Send Orders for Reprints to reprints@benthamscience.ae

282 *Current Neuropharmacology*, **2016**, *14*, **282-299**

Selenium in the Therapy of Neurological Diseases. Where is it Going?

Agnieszka Dominiak[1], Anna Wilkaniec[2,*], Piotr Wroczyński[1] and Agata Adamczyk[2]

[1]*Department of Bioanalysis and Drug Analysis, Medical University of Warsaw, 1 Banacha St., 02-097 Warsaw, Poland;* [2]*Department of Cellular Signaling, Mossakowski Medical Research Centre Polish Academy of Sciences, Pawińskiego 5 St., 02-106 Warsaw, Poland*

A. Wilkaniec

Abstract: Selenium ($_{34}$Se), an antioxidant trace element, is an important regulator of brain function. These beneficial properties that Se possesses are attributed to its ability to be incorporated into selenoproteins as an amino acid. Several selenoproteins are expressed in the brain, in which some of them, *e.g.* glutathione peroxidases (GPxs), thioredoxin reductases (TrxRs) or selenoprotein P (SelP), are strongly involved in antioxidant defence and in maintaining intercellular reducing conditions. Since increased oxidative stress has been implicated in neurological disorders, including Parkinson's disease, Alzheimer's disease, stroke, epilepsy and others, a growing body of evidence suggests that Se depletion followed by decreased activity of Se-dependent enzymes may be important factors connected with those pathologies. Undoubtedly, the remarkable progress that has been made in understanding the biological function of Se in the brain has opened up new potential possibilities for the treatment of neurological diseases by using Se as a potential drug. However, further research in the search for optimal Se donors is necessary in order to achieve an effective and safe therapeutic income.

Keywords: Antioxidative defence, inorganic selenium donor, neurological diseases, organic selenium donor, selenoprotein, therapy.

INTRODUCTION

Selenium ($_{34}$Se) is a trace element that is of fundamental importance to human health. In nature, this mineral occurs as a combination of organic and inorganic forms. Inorganic Se compounds, *i.e.* selenate (SeO_4^{2-}), selenite (SeO_3^{2-}) and selenide (Se^{2-}), are mainly present in water and soil, whereas the organic forms, selenomethionine (Se-Met) and selenocysteine (Sec), are synthesised in plants [1, 2]. Food is a considerable Se supplier, in particular brazil nuts, pork kidney and fish are known for their high Se concentration. The Se content greatly depends on regional soil, but it can be also modulated by food processing such as cooking, or roasting [3]. Humans suffer from health problems due to Se deficiency in areas that are poor in traces of this micronutrient [4]. Se is mainly consumed *via* food, which is a major source of organic Se at oxidation state II, which is better absorbed than the inorganic forms that are present in water. The total amount of Se in adult humans varies from between 10 to 20 mg and depends on many factors, such as place of living or health [3, 5].

The beneficial properties of Se are attributed to its ability to be incorporated in various proteins [6]. However, unlike other metals that are mainly co-factors of enzymes, Se becomes integrated into the polypeptide chain as part of the amino acid selenocysteine (Sec) [7]. In order to incorporate Se in the catalytic site of the protein chain, the organic form at oxidation level IV must be converted to an inorganic compound, hydrogen selenide. Se is co-translationally incorporated into the polypeptide chain at stop UGA codons located on mRNA. To ensure proper binding of Sec instead of termination of the translation process, mRNA encoding selenoprotein is required to contain a single, specific secondary stem-loop structure, called a selenocysteine insertion sequence (SECIS). Unlike the other 20 amino acids in the genetic code, Sec is synthesised universally on its own tRNA with the ACU anticodon (tRNA[Ser]Sec) by using serine as an intermediate (Seryl-tRNA[Ser]Sec) [8, 9] (Fig. **1**). A remarkable aspect of Sec biosynthesis is that this process requires the production of the active Se donor, monoselenophosphate (H_2Se-P), by selenophosphate synthetase (SPS2), which itself is a selenoprotein [10, 11]. Moreover, Se can be non-specifically incorporated into the polypeptide chain as a selenomethionine, by replacing sulphur in methionine. Finally, Se can be non-covalently bound by Se-binding proteins [12].

Most selenoproteins that contain Sec as an integral part of their polypeptide chain exhibit enzymatic activity that is dependent on the presence of Se in their catalytic domain. Based on the location of the Sec residue, mammalian selenoproteins can be divided into two groups. The first group, where Sec is located in the C-terminal region, consists of: thioredoxin reductases (TrxRs), selenoprotein I (SelI), selenoprotein O (SelO), selenoprotein R (SelR) and selenoprotein S (SelS). The second group, characterised by Sec in the N-terminal region, includes glutathione peroxidases (GPxs), iodothyronine deiodinases (Dios), selenophosphate synthetase (SPS2) and the other selenoproteins (Fig. **1**) [11, 13, 14]. Selenoproteins are involved in the regulation of

*Address correspondence to this author at the Department of Cellular Signaling, Mossakowski Medical Research Centre Polish Academy of Sciences, Pawińskiego 5 St., 02-106 Warsaw, Poland; Tel: +48 22 6086 600; Fax: +48 22 608 66 13; E-mail: awilkaniec@imdik.pan.pl

1570-159X/16 $58.00+.00

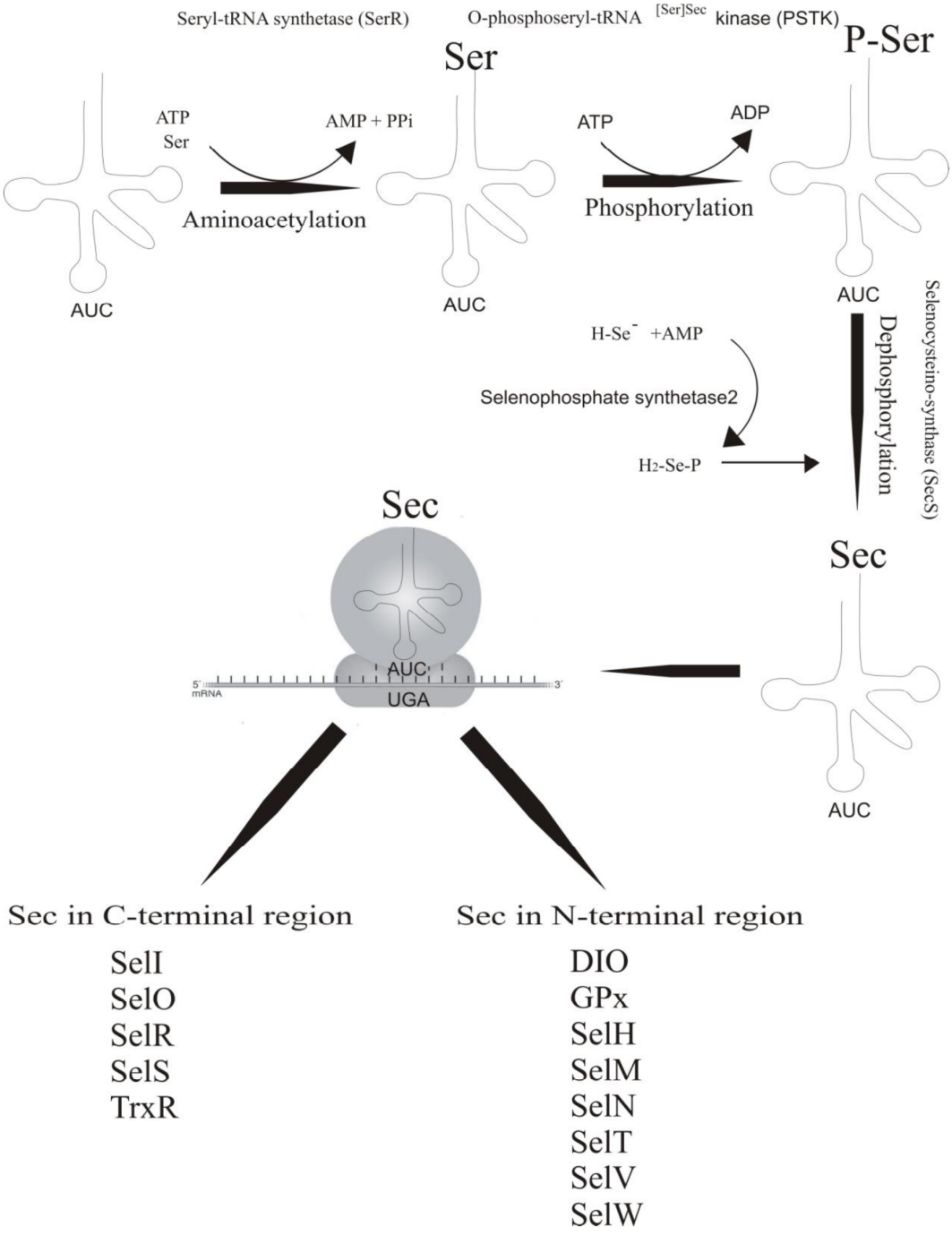

Fig. (1). Pathway of selenoprotein biosynthesis. Se-protein biosynthesis begins with the attachment of serine to Sec t-RNA, then Seryl-tRNA$^{[Ser]Sec}$ is phosphorylatedby phosphoseryl tRNA kinase and followed by replacement of phosphate by the Se donor selenide (H_2Se-P), yielding selenocysteyl-tRNA [Ser]Sec. The resulting selenocysteyl-tRNA [Ser]Sec molecule is a provider of Sec into the growing polypeptide chain. The Sec residue can be incorporated in the N-terminal or C-terminal region [10].

many cellular functions *e.g.* glutathione peroxidases are critical for cellular antioxidant defence (catalysing the reduction of organic hydroperoxides and hydrogen peroxide) [15], iodothyronine deiodinases regulate thyroid hormone activity [6], thioredoxin reductases are important in the regulation of gene expression and redox potential, cell proliferation as well as activation of the immune response [16].

Se-binding proteins also play an important role in maintaining cellular homeostasis. **Se-b**inding **p**rotein **1** (SeBP1) is implicated in detoxification processes [17], regulation of cellular growth [18], intra-Golgi protein transport [19] and lipid metabolism [20]. Other Se compounds, which are not related to proteins, have the ability to bind mercury [21], copper and iron [22], thus preventing the toxic effects evoked by these heavy metals

[23]. Moreover, selenite can regulate the generation ATP and stabilise the mitochondrial membrane potential [24].

Recent data have placed new emphasis on the long debated and largely unrecognised relationship between Se and brain physiology. However, the specific roles of selenoproteins for normal brain function and neurological diseases are to be elucidated. Here, we will review current findings in Se biology and in the impairment of selenoprotein activity in neurological disorders. We will primarily focus on the most common neurodegenerative diseases, whose incidence increases with age, *i.e.* especially Alzheimer's and Parkinson's diseases, but references to other diseases will also be presented here in order to shape a new view on the role of Se in the treatment and prevention of brain disorders.

