed in Table 1. Autosomal dominant Parkinson's disease includes those with mutations in *SNCA*, *LRRK2*, *VPS35* and *GBA*. Mutations in *PRKN*, *PINK1* and *PARK7* (also known *DJ1*) are autosomal recessive in familial Parkinson's disease. In addition, non-genetic factors such as exposures to environmental neurotoxins are known to participate in the pathogenesis of Parkinson's disease. Except for a physical interaction between *GPX4* mRNA and PARK7 protein (van der Brug et al., 2008), other selenoproteins are not known to be associated with any of the key Parkinson's disease-related genes or proteins. However, methionine sulfoxide reductase A, not a selenoprotein but a homolog of the selenoprotein methionine sulfoxide reductase B1, is known to suppress dopaminergic cell death and protein

Table 1
Key genes in familial Parkinson's disease and impacts of the genetic changes[a].

Genes	Inheritance	Pathological consequences with mutations	References
SNCA	Autosomal dominant	Accumulation of α-synuclein is found in Lewy bodies and other areas.	(Polymeropoulos et al., 1997)
LRRK2	Autosomal dominant	The most common Gly2019Ser mutation results in increased kinase activity of LRRK2 and accounts for 4% of familial and 1% sporadic Parkinson's disease.	(Healy et al., 2008)
VPS35	Autosomal dominant	*VPS35* encodes vacuolar protein sorting 35 for protein trafficking. Mice with *Vsp35* knockout display impaired striatal dopamine release.	(Ishizu et al., 2016; Lin et al., 2018)
GBA	Autosomal dominant	Defective β-glucocerebrosidase is associated with lysosomal-autophagy dysfunction in Gaucher disease, patients of which have a greatly increased risk of developing Parkinson's disease.	(Anheim et al., 2012)
PRKN	Autosomal recessive	Loss-of-function mutations in *PRKN* (also known as *PARK2*), encoding the Parkin RBR E3 ubiquitin protein ligase important for protein degradation in lysosomes and proteasomes, are the most common cause of autosomal recessive Parkinson's disease.	(Kitada et al., 1998)
PINK1	Autosomal recessive	*PINK1* encodes a serine/threonine kinase. Together with Parkin, they play important roles in mitophage to prevent the accumulation of damaged mitochondria in Parkinson's disease.	(Gladkova et al., 2018)
PARK7	Autosomal recessive	*PARK7* encodes a peroxiredoxin-like peroxidase whose mutations are also implicated in mitochondrial death in the neurons of Parkinson's disease.	(Andres-Mateos et al., 2007)

[a] Abbreviations and their full protein names of the listed genes: SNCA, synuclein alpha; LRRK2, leucine rich repeat kinase 2; VPS35, vacuolar protein sorting 35; GBA, glucosylceramidase beta; PINK1, PTEN (phosphatase and tensin homolog) induced kinase 1; PARK7, Parkinsonism associated deglycase.

aggregation in the presence of mutant α-synuclein (Liu et al., 2008). Furthermore, because oxidative damage and genome instability are common defects in Parkinson's disease, selenoproteins capable of redox-regulation and DNA-binding (Zhang et al., 2018) are plausible mediators of such neurodegenerative disorders.

4. Role of selenium and selenoproteins in Parkinson's disease

4.1. Selenium

Dietary Se deficiency in mice is not known to induce spontaneous neurological phenotypes (Burk and Hill, 2015); nonetheless, this does not suggest that Se is a dispensable component for brain functions. Rather, brain is considered to be the most important functional site of body Se because this organ has the highest priority to receive Se even in Se deficiency (detailed in Section 2). Consistent with this notion, many animal studies have suggested an inverse association between Se status and Parkinson's disease-like symptoms upon exposure to neurotoxins. For instance, dietary Se deficiency is known to aggravate toxicities of 1-methyl-4-phenylpyridinium or methamphetamine in the dopaminergic neurons of mice and rats (Kim et al., 1999; Vizuete et al., 1994). Conversely, intraperitoneal injection of sodium selenite (3 mg/kg) 30 min prior to that of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (30 mg/kg) renders the mice less vulnerable to depletion of striatal dopamine (Khan, 2010). Addition of sodium selenite to drinking water (11.2 μg/L) attenuates paraquat (10 mg/kg)-induced locomotor damage in male rats (Ellwanger et al., 2015). These neurotoxins are known to induce various forms of oxidative damage, which could presumably be counteracted by the glutathione peroxidase and thioredoxin reductase activities of many selenoproteins. Nonetheless, these neurotoxins induce Parkinson's disease-like symptoms during a short period of time such that the pathogeneses may not necessarily recapitulate what occurs during the aging process. Furthermore, Se, especially in inorganic forms, at levels exceeding nutritional needs is known to induce oxidative stress and only marginally increases the expression of selenoproteins (Combs, 2015; Sunde and Raines, 2011). Altogether, it is interesting to pinpoint key selenoproteins and elucidate the mechanism that account for the protection of Se against chemical-induced damage in dopaminergic neurons.