SELENIUM AND SELENOPROTEINS IN NORMAL BRAIN FUNCTION

The human brain is characterised by a low (2,3%) content of Se [5]; however, it shows high priority for Se uptake in the case of its dietary deficiency. Even markedly decreased levels of Se in blood as observed in young rats on an Se-deficient 13-week diet, did not induce the significant changes in Se concentration in the brain [25]. The same result was observed in rats that were kept on a Se-deficient diet up to 6 generations. Although a drastic decrease in the level of Se in skeletal muscles, liver and blood was observed, only a small Se decline in the brain was reported in these animals [12, 26]. It was also shown that after injection of a radiochemical labelled SeO_3^{2-} in rats on basal feed devoid of Se, the highest uptake of the radiotracer (^{75}Se) was observed in the brain, in contrast to selenium-adequate nourished rats, where a quite ubiquitous distribution of ^{75}Se was observed [27]. It has been suggested that this priority of the brain to use up Se is probably due to its enhanced susceptibility to oxidative stress, caused by intensified oxidative metabolism and limited antioxidant defence [28].

High metabolic activity of the brain causes excessive production of reactive oxygen and nitrogen species. Uncontrolled rise of free radicals caused by the imbalance between their overproduction and enzymatic or non-enzymatic detoxification has deleterious multi-directional effects that, in consequence, cause cell death. Moreover, the brain is abundant in iron, a substrate for the Fenton reaction, and is rich in polyunsaturated fatty acids, *i.e.* the potential target for peroxidation. These make the brain a privileged organ requiring efficient ROS scavenging that is mainly mediated by selenoenzymes [29, 30]. The expression of 24 selenoproteins was identified in the mouse brain, especially in the hippocampus, olfactory bulb and cerebral cortex (Table **1**) [31]. Among these, the highest level was observed for GPx4 as well as SelP and SelW [2], thus suggesting their essential role in the central nervous system. Moreover, the expression and activity of selenoproteins in the brain depend on the amount of Se that is supplied, as some selenoproteins are constitutively expressed while others are induced. This creates a hierarchical ladder of selenoproteins in the brain, where those that are the most important for brain activity remain constant, irrespectively of external Se intake [32].

Glutathione Peroxidases

Twenty percent of total Se in the brain is incorporated in the glutathione peroxidase (GPx) family of enzymes [33], which are responsible for catalysing the reduction of hydrogen peroxide, organic hydroperoxides and phospholipid hydroperoxides to alcohol or water by using glutathione, mercaptoethanol, cysteine or other protein thiols as reducing co-substrates [34]. Until now, several isoforms of GPx with different localisations within the cell and substrate specificity have been identified in humans [35, 36]. GPx1 is a major cytoplasmic and mitochondrial antioxidant enzyme, GPx3 is present in the extracellular space and GPx4 is expressed as a cytosolic (c-GPx4), mitochondrial (m-GPx4) or nuclear (n-GPx4) isoform [34, 37]. From the whole family of GPxs, only two isoforms, GPx1 and GPx4, have been detected in the human brain, both in the neurons and in glial cells [38].

Table 1. Selenoproteins in the mammalian brain.

Function	Selenoprotein	Brain Localisation	Subcellular Distribution
Antioxidant enzymes	GPx1	microglia activated astrocytes neurons	cytosolic
	GPx4	neurons astroglia	cytosol and membrane- associated
	SelW	neurons	cytosol
Redox signalling	TrxR1	astrocytes neurons	cytosol mitochondria
	TrxR2	neurons	mitochondria
Metabolism of thyroid the hormone	Dio2	glial	membrane-associated
	Dio3	neurons	membrane-associated
Transport and storage of Se	SelP	neurons	secreted protein binds to heparin
Calcium regulation	SelM	neurons astrocytes	Golgi apparatus, endoplasmic reticulum

Brain locations, subcellular distributions and functions of selenoproteins (GPx - glutathione peroxidase, TrxR - thioredoxin reductases, Sel - selenoprotein, Dio - iodothyronine deiodinases) are presented here [2, 10, 45, 67, 81].

GPx1, a widespread selenoenzyme mainly expressed in astroglial cells, is responsible for detoxifying hydrogen peroxides and alkyl hydroperoxides, thus limiting their deleterious effects [36]. Decreased activity of this enzyme resulted in higher brain vulnerability to oxidative damage induced by various toxins. GPx1 knockout mice were shown to be more prone to paraquat toxicity, manifested by a marked increase in H_2O_2 release and caspase-3 activation, thus leading to neurological abnormalities. Hence, full GPx1 expression is necessary, although more beneficial to protect against oxidative stress and neuronal injury is overexpression of the GPx1 [39, 40]. On the other hand, overexpression of GPx1 in mice caused insulin resistance and obesity *via* reducing the intracellular ROS required for insulin sensitizing. It was associated with a reduction in the insulin-stimulated phosphorylations of the insulin receptor (β-subunit) and impaired protein kinase B activation [41].

GPx4 is mainly expressed in the cerebral cortex, cerebellum and hippocampus, especially as a cytosolic and mitochondrial isoform. Its regional expression differs between the time of embryogenesis and after birth [36]. Firstly, GPx4 mRNA exists in the neural tube and later in the neuroepithelium of the fore-, mid-, and hind-brain in the embryo [42]. During postnatal development, GPx4 mRNA is the highest at postnatal day 15, with a gradual decline thereafter [36]. This enzyme is involved in the elimination of phospholipid hydroperoxides, however its detailed role in the central nervous system is unknown. GPx4-deficient heterozygous mice develop normally, while homozygous embryos die *in utero* [43]. Overexpression of GPx4 has been shown to be protective against oxidative damage in several cell lines. Besides these antioxidative capabilities, GPx4 possesses antiapoptotic properties, since its selective knockdown by small interfering RNA (siRNA) was shown to activate caspase-3 dependent apoptosis of neuronal cells [43].

Thioredoxin Reductases

Thioredoxin reductases (TrxRs) are a family of antioxidative enzymes that use NADPH to catalyse the reduction of protein disulfides in a variety of macromolecules and molecules. There are 3 types of distinct TrxR genes in mammals: cytosolic thioredoxin reductase (TrxR-1), mitochondrial thioredoxin reductase (TrxR-2) and thioredoxin-glutaredoxin reductase (TrxR-3). Among these, TrxR-1 and TrxR-2 are present in neuronal tissue, where they are responsible for maintaining a proper redox status and are involved in brain development. Expression and activity of TrxR in the brain is strongly retained and does not respond to an Se deficiency in the diet. Aside from its antioxidative role, TrxR is involved in communication between cells, transduction of cellular signalling, DNA synthesis and transcription regulation [44-46]. Trx also plays an important role in cell viability and in the regulation of apoptosis *in vitro* [47, 48]. Inactivation of TrxR-1 in mouse embryos disturbs cell proliferation, causing retardation of neural tube closure and consequently their death *in utero* [45, 49]. Likewise, a mitochondrial redox protein Trx-2 is required for proper embryonic development and it is necessary for actively respiring cells. A Trx-2 deficiency was associated with anterior neural tube dysfunction and fetal growth retardation [50]. Moreover, *in vitro* studies showed that TrxR inhibitor treatment led to enhancement of the ROS level and activation of N-terminal mitogen kinase [51].

Selenoprotein P

SelP, a ubiquitously expressed extracellular glycoprotein, is a useful biomarker of Se status. SelPs are an unusual family that can incorporate multiple Sec residues, while other selenoproteins can integrate only one. Therefore, SelP has been postulated as being involved in both Se intercellular transport and storage [52, 53]. The N-terminal domain of SelP contains one Sec residue, while the other nine are located in the C-terminal. Additionally, SelP has a cluster of histidine and lysine which enables the protein to associate with cellular membranes. SelP binds heparin in a pH-dependent manner, which suggests its attraction to inflammation sites [33]. The primary source of plasma SelP is the liver, from where SelP is transported to peripheral tissues, including brain [54, 55]. Its role in the CNS is unique, because brain tissue can take up tracer Se in a form of SelP and is unable to take up directly radioactive molecule ^{75}Se [52]. Yet, recent data show that a deficiency of hepatic SelP does not affect brain Se levels, which indicates that this protein could be produced locally. Hence, as long as SelP expression in the brain is preserved, the Se level in the brain is independent of its plasma concentration [56]. Moreover, during Se deficiency, the brain unregulated Se level, using a specific uptake of SelP by the receptor for apolipoprotein E2 (ApoER2) [54, 55]. Extracellular SelP binds to ApoER2, which initiates endocytosis and enables the selenocysteine supply. Presumably, in those conditions astrocytes are the main source of extracellular SelP, which in turn is taken up by neurons using the ApoER2 [57, 33]. Aside from evidence that SelP serves to transport Se to brain tissue and to maintain its homeostasis, other suggesting function is a survival factor for neurons [58] as well as microtubule stabiliser. Fluorescence resonance energy transfer and immunoprecipitation assay have shown that SelP interacts with tubulin. Hence, SelP can play an important role in regulating the dynamic property of microtubules, which in turn determines cell polarity [59]. Genetic defects in this selenoprotein are associated with severe health issues. SelP−/−knockout mice display a neurological phenotype with subtle disruption of memory processes and spatial learning [60]. Moreover, other researchers have shown reduction in brain Se levels followed by a decrease in Se-dependent enzyme activity and impaired motor coordination in the same model [52, 61, 62]. Burk *et al*. confirmed that the knock-out of SelP or apoER2 significantly depleted the brain's Se pool [63]. However, a combination of SelP KO with a restrictive Se-deficient diet resulted in severe degeneration of brainstem axons as well as neurological dysfunction within days of having started the Se deficient diet [64, 65].

Other Selenoproteins

SelM is abundant in the brain, with the highest expression in the olfactory bulb and cerebellum. In the SelM

structure, there are thioredoxin-like domains and an active-site in the form of the CXXU motif, where C represents cysteine (Cys) and U represents selenocystein (Sec). This sequence is responsible for the formation of reversible selenenylsulfide bonds as well as it may also function as a redox regulator. SelM is involved in antioxidant function, [66], neuroprotection and regulation of intracellular calcium homeostasis [67]. In addition the neuroprotective function of SelM may result from its direct interaction with galectin-1. This mammalian lectinis widely expressed in the brain, where it regulates cell proliferation, differentiation as well as cell death [68].

SelW is highly expressed in the developing and adult brain [69, 70]. This smallest mammalian selenoprotein is widespread in cortical and hippocampal neurons, especially in dendrites and synapses both in the cytosol and plasma membrane [71]. Its expression in the brain is well maintained under Se deficits and is highly dependent on the SelP concentration. It was shown that SelP deficiencies resulted in greatly reduced levels of SelW expression in the brain [72, 73]. Like most selenoproteins, SelW is involved in maintaining redox homeostasis [74]. It binds to glutathione, acting as a glutathione-dependent antioxidant, and its overexpression reduces cellular sensitivity to hydrogen peroxide [75]. SelW was additionally shown to bind with 14-3-3 proteins β and χ and to regulate their oxidation state towards reduction. Since 14-3-3 proteins coordinate interaction of various kinases and phosphatases with receptors and structural proteins in neurons, SelW may indirectly regulate phosphorylation-dependent processes in the brain [76, 77]. Additionally, SelW is involved in p53- and p21-dependent regulation of the cell cycle [78, 79]. Knocking down SelW resulted in cell cycle arrest at the G1 stage *via* modulation of mitogen-activated protein kinase kinase 4 (MKK4) and MAPK signalling [78].

SelR is a crucial cytoplasmic and nuclear selenoprotein that contributes to neuronal antioxidant defence *via* scavenging reactive oxygen species. It is a member of the methionine sulfoxide reductases family type B (MsrB1) which catalyse the reduction of methionine sulfoxide (R-MetO) to methionine [80, 81]. SelR interacts with Trx and the chaperone protein clusterin, however, the role of this interaction is still unknown [82].