There are mixed reports regarding Se status in patients of Parkinson's disease. Results of the InCHIANTI study (1012 Italians ≥65 years of age) (Shahar et al., 2010), a Tunisian study (84 participants, 62% ≥60 years of age) (Younes-Mhenni et al., 2013), and an American study (110 residents in Seattle) (Mischley et al., 2012) collectively show no association between plasma Se concentrations and Parkinson's disease. Nonetheless, low concentrations of plasma Se are associated with weak performances in neurological tests assessing coordination and motor speed according to the InCHINTI study (Shahar et al., 2010). In contrast, we have previously demonstrated that plasma Se concentrations are increased in patients with idiopathic Parkinson's disease based on a cohort of 540 participants (59% ≥65 years of age) in eastern China (Zhao et al., 2013). Overall, these seemingly different results may be plausibly ascribed to such confounding factors as race, diet, and environment that are intrinsic to human studies. Furthermore, interactions between Se and other minerals may influence pathogenesis of Parkinson's disease. In two of the above referenced reports (Shahar et al., 2010; Zhao et al., 2013), plasma copper concentrations are reduced in Parkinson's disease. Moreover, copper deficiency could reduce enzymatic activity of the Se-dependent glutathione peroxidase in rats (Arthur et al., 1987; Jenkinson et al., 1982).

4.2. Selenoproteins

Results of our selenotranscriptomic analyses reveal differential expression of brain selenoproteins in a mouse model of Parkinson's disease (Zhang et al., 2016). While 17 selenoproteins are downregulated and none is upregulated in the substantia nigra, there are mixed patterns of induced and suppressed expression of selenoprotein mRNAs in the cerebellum, cortex, hippocampus and pons. This suggests that the majority of selenoproteins in substantia nigra play critical roles to modulate Parkinson's disease. As detailed below, this notion is supported by physiological evidence generated from the use of mouse models with innovative manipulations of selenoprotein genes.

4.2.1. Selenoprotein T

SELENOT, a member of the thioredoxin-like family of selenoproteins, resides mainly in the endoplasmic reticulum and is highly conserved during evolution (Anouar et al., 2018; Boukhzar et al., 2016; Zhang et al., 2019). SELENOT expression is high in embryos and endocrine tissues within 1 week after birth (Tanguy et al., 2011). Results of many studies implicate SELENOT in endocrine regulation because this selenoprotein is necessary for the maturation and secretion of hormones from pituitary cells in response to endoplasmic reticulum stress (Hamieh et al., 2017) and from β cells for glucose homeostasis (Prevost et al., 2013). Interestingly, SELENOT is evolved relatively fast during evolution across ten species (Zhang et al., 2019), indicating that the expression level of this selenoprotein is low according to the current understanding of evolutionary biology (Zhang and Yang, 2015). In cells, SELENOT is known to counteract oxidative stress in the neuroblast-like SH-SY5Y cells treated with 1-methyl-4-phenylpyridinium (Boukhzar et al., 2016), suggesting a role in Parkinson's disease.

Together with GPX1, SELENOT is the only other selenoprotein

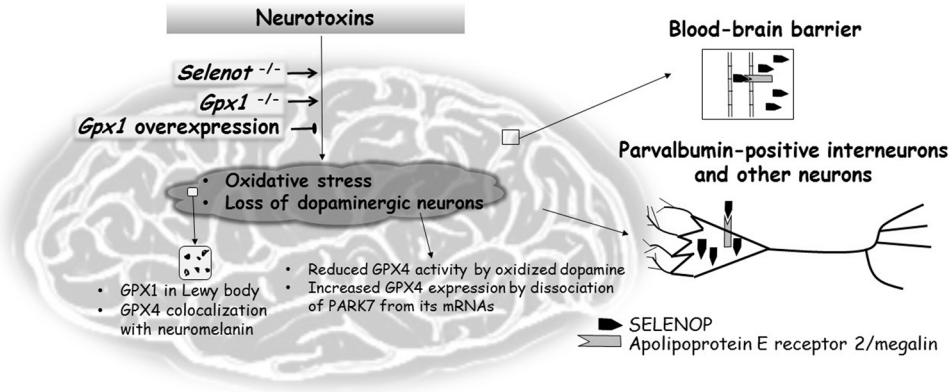

Fig. 3. Current evidence of the selenoprotein involvement in Parkinson's disease. After crossing the blood-brain barrier through apolipoprotein E receptor 2- and megalin-mediated endocytosis, SELENOP distributes its Se for the expression of brain selenoproteins. Apolipoprotein E receptor 2 is also expressed on Parvalbumin-positive interneurons (illustrated) and other neurons. Results of mouse studies demonstrate protective roles of SELENOT and GPX1 in response to neurotoxins that induce oxidative stress and loss of dopaminergic neurons. Results of molecular and cellular studies indicate 1) roles of GPX1 in Lewy body and interactions of GPX4 with neuromelanin; 2) reduced GPX4 activity by oxidized dopamine in the mitochondria and upregulation of GPX4 expression upon dissociation of its mRNA transcripts from PARK7 protein.