SELENIUM AND SELENOPROTEINS IN NEURO-LOGICAL DISORDERS

Since Se and selenoproteins have an important physiological function in neurons, astrocytes and microglia, their down-regulation or damage may lead to dysfunction of the brain. It was proved that the Se level in the brain shows a tendency to decrease during aging and is related to cognitive decline [83-85]. A 15-day Se-deficient diet decreased brain protection and as a result, significantly increased the dopamine turnover in SN concomitant with a decrease in GPx activity in the SN and striatum [86]. It has been suggested that Se deficiency may cause irreversible changes in the neurons, thus leading to cognitive impairment and neuro-degenerative diseases. Moreover, the genetic inactivation of selenoproteins leads to progression of pathology in CNS. Several Se compounds, such as sodium selenite, ebselen, or other organo-selenium donors have been shown to have promising therapeutic potential against neuropathology. Many studies *in vitro* and *in vivo* have postulated that Se is important to reduce oxidative stress and other detrimental agents in Alzheimer's and Parkinson's diseases as well as in epilepsy. Apart from direct antioxidative properties, Se was demonstrated to be involved in regulation of various abnormal molecular processes, that are common to all brain disorders.

A growing body of evidence suggest that mitochondria dysfunction, including increased mitochondrial fragmentation and decreased mitochondrial fusion, defects in oxidative phosphorylation, impaired calcium influx as well as mitochondrial membrane potential dissipation are associated with selective cell death [87]. Recently, it was demonstrated, that Se may regulate mitochondrial biogenesis and may improve mitochondrial function. Treatment of murine hippocampal HT22 cells with sodium selenite resulted in the increased of the level of PGC-1α (peroxisome proliferator-activated receptor gamma coactivator 1-alpha) and NRF1 (nuclear respiratory factor 1), as well as respiratory chain proteins: cytochrome c and cytochrome c oxidase IV (COX IV). This effect was shown to be independent from antioxidative properties of Se and, in general, lead to improvement of the mitochondrial respiratory rate [24]. The similar effect on mitochondrial level and function was observed in SelH overexpressing HT22 cells [88]. Moreover, the SelH elevated the mitochondrial biogenesis through activation of protein kinase A-CREB-PGC-1α and Akt/protein kinase B-CREB-PGC-1α pathways [89].

Apart from its stimulating effect on mitochondrial biogenesis, Se was also shown to regulate calcium homeostasis. Xu *et al*. demonstrated that Se-deficiency increased the intracellular calcium concentration in the brain of chicken, resulting in mitochondrial damage, fusion of nuclear membrane and nuclear shrinkage as well as apoptotic death of neuronal cells [90]. Moreover, treatment with selenium in a form of sodium selenite prevented the cellular calcium overload, oxidative damage and death of dorsal root ganglion (DRG) sensory neurons of rats [91]. Se was also speculated to have the important role in regulation of brain inflammation, since its deficiency resulted in the elevation of cytokines: tumor necrosis factor (TNFα), cyclooxygenase 2 (COX 2), inducible nitric oxide synthase (iNOS) and prostaglandin E (PGE) synthase level in different regions of chicken brain [92].

Additionally, one of the first studies in humans has confirmed Se participation in both prevention and treatment of brain diseases [93]. However, it remains controversial whether a high Se level is safe to human health. Some reports have showed that Se could have a cytotoxic effect by inducing nitric oxide synthase (iNOS), NO-liberation and activation of caspase-3 [94]. It was indicated that high doses of Se, through depletion of GSH, induced oxidative stress, which led to a decrease in cholinergic signalling and degeneration of cholinergic neurons [95]. More research has to be conducted to study the impact of Se on neurological diseases.

Alzheimer's Disease

Alzheimer's disease (AD) is a neurodegenerative disorder of the elderly which is characterised by deposition of amyloid β (Aβ) in extracellular senile plaques and hyperphosphorylated tau in intracellular neurofibrillary tangles (NFT) [96-98]. A clinical picture of the disease is manifested by progressive loss of memory and speech as well as by cognition and behavioural deficits [99]. According to the classical hypothesis, the neurotoxic effect of Aβ is mediated by excessive free radical liberation and disturbances in Ca^{2+} homeostasis [96, 100]. An imbalance between free radical formation and efficiency of the antioxidant system is responsible for the widespread occurrence of protein and lipid oxidation, nucleic acid damage and mitochondrial abnormalities [99]. In addition, transient or sustained mitochondrial complex dysfunctions resulting in massive leakage of ROS lead to further neuronal oxidative injuries. Oxidative stress and neuronal disturbances result in cytokine release and in the activation of microglial inflammatory processes [101, 102].

Studies in humans have suggested the possible role of Se in the prevention and treatment of AD, either alone or in combination with other elements [93]. Some research showed a direct correlation between the reduced plasma concentration of Se and the cognitive decline in AD patients when compared to healthy individuals [103]. The decline in Se levels in the plasma, observed in the early stage of AD, was independent of nutritional status [104, 105, 106, 107]. The Se level was also significantly decreased in AD brain tissue, especially in the hippocampus and frontal, parietal, temporal and occipital lobes [108, 109]. Inversely, the latest study showed a significant increase in Se levels in the globus pallidus, superior temporal gyrus, and frontal cortex of Alzheimer's disease patients [110]. Moreover, Gerhardsson *et al*. showed that the level of Se in the plasma and in cerebrospinal fluid from AD patients did not change when compared with the control group [111]. Despite these inconsistencies, which need to be further examined and interpreted, disturbances in selenoproteins, which are responsible for antioxidant defence in AD, have been better documented [112].

It was previously shown that changes in the GSH level and the increase of its oxidised form in the frontal cortex are associated with AD. This is probably connected with an increased level of peroxides that leads to activation of GPx which oxidises GSH to GSSG. Oxidised glutathione can be further reconverted to a reduced form by GR. Although the activity of GR was elevated in the hippocampus of AD mice [99, 113], it was unable to metabolise the whole pool of GSSG [112]. This leads to disturbances in the GSH/GSSG ratio shifting the balance to the oxidised form in the human AD brain [114]. Disturbances of GSH-dependent enzymes were confirmed in brain homogenates prepared from triple-transgenic mice with the PS1 $_{M146\ V}$, APP $_{Swe}$, and tau $_{P301L}$ mutation [115].

A noteworthy aspect is that in AD both the level and activity of other selenoenzymes are significantly altered. Overactivation of TrxR concomitant with the decrease of its substrate (Trx) were observed in the amygdala and cerebellum [116]. This is probably a compensation mechanism that is activated in order to prevent cells from oxidative stress. However, the decline in the Trx level was responsible for increased sensitivity to peroxynitrite [117], thus further exacerbating the process of neurodegeneration. Moreover, the level of SelM was significantly decreased in the brains of transgenic mice with human mutant presenilin-2 (N141I) [118, 119]. On the contrary, the concentration of SelP was significantly increased in the choroid plexus and the cerebrospinal fluid of AD patients, as compared to healthy controls, thus suggesting a higher brain Se requirement in order to prevent neurodegeneration [120]. A recent study of gene expression in AD determined that SelP was one of 240 genes upregulated in AD as compared to age-matched controls [121]. Additionally, SelP was detected in Aβ plaques and NFT tangles [118, 122]. Besides the important role of SelP and SelM in the global response to oxidative stress, they were shown to protect against transition metal-induced Aβ aggregation and toxicity [123, 124].

Although the Se and selenoprotein level is altered in the brain, cerebrospinal fluid and blood of patients with AD, and an association between Se status and cognitive function was observed, until now there has been no consistent clinical evidence showing the beneficial effects of Se supplementation in the treatment of AD. However, findings in molecular biology allow to make speculations on its potential preventive relevance. The treatment of rat hippocampal neurons with organo-Se-compounds- $(PhSe)_2$ and ebselen- had a protective effect against Aβ peptide toxicity and increased the level of SNAP-25, which is a marker of nerve terminals [125]. Supplementation with inorganic Se in a form of sodium selenite resulted in a significant reduction of lipid peroxidation and protein carbonylation in the cerebral cortex and hippocampus of rats after intracerebroventricular injection (ICV) with streptozotocin (STZ) [84]. Chronic administration of the inorganic Se compound as sodium selenate, characterized by less toxicity than selenite, was shown to reduce NFT formation and to prevent memory and motor deficits. These effects were mediated by the stabilisation of PP2A-tau complexes, thus resulting in a decrease in tau phosphorylation [126, 127]. Sodium selenate also attenuated the inhibition of PP2A and tau hyper-phosphorylation induced by traumatic brain injury [128]. Moreover, selenate treatment was shown to positively alter the phosphorylation status of key proteins involved in oxidative stress, energy metabolism and protein degradation in cellular model of AD as indicated in broad phospho-proteomics study. Apart from playing important roles in regulation of redox homeostasis, ATP generation, and misfolded proteins clearance, selenate-treatment also resulted in reduction of homocysteine, phospho-tau as well as Aβ levels [129].

In accordance with these data, SeMet treatment of triple transgenic AD mice ameliorated cognitive deficits by reducing the level of total tau and decreasing its phosphorylation *via* modulation of the expression and activity of PP2A and glycogen synthase kinase 3β. Moreover, the restoration of synaptic proteins, including synaptophysin and postsynaptic density protein 95 in the hippocampus and cortex, and inhibition of inflammatory

response were observed in these mice treated with SeMet [130]. A recent study has shown the therapeutic effect of the novel organic Se compound p,p'-methoxyl-diphenyl diselenide $(MeOPhSe)_2$ against oxidative-nitrosative stress caused by ICV-STZ. Supplementation with organic Se improved spatial learning and memory in rats after STZ administration. This beneficial effect observed in the rat cerebral cortex and hippocampus was mediated by a reduction of the ROS level and nitration of tyrosine residues [131]. Some data point to the protective effects of another organic Se compound, ebselen [2-phenyl-1,2-benzisoselenazol-3(2H)-one], which possesses antioxidant activity *in vitro* and was shown to affect GPx and AchE activity in rat brains treated with STZ [132, 133]. Moreover, a recent study confirmed the beneficial effect of Se on neurotoxicity induced by aluminium chloride ($AlCl_3$). Lakshmi *et al*. showed that this micronutrition effectively prevented the harmful effects of this toxin in behaviour and biochemical changes, and a decrease in brain oxidative damages, neuronal inflammation and improvement of the working and attention memory were observed [134].

Furthermore, the beneficial effects were demonstrated of Se treatment when administered with other neuroprotective compounds. Combined therapy of inorganic Se in a form of sodium selenite with natural carotenoid dicarboxylic acid provided better neuroprotection in rats treated with STZ by significantly reducing the level of lipid peroxidation and elevating the content of GSH as well as GPx, glutathione S-transferase (GST) and catalase activities [135]. Shrivastava *et al*. presented the beneficial effect of the co-administration of Se and N(2-hydroxyethyl) ethylenediamine triacetic acid (HEDTA) against aluminium (Al)-induced toxicity in rats. These positive effects of combination therapy with Se resulted from ameliorating the increase of acetylcholinesterase (AChE) and at the same time elevated butyrylcholinesterase (BuChE) activities in the plasma after Al administration. Moreover, this combined therapy led to an increase in antioxidative enzyme activities (GR, GST, GPx, glucose-6-phosphate dehydrogenase-G6PDH) in the forebrain [136].

Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative disease after AD. PD is a progressive and complex disease with heterogeneous clinical features including motor and non-motor symptoms. This disease is characterised by progressive neuronal loss, especially in the substantia nigra pars compacta (SN), and by the development of intraneuronal α-synuclein (ASN) inclusions known as Lewy bodies (LB). Moreover, the latest data have implicated the importance of extracellular ASN oligomers in the progression of PD pathology in the brain. Our own data indicated that extracellular ASN stimulated free radical generation, NOS activation and induced NO-dependent caspase-3 activation and poly(ADP-ribose)polymerase 1 (PARP-1) cleavage, thus leading to apoptotic cell death [137, 138, 139, 102]. On the other hand, oxidative stress induced ASN oligomerisation and its extracellular liberation, thus promoting its brain propagation. [102, 137, 139-141].

Although the possible role of Se in the etiology of PD as well as its significance in the treatment of this disease have not been studied in as much detail as in AD, some new promising data have emerged. It was observed, for example, that there were no differences in the serum Se concentration between PD and control groups [142], but its midbrain level was significantly increased in PD [110]. However, these studies were conducted on a small population and need to be further confirmed using large cohorts. Nevertheless, deregulation of oxidative defence in PD has been better documented. *Post-mortem* studies demonstrated a significant decrease of the total GSH level and changes in the expression and activity of GSH-dependent enzymes exclusively in the SN and striatum of PD patients which did not involve other brain regions [143, 144]. Using immunohistochemistry, it was shown that the level of GPx-1 was significantly increased in the hypertrophied microglia as well as in degenerated neurons. Moreover, this enzyme was shown to be mainly localised around LB, thus suggesting its protective role against oxidation of LB-degrading enzymes [38]. The potent antioxidative role of this enzyme in PD was further confirmed by showing that GPx1 knockout mice were more sensitive to neurotoxin-induced SN injury [105]. Interestingly, GPx1 overexpression in nigral dopaminergic neurons *in vivo* had a protective effect against 6-OHDA toxicity [145, 146]. Not only the GPx1 but also the GPx4 level was changed in the PD brain. P*ost-mortem* immunostaining showed that the total expression of GPx4 in SN was significantly reduced in PD brains as compared to control, but when related to the density of surviving nigral neurons it was increased [147]. Moreover, this enzyme was shown to be associated with TH-positive degenerating axons in the putamen, thus suggesting that up-regulation of GPx4, evoked by a buildup of oxidised dopamine in the axons, mitigates oxidative stress. It was also speculated that changes in GPx4 in dystrophic neurons could be related to this enzyme's colocalisation with neuromelanin [148]. GPx4 was also shown to co-localise with ASN-positive LB in SN, which may be a response to elevated oxidation of this protein [147]. Another selenoprotein indicated to be concentrated within the cores of LB is SelP. Similar as in GPx4, expression of this protein in relation to cell density was increased in the SN of PD patients, but its level in the putamen was not changed [149]. In PD pathology not only Se-dependent antioxidative enzymes are affected; both the level and activity of other enzymes related to the GSH metabolism are also changed. Increased expression of glutathione S-transferase (GST), which is a major enzyme involved in the regulation of oxidative stress, was observed in SN as well as in cerebrospinal fluid from PD patients [150-152].

Previous *in vitro* studies pointed to the neuroprotective effect of Se against various toxins that cause permanent symptoms of Parkinson's disease. Se dietary supplementation reduced the generation of reactive nitrogen species (RNS) and ameliorated the reduction of GPx levels induced by methamphetamine (MA) in dopaminergic neurons [123, 153]. Moreover, sodium selenite blocked the decrease in DA and its metabolites caused by the administration of MA [154] or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [154, 155]. It was also documented that Se prevented dopaminergic cell death in murine SN induced by the administration of MA or MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) [154, 155]. Furthermore, sodium

selenite enhanced the activity of antioxidant enzymes, particularly GPx, GR, GST, and CAT, and it elevated the GSH level and GSH/GSSG ratio in rats after 6-hydroxydopamine treatment [156]. Moreover, sodium selenite administration led to an improvement in locomotion and muscular co-ordination in the rat model of PD [157]. More recent neurochemical, histopathological and behavioural data have pointed to the potent neuroprotective effect of novel organic Se compounds, such as ebselen in various PD models. Both *in vitro* and *in vivo* research has suggested that ebselen reversed the toxic effects mediated by MPP^+ or MPTP treatment, prevented dopaminergic cell apoptosis, thus leading to improvement in motor performance, locomotor activity and neurological score. Apart from increasing GPx activity, ebselen was shown to act directly on mitochondrial complex I activity, thus leading to a decrease in free radical generation and energy deficits [158].

Other Diseases

Epilepsy

Epilepsy was one of the earliest characterised neurological diseases manifested by recurrent unprovoked seizures [159]. The endpoint of untreated intractable epilepsy is extensive hippocampal neuronal loss and reactive gliosis [103]. The mechanisms underlying this disease are still substantially unknown. However, there is experimental evidence suggesting that oxidative stress may be involved in the etiopathology of this disease. Frequent and chronic seizures lead to anoxia, which it turn evokes oxidative stress [159, 160] that is concomitant with elevated protein carbonylation and DNA oxidation [161, 162]. On the other hand, high oxidative status increased the severity and recurrence of epileptic seizures, thus creating a self-perpetuating vicious cycle.

It was previously suggested that the utilisation of Se may be increased in epilepsy since a decreased level in Se in the serum and erythrocytes from epileptic patients was noted [163, 164]. It is also believed that Se depletion in the brain during epilepsy constitutes a vital factor for the origin of seizures [163, 165, 166]. Nevertheless, information on the role and contribution of selenoproteins in brain disease is still limited. Some antioxidant abnormalities, such as increased activity of CAT concomitant with decreased activity of GPx, were observed in this disease [162]. However, experimental data from animal studies showed that Se-related anti-oxidative defence is markedly changed in epilepsy; for example, treatment with pilocarpine, which induced seizures and an epilepticus-like state, resulted in enhancement of the activity of SOD, GPx and CAT [167]. Similarly, kainic acid induced a significant increase in GSH oxidation, but it did not change the total GSH level in the rodent brain cortex [168]. Moreover, animals kept on an Se-deficient diet were more susceptible to neuropathological changes when exposed to glutamate or kainate [64, 169]. Interestingly, SelP and GPx-4 knockout mice displayed the tendency to develop neurological seizures [62, 170].

Based on these data, it seems plausible that Se administration might be beneficial in the therapy of epilepsy. A study on a pentylentetrazole (PTZ) rat model of epilepsy showed that Se treatment inhibited free radical production, regulated calcium-dependent processes, and supported the antioxidant redox system [171]. Additionally, chronic treatment of sodium selenate reduced the number of seizures induced by either PTZ injection or electrical stimulus of cornea or by amygdala kindling [172]. Sodium selenite or seleno-DL-methionine attenuated PTZ induced seizures in mice *via* inhibition of cyclooxygenase and reduction in prostaglandin E1 receptor activation [168]. There have also been human case reports showing that Se treatment has protective effects on epilepsy and refractory epilepsy-induced oxidative injury. It was shown that sodium selenite supplementation leads to reduction in the number of seizures and a decrease in neuronal damage [166]. Moreover, selenite inhibited free radical production and supported the antioxidant redox system *via* an increase in the GSH level and GPx activity in human erythrocytes [163, 173].

Cerebral Ischemia

Cerebral ischemia, characterised by high morbidity and mortality, remains the third main cause of human death and disability. Occlusion of brain arteries responsible for cerebral ischemia leads to insufficient oxygen and glucose delivery to support cellular homeostasis. This initiates a complex cascade of metabolic events, involving oxidative-nitrosative stress, inflammation and apoptosis, thus leading to neuronal damage and death [174]. The main result of ischemia is elevated glutamate release, which is responsible for excitotoxicity and an increased cytosolic calcium concentration. The NMDA-receptor - mediated calcium influx was shown to activate both constitutive (neuronal and endothelial) and inducible isoforms of nitric oxide (NO) synthase. In addition to an elevated NO level, brain ischemia leads to the generation of superoxide through various mechanisms, such as activation of NOS and xanthine oxidase, or disturbances of the mitochondrial electron transport chain [175]. Overproduction of free radicals, leads to inactivation of detoxification systems and perturbation of antioxidative defence mechanisms. It was previously demonstrated that elevated consumption of GSH with its maximum loss in the striatum and hippocampus as well as depletion of the enzymatic defence system (GPx, GR, GST) take place in ischemic brain tissue [176, 177]. In cerebral ischemia, oxidative stress is often accompanied by depletion of essential trace elements in the organism [175]. This also relates to Se, which was documented to be significantly decreased in the ischemic brain as compared with the control subject [175]. Taking into account the scavenging features of Se, treatment with Se-derived compounds was suggested as a valuable therapy in ischemia reperfusion damages [178]. An *in vitro* study using murine hippocampal HT22 cells indicated that Se as sodium selenite protected against glutamate toxicity and hypoxia-induced cell death by preventing changes in the mitochondrial membrane potential and ROS generation. Moreover, Se increased the expression of mitochondrial biogenesis regulators while at the same time decreasing the level of autophagy modulators [179]. In the rat ischemia model with middle cerebral artery occlusion (MCAO), sodium selenite administration increased the activity of CAT, SOD and GPx, and prevented the GSH decline, leading to decreased brain lipid peroxidation [178].

Another report indicated that sodium selenite restored the level of mitochondrial ATP, cellular Ca^{2+} and decreased the activity of caspase-3 [180]. Moreover, Se as sodium selenite inhibited monoamine oxidase activity in the mitochondria, which are also capable of producing ROS during ischemia/reperfusion. The intake of inorganic Se can also have a suppressive effect against DNA damages and PARP activation [178, 180]. More recent data based on histopathological analyses have suggested that sodium selenite treatment improved neuron density and decreased perineuronal and pericapillary edema in the prefrontal cortex and hippocampus of the rat model of ischemia/reperfusion. Moreover, the same study showed that inorganic Se treatment significantly decreased the level of inflammatory cytokines such as interleukin-1 beta (IL-1β), tumor necrosis factor alfa (TNF-α) and, at the same time, increased the levels of NGF in the prefrontal cortex and hippocampus [148]. Interestingly, the organic Se compound, ebselen, significantly decreased malondialdehyde (MDA) and NO levels as well as increased the activity of antioxidative enzymes, thus leading to morphological improvement of brain tissue in the rat ischemia/reperfusion model [181]. A promising effect was observed using a combination of sodium selenite and melatonin (Se-Mel) therapy on transient cerebral ischemia [176]. In the MCAO model, Se-Mel attenuated protein and lipid oxidation, caspase-3 activity and the NO level were reflected in improvement of animal behaviour [176].

DOES A SELENIUM-BASED DRUG DESIGN HAVE THERAPEUTIC POTENTIAL?