currently known to protect against Parkinson's disease on the basis of knockout mouse models. While whole-body *Selenot* knockout in mice results in embryonic death, nerve cell-specific *Nes-Cre/Selenot*$^{fl/fl}$ knockout mice show increased oxidative stress and exacerbated loss of dopaminergic neurons upon 1-methyl-4-phenylpyridinium treatment, a neurotoxin that can induce the death of dopaminergic neurons in the substantia nigra (Boukhzar et al., 2016). These results suggest protective roles of SELENOT in Parkinson's disease through redox regulation, although the underlying mechanism awaits further investigation.

4.2.2. Glutathione peroxidase 1

In contrast to SELENOT, GPX1 is ubiquitously expressed and *Gpx1*$^{-/-}$ mice are fertile and display no or little age-related phenotypes except cataracts (Ho et al., 1997). Nonetheless, *Gpx1*$^{-/-}$ mice are hypersensitive to paraquat (Cheng et al., 1998; de Haan et al., 1998), a prooxidative herbicide recently being demonstrated to be a strong inducer of Parkinson's disease based on a systems biology study of CRISPR screening (Reczek et al., 2017). In fact, it was observed two decades ago that *Gpx1*$^{-/-}$ mice intraperitoneally injected with high levels of paraquat died within 4–6 h in company with severe motor symptoms and increased oxidation of protein, lipids, NADH and NADPH in the liver and lungs, as compared to wild-type mice that survived 3 days (Cheng et al., 1999, 1998). Furthermore, GPX1 is known to localize in Lewy bodies (Power and Blumbergs, 2009) and its overexpression mitigates loss of tyrosine hydroxylase-positive dopaminergic neurons in substantia nigra and striatum in mice intracerebroventricularly injected with the neurotoxin 6-hydroxydopamine (Bensadoun et al., 1998). Moreover, *Gpx1*$^{-/-}$ mice treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine are prone to dopamine depletion and exhibit increased 3-nitrotyrosine formation in the striatum (Klivenyi et al., 2000). Thus, GPX1 may be protective at normal levels and beneficial when overexpressed to maintain dopaminergic neurons, implicating this H_2O_2-decomposing selenoprotein in the protection against Parkinson's disease upon exposure to certain environmental neurotoxins through redox regulation.

4.2.3. Selenoprotein P

Considering that SELENOP plays pivotal roles in the delivery of Se to the brain and subsequently releasing Se for the synthesis of all brain selenoproteins, SELENOP in principle could participate in all the Se-dependent neurological maintenance. Consistent with this notion, while poor motor coordination and seizures are characteristic of *Selenop*$^{-/-}$ mice, they are not limited to Parkinson's disease (Hill et al., 2003, 2004; Schweizer et al., 2004). Interestingly, these neurological phenotypes can be alleviated by additionally providing *Selenop*$^{-/-}$ mice with Se above nutritional needs (Fig. 2); however, how Se is delivered to the brain in the absence of SELENOP is not understood. Biochemically, SELENOP is known to exhibit phospholipid hydroperoxide glutathione peroxidase activity and be concentrated in Lewy bodies (Bellinger et al., 2012; Saito et al., 1999).

4.2.4. Glutathione peroxidase 4

GPX4 has substrate preference toward phospholipid hydroperoxides and is a key regulator of ferroptosis, a form of necrotic cell death characterized by iron-dependent lipid peroxidation (Seibt et al., 2019). The same as SELENOT, *Gpx4*$^{-/-}$ mice die as embryos, but neuron-specific *CamKIIα-Cre/Gpx4*$^{fl/fl}$ mice are viable and show phenotypes of atactic gait and seizures, loss of parvalbumin-expressing interneurons, and reduced capability to sense and transmit oxidative stress (Seiler et al., 2008). Remarkably, recent evidence demonstrates that the most important neuroprotective role of GPX4 is provided by Se of the selenocysteine residue necessary for its peroxidase activity (Ingold et al., 2018). With the use of an elegantly developed knockin mouse model through replacement of the selenocysteine residue of GPX4 by cysteine, these mice show similar neurodegeneration phenotypes as observed in the *CamKIIα-Cre/Gpx4*$^{fl/fl}$ mice (Ingold et al., 2018). This suggests that the oxidoreductase activity of GPX4 is indispensable in the protection against neurodegeneration. While a direct link between GPX4 and Parkinson's disease is lacking, such a view is supported by recent studies employing biochemical and cellular approaches. Evidence includes that 1) GPX4 co-localizes with neuromelanin in substantia nigra and its level is increased in dystrophic axons and cortex of the Parkinson's disease brain (Bellinger et al., 2011; Blackinton et al., 2009); 2) GPX4 expression is increased upon dissociation of PARK7 from its mRNA in response to oxidative stress (van der Brug et al., 2008); 3) oxidized dopamine is known to covalently target mitochondrial GPX4 and reduce its activity in dopaminergic neurons (Hauser et al., 2013).

5. Conclusions and future perspectives

As summarized and illustrated in Fig. 3, Se retention and selenoprotein expression are prioritized in the brain conceivably to mediate the pathophysiology of Parkinson's disease. With the use of genetically engineered mouse models, current evidence implicates SELENOT and GPX1, and plausibly SELENOP and GPX4, in the protection against Parkinson's disease. It is of future interest to conduct meta-analysis and large-scale human studies for better understanding the association between Parkinson's disease and Se status, particularly with the use of samples not only from plasma but also cerebrospinal fluid and even postmortem brains. Furthermore, analyses of selenoproteomes and Se concentrations in the entire brain of Parkinson's disease shall provide mechanistic insights into Se functions in this disease, although

selenotranscriptomes have been analyzed in the brain of a mouse model of Parkinson's disease (Zhang et al., 2016).

Given that results of animal and cellular studies point to protective roles of body Se and some selenoproteins against Parkinson's disease, it is intuitive to consider Se supplementation for optimal geriatric or neurological health. However, cautious considerations are needed because brain is at the top of the tissue hierarchy of Se such that Se supplementation, even to moderately deficient individuals, may not result in increased Se status or selenoprotein expression in the brain. Among the four Parkinson's disease-related selenoproteins discussed herein, even the low hierarchical GPX1 likely expresses sufficiently in the brain when the body Se status is suboptimal (Sunde and Raines, 2011). This is not to mention that levels of high hierarchical SELENOT, SELENOP and GPX4 in the brain are unlikely to be changed by Se supplementation in humans from a practical perspective. It is noteworthy to reiterate that brain Se status is unlikely or rarely to be low in humans worldwide by dietary deficiency because brain is a top organ to receive Se even in Se insufficiency. Furthermore, side effects of high Se status such as increased susceptibility to type-2 diabetes should be of particular concerns (Lei et al., 2016). At minimum, only those with severe Se deficiency or mutations in genes for Se delivery and selenoprotein synthesis may benefit from Se supplementation for optimized brain health; however, such abnormalities are extremely rare and careful considerations as to whether advantages outweigh disadvantages need to be prudently taken. It is thus interesting to also explore linkages of Se to Parkinson's disease and possibly other forms of neurodegeneration through mediators of Se metabolism and selenoprotein actions. For instance, dietary Se may interact with gut microbiota and mediate the secretion and circulation of their metabolites to impact brain functions. Such a gut-brain axis has recently been revealed (Sampson et al., 2016). This is a justifiable conjecture because 21.5% of sequenced bacteria express selenoproteins (Zhang et al., 2006); therefore, they may compete with the host for Se in the gut and/or secrete Se-dependent metabolites entering the gut-brain axis. Indeed, available lines of recent evidence strongly implicate the gut-brain axis in the pathogenesis of Parkinson's disease (Perez-Pardo et al., 2018; Sampson et al., 2016). Furthermore, selenoproteins may interact with other antioxidant proteins to modulate Parkinson's disease (Lei et al., 2016). Another noteworthy area of research is to pinpoint selenoprotein expression in various types of brain cells in Parkinson's disease.

All the four selenoproteins discussed herein are experimentally demonstrated to be antioxidative (Dikiy et al., 2007; Labunskyy et al., 2014). Thus, redox regulation appears to be central for selenoproteins to mediate the pathophysiology of Parkinson's disease displaying increased oxidative stress. Moreover, the selenocysteine residue and the CxxU motif, such as that of SELENOW, may bind 14-3-3 proteins (Jeon et al., 2016), which are highly expressed during neurogenesis (Cornell and Toyo-Oka, 2017). Furthermore, some selenoproteins, including the thioredoxin-like family members SELENOH, SELENOT and SELENOW, are known to be preferentially distributed in the brain or protect against Parkinson's disease in adult mice (Zhang et al., 2019). While the mechanism by which distinct selenoproteins modulate the pathogenesis of Parkinson's disease and a full list of them are far from being understood, current systems biology, biochemical, cellular, mouse and clinical data collectively advance our understanding in the unique and critical roles of brain Se and selenoproteins in Parkinson's and other neurodegenerative diseases.

Conflict of interest

Authors declare that there is no conflict of interest

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