With accumulating evidence for oxidative injuries and disturbance of antioxidative defence as important factors in disorders of CNS, several trials have explored the efficiency of antioxidants in the prevention and treatment of those diseases. The anti-inflammatory and anti-aging properties of vitamin E, C or β-carotene have been demonstrated in various studies. Unfortunately, promising results were not reflected in clinical trials [182-185]. Therefore, the search for new compounds that might have potential application in the treatment of neurodegenerative and other brain diseases still continues. Taking into account the multiple protective effects of Se, the possibility of using this compound as a protective drug against neuronal cell death can be plausible. Thus current scientific challenge is finding the appropriate Se donor with high bioavailability and respectively low toxicity. The large number of experimental data suggests that neurotoxicity of inorganic Se species exceeds that of the organic-Se-compounds [186]. However, there are some exceptions, like methylseleninic acid, L-selenocystine or selenodiglutathione, that were shown to induce cell death already in low μM concentrations. On the other hand, despite its high bioavailability, the toxicity of inorganic sodium selenite (LD50 3.5 mg/kg body weight in rats [187] and 1.2-1.9 mg/kg body weight in sheep after oral administration [188]) is significantly higher than that of ebselen or SeMet [189]. Interestingly, it was demonstrated that the cytotoxicity of sodium selenite strongly depends on its uptake and cellular accumulation, which in turn is regulated by the extracellular environment. The extracellular reduction of selenite to selenide is mainly mediated by cysteine and leads to a high-affinity uptake of this reduced Se form, causing its accumulation and cell death. The efficacy of this process is determined by the cystine/glutamate antiporter (x_c^-)-dependent cystine uptake, its intracellular reduction to cysteine by NADPH-dependent redox systems and cysteine resecretion by multidrug resistance proteins [190, 191]. These findings highlight that therapeutic potential of reducible selenium compounds strongly depend on the type of the tissue and conditions of individual patients, hence the possibility of using certain Se species in therapy is limited and controversial [189]. Noteworthy is that organic forms of Se at IV oxidation state are characterized by higher bioavailability and lower toxicity, thus administration of these compounds allows to achieve a higher Se concentration in tissue [192-194].

One of the first synthetic organic Se compounds, ebselen, a mimetic for glutathione peroxidases, was previously considered as a potential pharmacological agent (Fig. **2A**) [158, 195, 196]. The mechanisms underlying the neuroprotective effect of ebselen are still not completely understood, but they

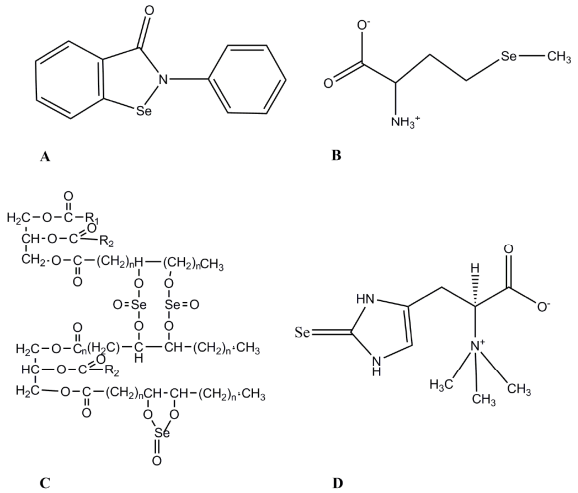

Fig. (2). Molecular structure of organic selenium compounds. Ebselen (A) [133], Selenomethionine (B) [215], Selol (C) [210], Selenoneine (D) [216] described in this study.

are certainly related to its antioxidant and anti-inflammatory properties [197, 198]. Several pre-clinical animal studies have supported the neuroprotective effect of this chemical in stroke. It was shown that ebselen not only provided protection against oxidative damage-induced neuronal death from focal ischemia in hypertensive rats [199], but that is also had beneficial effects in transient forebrain ischemia [200, 201]. Moreover, initial clinical studies with humans indicated that ebselen may be a prophylactic neuroprotective agent in acute ischemic stroke [202, 203]. More recent ongoing trials have demonstrated that ebselen displayed efficacy for reducing the infarct volume by 27% on average in nine focal ischemia studies, with 10 of the 16 experimental contrasts showing protection [204], which seems promising for future therapies for stroke.

Other clinical trials that have been conducted concerned the therapeutic use of Se in AD treatment. However, in those studies Se was tested in combination with other compounds. In one small study, geriatric patients received a mixture of inorganic and organic Se with Vitamin E. These patients significantly improved in several cognitive parameters as compared to control placebo [205]. A larger study with Se in the form of SeMet (Fig. **2B**) and Vitamin E is currently undergoing the "preadvise" trial, which is being held on more than 10,000 healthy men between 60 and 90 years old. The initial goal of this trial is to study the effect of this treatment formulation on preventing AD and other brain disorders [206]. However, the latest study coming from "SELECT" clinical trial bring negative reports about possible application of SeMet in treatment of human diseases. In this experiment the L-selenomethionine intake not only had any positive impact on prostate cancer prevention, but also increased the risk to develop type 2 diabetes mellitus. The adverse effects of this compound resulted from its random incorporation into various proteins instead of methionine that, together with its long biological half-life, constitutes the reason for the failure of the therapy [207, 208].

Furthermore, research is being conducted in several research centres on a new Se compound, called Selol (Fig. **2C**) [209-211]. Selol is an organic mixture of selenitetriglycerides which are obtained on the basis of sunflower oil. A compound containing Se at IV oxidation state meets the requirements of low toxicity and is characterised by fast absorption and distribution as well as high bioavailability [192, 193, 212, 213]. Until now, Selol has undergone various experimental and clinical investigations as an anticancer drug, and currently it is at the final stage of pre-clinical studies [211, 212, 214]. Additionally, due to the ability for Selol to provide a high Se concentration in the brain [193], its neuroprotective effects are currently being investigated. While testing this compound *in vitro,* it was found that it has the ability to suppress oxidative-nitrosative stress in neuronal cells. The mechanism of Selol's cytoprotective effect involves stimulation of the endogenous antioxidant system *via* elevation

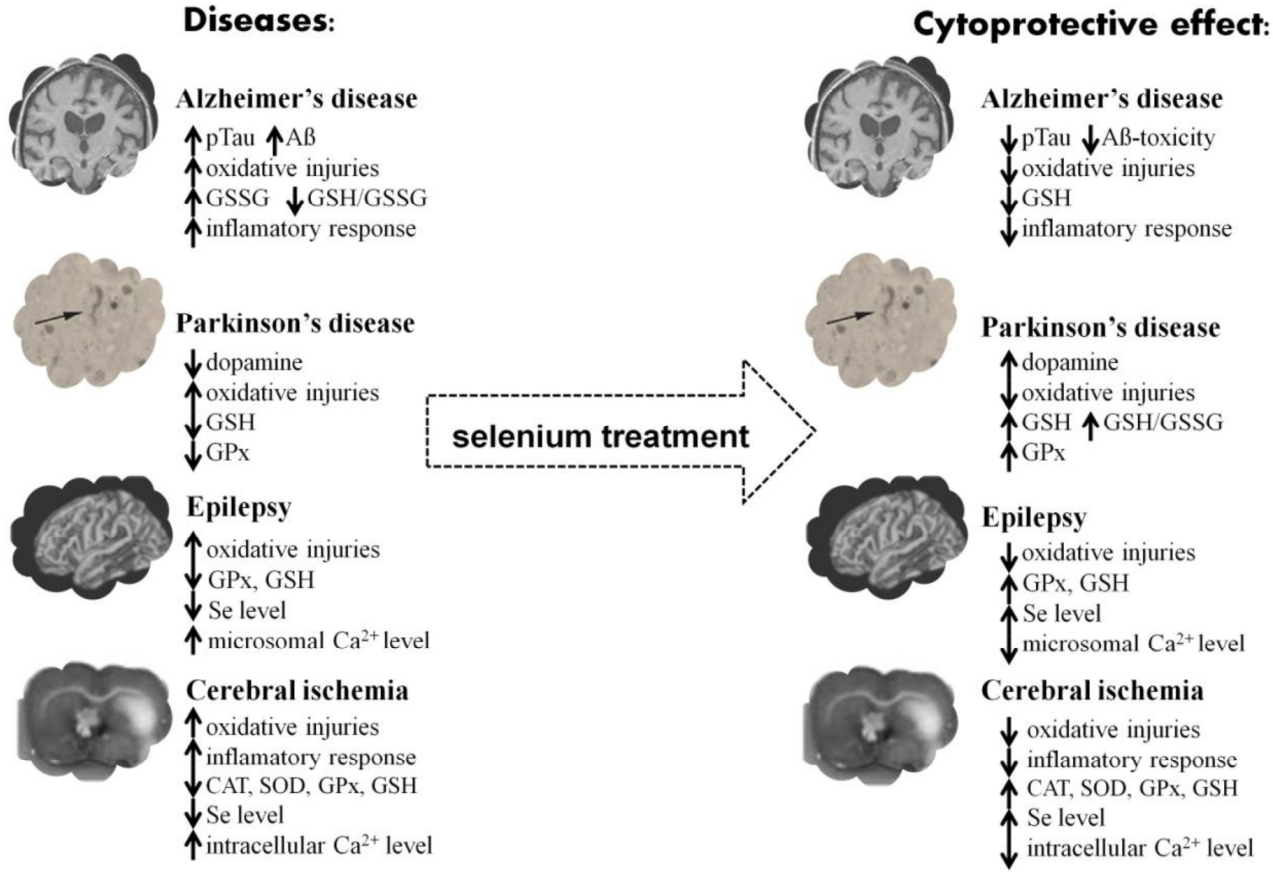

Fig. (3). Summary of selenium therapy effects in neurological diseases. Aß-amyloid β, **CAT**-catalase,**GPx**-glutathione peroxidase, **GSH**-glutathione, **pTau**-phosphorylated tau protein, **Sel**-selenoprotein, **SOD**-superoxide dismutase [167, 217-219].

of the level and activity of the Se-dependent enzyme – glutathione peroxidase (GPx) [220]. However, many more studies should be conducted so that the potential *in vitro* antioxidant effects of the organic Se (IV) form can be harnessed in the clinic of neurological diseases.

The latest studies introduced a novel organic Se-containing compound, selenoneine (Fig. **2D**), isolated from the blood and tissues of bluefin tuna. However, the biological significance of this compound is still unclear. It was demonstrated that apart from strong antioxidant capacity, selenoneine has the ability to bind heme proteins, such as hemoglobin and myoglobin and to protect them from iron auto-oxidation. It was also shown to prevent MeHg accumulation and toxicity *via* acting on organic cations/ carnitine transporter, OCTN1 [216, 221].

CONCLUSIONS

Recent studies have identified Se as crucial for preserving brain function and preventing age-related neurodegenerative disorders. An insufficient supply of Se may have a detrimental effect on brain cells by exacerbating neuronal dysfunction and death. Undoubtedly, the remarkable progress that has been made in understanding the biological function of Se in the brain, especially in relation to the antioxidative and anti-inflammatory functions of selenenoproteins, has also opened up new, potential possibilities for treatment of neurodegenerative diseases by using Se as a potential drug (Fig. **3**). Thus, an assessment of optimal doses and forms of Se supplementation is still a matter of debate. On account of the higher toxicity of inorganic Se forms and, in consequence, their limited application in therapy, there is a need for a further search for Se donors, especially in organic form, in order to achieve an effective and safe therapeutic income.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

This study was supported by a minigrant, FW27/PM34D/ 14, of the Medical University of Warsaw and the statutory budget of the Mossakowski Medical Research Centre, Polish Academy of Sciences (Theme No. 17).

LIST OF ABBREVIATIONS

Aß	=	amyloid β
AChE	=	acetylcholinesterase
AD	=	Alzheimer's disease
APP	=	β-amyloid precursor protein
ALS	=	amyotrophic lateral sclerosis
ApoER2	=	apolipoprotein receptor 2
ASN	=	α-synuclein
CAT	=	catalase
CSF	=	cerebrospinal fluid
Dio	=	iodothyronine deiodinase
GPx	=	glutathione peroxidise
GSH	=	glutathione
GR	=	glutathione reductase
GSSG	=	glutathione disulfide
GST	=	glutathione S-transferase
G6PDH	=	glucose-6-phosphate dehydrogenase
HEDTA	=	N(2-hydroxyethyl)ethylenediamine triacetic acid
ICV-STZ	=	intracerebroventricular injection of streptozotocin
iNOS	=	inducible nitric oxide synthase
LD50	=	median lethal dose
LB	=	Lewy bodies
MCAO	=	ischemia model with middle cerebral artery occlusion
MDA	=	malondialdehyde
MPP^+	=	1-methyl-4-phenylpyridinium
MPTP	=	1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine
NFT	=	neurofibrillary tangle
NRF1	=	nuclear respiratory factor 1
PARP-1	=	poly(ADP-ribose) polymerase-1
PD	=	Parkinson's disease
PGC-1α	=	peroxisome proliferator-activated receptor-γ coactivator 1 alpha
PGE	=	prostaglandin E
PP2	=	protein phosphatase 2
pro-NGF	=	precursor of nerve growth factor
ROS	=	reactive oxygen species
Sec	=	selenocysteine
SECIS	=	selenocysteine insertion sequence
Sel	=	selenoprotein
SeBP1	=	selenium-binding protein 1
SeMet	=	selenomethionine
SN	=	substantia nigra pars compacta
SPS2	=	selenophosphate synthetase
TH	=	tyrosine hydroxylase
Trx	=	thioredoxin
TrxR	=	thioredoxin reductase

REFERENCES

[1] NTP Toxicity Studies of Sodium Selenate and Sodium Selenite (CAS Nos. 13410-01-0 and 10102-18-8) Administered in Drinking Water to F344/N Rats and B6C3F1 Mice. *Toxi.c Rep. Ser.*, **1994**, *38*, 1-e5.

[2] Adamczyk, A.; Czapski, G.A.; Jesko, H.; Strosznajder, R.P. Non A beta component of Alzheimer's disease amyloid and amyloid beta peptides evoked poly(ADP-ribose) polymerase-dependent release of apoptosis-inducing factor from rat brain mitochondria. *J. Physiol. Pharmacol*, **2005**, *56 Suppl 2*, 5-13.

[3] Adamczyk, A.; Jesko, H.; Strosznajder, R.P. Alzheimer's disease related peptides affected cholinergic receptor mediated poly(ADP-ribose) polymerase activity in the hippocampus. *Folia Neuropathol.*, **2005**, *43*(3), 139-142.

[4] Adamczyk, A.; Kazmierczak, A.; Czapski, G.A.; Strosznajder, J.B. Alpha-synuclein induced cell death in mouse hippocampal (HT22) cells is mediated by nitric oxide-dependent activation of caspase-3. *FEBS Lett.*, **2010**, *584*(15), 3504-3508. http://dx.doi.org/10.1016/j.febslet.2010.07.019

[5] Ahmad, A.; Khan, M.M.; Ishrat, T.; Khan, M.B.; Khuwaja, G.; Raza, S.S.; Shrivastava, P.; Islam, F. Synergistic effect of selenium and melatonin on neuroprotection in cerebral ischemia in rats. *Biol. Trace Elem. Res.*, **2011**, *139*(1), 81-96. http://dx.doi.org/10.1007/s12011-010-8643-z

[6] Akbaraly, T.N.; Hininger-Favier, I.; Carriere, I.; Arnaud, J.; Gourlet, V.; Roussel, A.M.; Berr, C. Plasma selenium over time and cognitive decline in the elderly. *Epidemiology*, **2007**, *18*(1), 52-58. http://dx.doi.org/10.1097/01.ede.0000248202.83695.4e

[7] Ano, Y.; Sakudo, A.; Kimata, T.; Uraki, R.; Sugiura, K.; Onodera, T. Oxidative damage to neurons caused by the induction of microglial NADPH oxidase in encephalomyocarditis virus infection. *Neurosci. Lett.*, **2010**, *469*(1), 39-43. http://dx.doi.org/10.1016/j.neulet.2009.11.040

[8] Ansari, M.A.; Ahmad, A.S.; Ahmad, M.; Salim, S.; Yousuf, S.; Ishrat, T.; Islam, F. Selenium protects cerebral ischemia in rat brain mitochondria. *Biol. Trace Elem. Res.*, **2004**, *101*(1), 73-86. http://dx.doi.org/10.1385/BTER:101:1:73

[9] Aras, M.; Altas, M.; Meydan, S.; Nacar, E.; Karcioglu, M.; Ulutas, K.T.; Serarslan, Y. Effect of ebselen on ischemia/reperfusion injury in rat brain. *Int. J. Neurosci.*, **2014**. http://dx.doi.org/10.3109/00207454.2013.879581

[10] Ashrafi, M.R.; Shabanian, R.; Abbaskhanian, A.; Nasirian, A.; Ghofrani, M.; Mohammadi, M.; Zamani, G.R.; Kayhanidoost, Z.; Ebrahimi, S.; Pourpak, Z. Selenium and intractable epilepsy: is there any correlation? *Pediatr. Neurol.*, **2007**, *36*(1), 25-29. http://dx.doi.org/10.1016/j.pediatrneurol.2006.09.001

[11] Barayuga, S.M.; Pang, X.; Andres, M.A.; Panee, J.; Bellinger, F.P. Methamphetamine decreases levels of glutathione peroxidases 1 and 4 in SH-SY5Y neuronal cells: protective effects of selenium. *Neurotoxicology*, **2013**, *37*, 240-246. http://dx.doi.org/10.1016/j.neuro.2013.05.009

[12] Battin, E.E.; Zimmerman, M.T.; Ramoutar, R.R.; Quarles, C.E.; Brumaghim, J.L. Preventing metal-mediated oxidative DNA damage with selenium compounds. *Metallomics*, **2011**, *3*(5), 503-512. http://dx.doi.org/10.1039/c0mt00063a

[13] Behne, D.; Kyriakopoulos, A. Mammalian selenium-containing proteins. *Annu. Rev. Nutr.*, **2001**, *21*, 453-473. http://dx.doi.org/10.1146/annurev.nutr.21.1.453

[14] Beilstein, M.A.; Vendeland, S.C.; Barofsky, E.; Jensen, O.N.; Whanger, P.D. Selenoprotein W of rat muscle binds glutathione and an unknown small molecular weight moiety. *J. Inorg. Biochem.*, **1996**, *61*(2), 117-124. http://dx.doi.org/10.1016/0162-0134(95)00045-3

[15] Bellinger, F.P.; Bellinger, M.T.; Seale, L.A.; Takemoto, A.S.; Raman, A.V.; Miki, T.; Manning-Bog, A.B.; Berry, M.J.; White, L.R.; Ross, G.W. Glutathione Peroxidase 4 is associated with Neuromelanin in Substantia Nigra and Dystrophic Axons in Putamen of Parkinson's brain. *Mol. Neurodegener.*, **2011**, *6*(1), 8. http://dx.doi.org/10.1186/1750-1326-6-8

[16] Bellinger, F.P.; He, Q.P.; Bellinger, M.T.; Lin, Y.; Raman, A.V.; White, L.R.; Berry, M.J. Association of selenoprotein p with Alzheimer's pathology in human cortex. *J. Alzheimers Dis.*, **2008**, *15*(3), 465-472.

[17] Bellinger, F.P.; Raman, A.V.; Reeves, M.A.; Berry, M.J. Regulation and function of selenoproteins in human disease. *Biochem. J.*, **2009**, *422*(1), 11-22. http://dx.doi.org/10.1042/BJ20090219

[18] Bellinger, F.P.; Raman, A.V.; Rueli, R.H.; Bellinger, M.T.; Dewing, A.S.; Seale, L.A.; Andres, M.A.; Uyehara-Lock, J.H.; White, L.R.; Ross, G.W.; Berry, M.J. Changes in selenoprotein P in substantia nigra and putamen in Parkinson's disease. *J. Parkinsons Dis.*, **2012**, *2*(2), 115-126.

[19] Bensadoun, J.C.; Mirochnitchenko, O.; Inouye, M.; Aebischer, P.; Zurn, A.D. Attenuation of 6-OHDA-induced neurotoxicity in glutathione peroxidase transgenic mice. *Eur. J. Neurosci.*, **1998**, *10*(10), 3231-3236. http://dx.doi.org/10.1046/j.1460-9568.1998.00345.x

[20] Berg, D.; Holzmann, C.; Riess, O. 14-3-3 proteins in the nervous system. *Nat. Rev. Neurosci.*, **2003**, *4*(9), 752-762. http://dx.doi.org/10.1038/nrn1197

[21] Berry, M.J.; Tujebajeva, R.M.; Copeland, P.R.; Xu, X.M.; Carlson, B.A.; Martin, G.W., 3rd; Low, S.C.; Mansell, J.B.; Grundner-Culemann, E.; Harney, J.W.; Driscoll, D.M.; Hatfield, D.L. Selenocysteine incorporation directed from the 3'UTR: characterization of eukaryotic EFsec and mechanistic implications. *Biofactors*, **2001**, *14*(1-4), 17-24. http://dx.doi.org/10.1002/biof.5520140104

[22] Borchert, A.; Wang, C.C.; Ufer, C.; Schiebel, H.; Savaskan, N.E.; Kuhn, H. The role of phospholipid hydroperoxide glutathione peroxidase isoforms in murine embryogenesis. *J. Biol. Chem.*, **2006**, *281*(28), 19655-19664. http://dx.doi.org/10.1074/jbc.M601195200

[23] Brigelius-Flohe, R.; Maiorino, M. Glutathione peroxidases. *Biochim. Biophys. Acta*, **2013**, *1830*(5), 3289-3303. http://dx.doi.org/10.1016/j.bbagen.2012.11.020

[24] Burk, R.F.; Brown, D.G.; Seely, R.J.; Scaief, C.C., 3rd. Influence of dietary and injected selenium on whole-blody retention, route of excretion, and tissue retention of 75SeO3 2- in the rat. *J. Nutr.*, **1972**, *102*(8), 1049-1055.

[25] Burk, R.F.; Hill, K.E. Selenoprotein P. A selenium-rich extracellular glycoprotein. *J. Nutr.*, **1994**, *124*(10), 1891-1897.

[26] Burk, R.F.; Hill, K.E. Selenoprotein P: an extracellular protein with unique physical characteristics and a role in selenium homeostasis. *Annu. Rev. Nutr.*, **2005**, *25*, 215-235. http://dx.doi.org/10.1146/annurev.nutr.24.012003.132120

[27] Burk, R.F.; Hill, K.E.; Motley, A.K. Selenoprotein metabolism and function: evidence for more than one function for selenoprotein P. *J. Nutr.*, **2003**, *133*(5 Suppl 1), 1517s-1520s.

[28] Burk, R.F.; Hill, K.E.; Motley, A.K.; Winfrey, V.P.; Kurokawa, S.; Mitchell, S.L.; Zhang, W. Selenoprotein P and apolipoprotein E receptor-2 interact at the blood-brain barrier and also within the brain to maintain an essential selenium pool that protects against neurodegeneration. *Faseb J.*, **2014**, *28*(8), 3579-3588. http://dx.doi.org/10.1096/fj.14-252874

[29] Burk, R.F.; Hill, K.E.; Read, R.; Bellew, T. Response of rat selenoprotein P to selenium administration and fate of its selenium. *Am. J. Physiol.*, **1991**, *261*(1 Pt 1), E26-30.

[30] Cardoso, B.R.; Ong, T.P.; Jacob-Filho, W.; Jaluul, O.; Freitas, M.I.; Cozzolino, S.M. Nutritional status of selenium in Alzheimer's disease patients. *Br. J. Nutr.*, **2010**, *103*(6), 803-806. http://dx.doi.org/10.1017/S0007114509992832

[31] Castano, A.; Cano, J.; Machado, A. Low selenium diet affects monoamine turnover differentially in substantia nigra and striatum. *J. Neurochem.*, **1993**, *61*(4), 1302-1307. http://dx.doi.org/10.1111/j.1471-4159.1993.tb13622.x

[32] Chen, P.; Wang, C.; Ma, X.; Zhang, Y.; Liu, Q.; Qiu, S.; Liu, Q.; Tian, J.; Ni, J. Direct Interaction of Selenoprotein R with Clusterin and Its Possible Role in Alzheimer's Disease. *PLoS One*, **2013**, *8*(6), e66384. http://dx.doi.org/10.1371/journal.pone.0066384

[33] Chen, P.; Wang, L.; Wang, Y.; Li, S.; Shen, L.; Liu, Q.; Ni, J. Phosphoproteomic profiling of selenate-treated Alzheimer's disease model cells. *PLoS One*, **2014**, *9*(12), e113307. http://dx.doi.org/10.1371/journal.pone.0113307

[34] Chen, Y.; Cai, J.; Murphy, T.J.; Jones, D.P. Overexpressed human mitochondrial thioredoxin confers resistance to oxidant-induced apoptosis in human osteosarcoma cells. *J. Biol. Chem.*, **2002**, *277*(36), 33242-33248. http://dx.doi.org/10.1074/jbc.M202026200

[35] Cheng, W.H.; Ho, Y.S.; Valentine, B.A.; Ross, D.A.; Combs, G.F., Jr.; Lei, X.G. Cellular glutathione peroxidase is the mediator of

body selenium to protect against paraquat lethality in transgenic mice. *J. Nutr.*, **1998**, *128*(7), 1070-1076.

[36] Cogun, H.Y.; Firat, O.; Firat, O.; Yuzereroglu, T.A.; Gok, G.; Kargin, F.; Kotemen, Y. Protective effect of selenium against mercury-induced toxicity on hematological and biochemical parameters of Oreochromis niloticus. *J. Biochem. Mol .Toxicol.*, **2012**, *26*(3), 117-122. http://dx.doi.org/10.1002/jbt.20417

[37] Corcoran, N.M.; Martin, D.; Hutter-Paier, B.; Windisch, M.; Nguyen, T.; Nheu, L.; Sundstrom, L.E.; Costello, A.J.; Hovens, C.M. Sodium selenate specifically activates PP2A phosphatase, dephosphorylates tau and reverses memory deficits in an Alzheimer's disease model. *J. Clin. Neurosci.*, **2010**, *17*(8), 1025-1033. http://dx.doi.org/10.1016/j.jocn.2010.04.020

[38] Corrigan, F.M.; Reynolds, G.P.; Ward, N.I. Hippocampal tin, aluminum and zinc in Alzheimer's disease. *Biometals*, **1993**, *6*(3), 149-154. http://dx.doi.org/10.1007/BF00205853

[39] Cui, K.; Luo, X.; Xu, K.; Ven Murthy, M.R. Role of oxidative stress in neurodegeneration: recent developments in assay methods for oxidative stress and nutraceutical antioxidants. *Prog Neuropsychopharmacol. Biol .Psychiatry*, **2004**, *28*(5), 771-799. http://dx.doi.org/10.1016/j.pnpbp.2004.05.023

[40] Cutts, D.A.; Maguire, R.P.; Stedman, J.D.; Leenders, K.L.; Spyrou, N.M. A comparative study in Alzheimer's and normal brains of trace element distribution using PIXE and INA analyses and glucose metabolism by positron emission tomography. *Biol. Trace Elem. Res.*, **1999**, *71-72*, 541-549. http://dx.doi.org/10.1007/BF02784242

[41] Czapski, G.A.; Gassowska, M.; Wilkaniec, A.; Cieslik, M.; Adamczyk, A. Extracellular alpha-synuclein induces calpain-dependent overactivation of cyclin-dependent kinase 5 *in vitro*. *FEBS Lett.*, **2013**, *587*(18), 3135-3141. http://dx.doi.org/10.1016/j.febslet.2013.07.053

[42] Damdimopoulos, A.E.; Miranda-Vizuete, A.; Pelto-Huikko, M.; Gustafsson, J.A.; Spyrou, G. Human mitochondrial thioredoxin. Involvement in mitochondrial membrane potential and cell death. *J. Biol. Chem.*, **2002**, *277*(36), 33249-33257. http://dx.doi.org/10.1074/jbc.M203036200

[43] de Haan, J.B.; Bladier, C.; Griffiths, P.; Kelner, M.; O'Shea, R.D.; Cheung, N.S.; Bronson, R.T.; Silvestro, M.J.; Wild, S.; Zheng, S.S.; Beart, P.M.; Hertzog, P.J.; Kola, I. Mice with a homozygous null mutation for the most abundant glutathione peroxidase, Gpx1, show increased susceptibility to the oxidative stress-inducing agents paraquat and hydrogen peroxide. *J. Biol. Chem.*, **1998**, *273*(35), 22528-22536. http://dx.doi.org/10.1074/jbc.273.35.22528

[44] de Souza, L.; Muehlmann, L.; Dos Santos, M.; Ganassin, R.; Simon-Vazquez, R.; Joanitti, G.; Mosiniewicz-Szablewska, E.; Suchocki, P.; Morais, P.; Gonzalez-Fernandez, A.; Azevedo, R.; Bao, S. PVM/MA-shelled selol nanocapsules promote cell cycle arrest in A549 lung adenocarcinoma cells. *J. Nanobiotechnology*, **2014**, *12*(1), 32. http://dx.doi.org/10.1186/s12951-014-0032-x

[45] Dominiak, A.; Wilkaniec, A.; Wroczynski, P.; Adamczyk, A. P.5.a.005 Selol exhibits antioxidative and cytoprotective properties in PC12 cells by activating glutathione peroxidase. *Eur. Neuropsychopharmacol.*, *24*, S627-S628. http://dx.doi.org/10.1016/S0924-977X(14)71007-7

[46] Du, X.; Li, H.; Wang, Z.; Qiu, S.; Liu, Q.; Ni, J. Selenoprotein P and selenoprotein M block Zn2+ -mediated Abeta42 aggregation and toxicity. *Metallomics*, **2013**, *5*(7), 861-870. http://dx.doi.org/10.1039/c3mt20282h

[47] Du, X.; Qiu, S.; Wang, Z.; Wang, R.; Wang, C.; Tian, J.; Liu, Q. Direct interaction between selenoprotein P and tubulin. *Int. J. Mol. Sci.*, **2014**, *15*(6), 10199-10214. http://dx.doi.org/10.3390/ijms150610199

[48] Du, X.; Wang, Z.; Zheng, Y.; Li, H.; Ni, J.; Liu, Q. Inhibitory effect of selenoprotein P on Cu(+)/Cu(2+)-induced Abeta42 aggregation and toxicity. *Inorg. Chem.*, **2014**, *53*(3), 1672-1678. http://dx.doi.org/10.1021/ic4028282

[49] Estevanato, L.L.; Da Silva, J.R.; Falqueiro, A.M.; Mosiniewicz-Szablewska, E.; Suchocki, P.; Tedesco, A.C.; Morais, P.C.; Lacava, Z.G. Co-nanoencapsulation of magnetic nanoparticles and selol for breast tumor treatment: *in vitro* evaluation of cytotoxicity and magnetohyperthermia efficacy. *Int . J. Nanomedicine*, **2012**, *7*, 5287-5299.

[50] Estevez, A.O.; Mueller, C.L.; Morgan, K.L.; Szewczyk, N.J.; Teece, L.; Miranda-Vizuete, A.; Estevez, M. Selenium induces cholinergic motor neuron degeneration in Caenorhabditis elegans. *Neurotoxicology*, **2012**, *33*(5), 1021-1032. http://dx.doi.org/10.1016/j.neuro.2012.04.019

[51] Etminan, M.; Gill, S.S.; Samii, A. Intake of vitamin E, vitamin C, and carotenoids and the risk of Parkinson's disease: a meta-analysis. *Lancet Neurol.*, **2005**, *4*(6), 362-365. http://dx.doi.org/10.1016/S1474-4422(05)70097-1

[52] Fang, K.M.; Cheng, F.C.; Huang, Y.L.; Chung, S.Y.; Jian, Z.Y.; Lin, M.C. Trace element, antioxidant activity, and lipid peroxidation levels in brain cortex of gerbils after cerebral ischemic injury. *Biol. Trace Elem. Res.*, **2013**, *152*(1), 66-74. http://dx.doi.org/10.1007/s12011-012-9596-1

[53] Farahani, H.N.; Ashthiani, A.R.; Masihi, M.S. Study on serum zinc and selenium levels in epileptic patients. *Neurosciences (Riyadh)*, **2013**, *18*(2), 138-142.

[54] Flis, A.; Suchocki, P.; Krolikowska, M.A.; Suchocka, Z.; Remiszewska, M.; Sliwka, L.; Ksiazek, I.; Sitarz, K.; Sochacka, M.; Hoser, G.; Anuszewska, E.; Wroczynski, P.; Jastrzebski, Z. Selenitetriglycerides-Redox-active agents. *Pharmacol. Rep.*, **2015**, *67*(1), 1-8. http://dx.doi.org/10.1016/j.pharep.2014.07.017

[55] Fomenko, D.E.; Gladyshev, V.N. Identity and functions of CxxC-derived motifs. *Biochemistry*, **2003**, *42*(38), 11214-11225. http://dx.doi.org/10.1021/bi034459s

[56] Gasmi, A.; Garnier, R.; Galliot-Guilley, M.; Gaudillat, C.; Quartenoud, B.; Buisine, A.; Djebbar, D. Acute selenium poisoning. *Vet. Hum. Toxicol.*, **1997**, *39*(5), 304-308.

[57] Gassowska, M.; Czapski, G.A.; Pajak, B.; Cieslik, M.; Lenkiewicz, A.M.; Adamczyk, A. Extracellular alpha-synuclein leads to microtubule destabilization *via* GSK-3beta-dependent Tau phosphorylation in PC12 cells. *PLoS One*, **2014**, *9*(4), e94259. http://dx.doi.org/10.1371/journal.pone.0094259

[58] Gerhardsson, L.; Lundh, T.; Minthon, L.; Londos, E. Metal concentrations in plasma and cerebrospinal fluid in patients with Alzheimer's disease. *Dement. Geriatr. Cogn. Disord.*, **2008**, *25*(6), 508-515. http://dx.doi.org/10.1159/000129365

[59] Giometti, C.S.; Liang, X.; Tollaksen, S.L.; Wall, D.B.; Lubman, D.M.; Subbarao, V.; Rao, M.S. Mouse liver selenium-binding protein decreased in abundance by peroxisome proliferators. *Electrophoresis*, **2000**, *21*(11), 2162-2169. http://dx.doi.org/10.1002/1522-2683(20000601)21:11%3C2162::AID-ELPS2162%3E3.0.CO;2-S

[60] Glaser, V.; Moritz, B.; Schmitz, A.; Dafre, A.L.; Nazari, E.M.; Rauh Muller, Y.M.; Feksa, L.; Straliottoa, M.R.; de Bem, A.F.; Farina, M.; da Rocha, J.B.; Latini, A. Protective effects of diphenyl diselenide in a mouse model of brain toxicity. *Chem. Biol. Interact.*, **2013**, *206*(1), 18-26. http://dx.doi.org/10.1016/j.cbi.2013.08.002

[61] Godoi, G.L.; de Oliveira Porciuncula, L.; Schulz, J.F.; Kaufmann, F.N.; da Rocha, J.B.; de Souza, D.O.; Ghisleni, G.; de Almeida, H.L., Jr. Selenium compounds prevent amyloid beta-peptide neurotoxicity in rat primary hippocampal neurons. *Neurochem. Res.*, **2013**, *38*(11), 2359-2363. http://dx.doi.org/10.1007/s11064-013-1147-4

[62] Gu, Q.P.; Sun, Y.; Ream, L.W.; Whanger, P.D. Selenoprotein W accumulates primarily in primate skeletal muscle, heart, brain and tongue. *Mol. Cell. Biochem.*, **2000**, *204*(1-2), 49-56. http://dx.doi.org/10.1023/A:1007065829068

[63] Hawkes, W.C.; Alkan, Z. Delayed cell cycle progression from SEPW1 depletion is p53- and p21-dependent in MCF-7 breast cancer cells. *Biochem. Biophys. Res. Commun.*, **2011**, *413*(1), 36-40. http://dx.doi.org/10.1016/j.bbrc.2011.08.032

[64] Hawkes, W.C.; Printsev, I.; Alkan, Z. Selenoprotein W depletion induces a p53- and p21-dependent delay in cell cycle progression in RWPE-1 prostate epithelial cells. *J. Cell. Biochem.*, **2012**, *113*(1), 61-69. http://dx.doi.org/10.1002/jcb.23328

[65] He, M.; Xing, S.; Yang, B.; Zhao, L.; Hua, H.; Liang, Z.; Zhou, W.; Zeng, J.; Pei, Z. Ebselen attenuates oxidative DNA damage and enhances its repair activity in the thalamus after focal cortical infarction in hypertensive rats. *Brain Res.*, **2007**, *1181*, 83-92. http://dx.doi.org/10.1016/j.brainres.2007.08.072

[66] Hill, K.E.; Lloyd, R.S.; Burk, R.F. Conserved nucleotide sequences in the open reading frame and 3' untranslated region of selenoprotein P mRNA. *Proc. Natl. Acad. Sci. U.S.A.*, **1993**, *90*(2), 537-541. http://dx.doi.org/10.1073/pnas.90.2.537

[67] Hill, K.E.; Zhou, J.; McMahan, W.J.; Motley, A.K.; Atkins, J.F.; Gesteland, R.F.; Burk, R.F. Deletion of selenoprotein P alters distribution of selenium in the mouse. *J. Biol. Chem.*, **2003**, *278*(16), 13640-13646. http://dx.doi.org/10.1074/jbc.M300755200

[68] Hill, K.E.; Zhou, J.; McMahan, W.J.; Motley, A.K.; Burk, R.F. Neurological dysfunction occurs in mice with targeted deletion of the selenoprotein P gene. *J. Nutr.*, **2004**, *134*(1), 157-161.

[69] Hoefig, C.S.; Renko, K.; Kohrle, J.; Birringer, M.; Schomburg, L. Comparison of different selenocompounds with respect to nutritional value vs. toxicity using liver cells in culture. *J. Nutr. Biochem.*, **2011**, *22*(10), 945-955. http://dx.doi.org/10.1016/j.jnutbio.2010.08.006

[70] Hoffmann, P.R.; Hoge, S.C.; Li, P.A.; Hoffmann, F.W.; Hashimoto, A.C.; Berry, M.J. The selenoproteome exhibits widely varying, tissue-specific dependence on selenoprotein P for selenium supply. *NucleiC Acids Res.*, **2007**, *35*(12), 3963-3973. http://dx.doi.org/10.1093/nar/gkm355

[71] Hwang, D.Y.; Cho, J.S.; Oh, J.H.; Shim, S.B.; Jee, S.W.; Lee, S.H.; Seo, S.J.; Lee, S.K.; Lee, S.H.; Kim, Y.K. Differentially expressed genes in transgenic mice carrying human mutant presenilin-2 (N141I): correlation of selenoprotein M with Alzheimer's disease. *Neurochem. Res.*, **2005**, *30*(8), 1009-1019. http://dx.doi.org/10.1007/s11064-005-6787-6

[72] Hwang, D.Y.; Sin, J.S.; Kim, M.S.; Yim, S.Y.; Kim, Y.K.; Kim, C.K.; Kim, B.G.; Shim, S.B.; Jee, S.W.; Lee, S.H.; Bae, C.J.; Lee, B.C.; Jang, M.K.; Cho, J.S.; Chae, K.R. Overexpression of human selenoprotein M differentially regulates the concentrations of antioxidants and H2O2, the activity of antioxidant enzymes, and the composition of white blood cells in a transgenic rat. *Int. J. Mol. Med.*, **2008**, *21*(2), 169-179. http://dx.doi.org/10.3892/ijmm.21.2.169

[73] Hwang, O. Role of oxidative stress in Parkinson's disease. *Exp. Neurobiol.*, **2013**, *22*(1), 11-17. http://dx.doi.org/10.5607/en.2013.22.1.11

[74] Imam, S.Z.; el-Yazal, J.; Newport, G.D.; Itzhak, Y.; Cadet, J.L.; Slikker, W., Jr.; Ali, S.F. Methamphetamine-induced dopaminergic neurotoxicity: role of peroxynitrite and neuroprotective role of antioxidants and peroxynitrite decomposition catalysts. *Ann. N. Y. Acad. Sci.*, **2001**, *939*, 366-380. http://dx.doi.org/10.1111/j.1749-6632.2001.tb03646.x

[75] Ishrat, T.; Parveen, K.; Khan, M.M.; Khuwaja, G.; Khan, M.B.; Yousuf, S.; Ahmad, A.; Shrivastav, P.; Islam, F. Selenium prevents cognitive decline and oxidative damage in rat model of streptozotocin-induced experimental dementia of Alzheimer's type. *Brain Res.*, **2009**, *1281*, 117-127. http://dx.doi.org/10.1016/j.brainres.2009.04.010

[76] Jastrzebski, Z.; Czyzewska-Szafran, H.; Fijatek, Z.; Suchocki, P.; Fitak, B.A. Toxicity studies of a new selenium compound, Selol, in rats. *Drugs Exp. Clin. Res.*, **1995**, *21*(6), 217-220.

[77] Jastrzebski, Z.; Czyzewska-Szafran, H.; Remiszewska, M.; Fijalek, Z.; Fitak, B.A.; Suchocki, P. Pharmacokinetics of selol, a new agent containing selenium, in rats. *Drugs Exp. Clin. Res.*, **1997**, *23*(1), 7-11.

[78] Jeong, D.; Kim, T.S.; Chung, Y.W.; Lee, B.J.; Kim, I.Y. Selenoprotein W is a glutathione-dependent antioxidant *in vivo*. *FEBS Lett.*, **2002**, *517*(1-3), 225-228. http://dx.doi.org/10.1016/S0014-5793(02)02628-5

[79] Johansson, L.; Gafvelin, G.; Arner, E.S. Selenocysteine in proteins-properties and biotechnological use. *Biochim. Biophys. Acta*, **2005**, *1726*(1), 1-13. http://dx.doi.org/10.1016/j.bbagen.2005.05.010

[80] Jones, N.C.; Nguyen, T.; Corcoran, N.M.; Velakoulis, D.; Chen, T.; Grundy, R.; O'Brien, T.J.; Hovens, C.M. Targeting hyperphosphorylated tau with sodium selenate suppresses seizures in rodent models. *Neurobiol. Dis.*, **2012**, *45*(3), 897-901. http://dx.doi.org/10.1016/j.nbd.2011.12.005

[81] Kazmierczak, A.; Adamczyk, A.; Benigna-Strosznajder, J. The role of extracellular alpha-synuclein in molecular mechanisms of cell death. *Postepy Hig. Med. Dosw.,* **2013**, *67*, 1047-1057. http://dx.doi.org/10.5604/17322693.1074666

[82] Kazmierczak, A.; Czapski, G.A.; Adamczyk, A.; Gajkowska, B.; Strosznajder, J.B. A novel mechanism of non-Abeta component of Alzheimer's disease amyloid (NAC) neurotoxicity. Interplay between p53 protein and cyclin-dependent kinase 5 (Cdk5). *Neurochem. Int.*, **2011**, *58*(2), 206-214. http://dx.doi.org/10.1016/j.neuint.2010.11.018

[83] Khan, H.A. Selenium partially reverses the depletion of striatal dopamine and its metabolites in MPTP-treated C57BL mice. *Neurochem. Int.*, **2010**, *57*(5), 489-491. http://dx.doi.org/10.1016/j.neuint.2010.06.020

[84] Khan, M.B.; Hoda, M.N.; Ishrat, T.; Ahmad, S.; Moshahid Khan, M.; Ahmad, A.; Yusuf, S.; Islam, F. Neuroprotective efficacy of Nardostachys jatamansi and crocetin in conjunction with selenium in cognitive impairment. *Neurol. Sci.*, **2012**, *33*(5), 1011-1020. http://dx.doi.org/10.1007/s10072-011-0880-1

[85] Khurana, D.S.; Valencia, I.; Goldenthal, M.J.; Legido, A. Mitochondrial dysfunction in epilepsy. *Semin. Pediatr. Neurol.*, **2013**, *20*(3), 176-187. http://dx.doi.org/10.1016/j.spen.2013.10.001

[86] Kim, H.; Jhoo, W.; Shin, E.; Bing, G. Selenium deficiency potentiates methamphetamine-induced nigral neuronal loss; comparison with MPTP model. *Brain Res.*, **2000**, *862*(1-2), 247-252. http://dx.doi.org/10.1016/S0006-8993(00)02085-0

[87] Kim, H.C.; Jhoo, W.K.; Choi, D.Y.; Im, D.H.; Shin, E.J.; Suh, J.H.; Floyd, R.A.; Bing, G. Protection of methamphetamine nigrostriatal toxicity by dietary selenium. *Brain Res.*, **1999**, *851*(1-2), 76-86. http://dx.doi.org/10.1016/S0006-8993(99)02122-8

[88] Kim, H.Y.; Gladyshev, V.N. Methionine sulfoxide reductases: selenoprotein forms and roles in antioxidant protein repair in mammals. *Biochem. J.*, **2007**, *407*(3), 321-329. http://dx.doi.org/10.1042/BJ20070929

[89] Koizumi, H.; Fujisawa, H.; Suehiro, E.; Shirao, S.; Suzuki, M. Neuroprotective effects of ebselen following forebrain ischemia: involvement of glutamate and nitric oxide. *Neurol. Med. Chir. (Tokyo)*, **2011**, *51*(5), 337-343. http://dx.doi.org/10.2176/nmc.51.337

[90] Krol, M.B.; Gromadzinska, J.; Wasowicz, W. SeP, ApoER2 and megalin as necessary factors to maintain Se homeostasis in mammals. *J. Trace Elem. Med. Biol.*, **2012**, *26*(4), 262-266. http://dx.doi.org/10.1016/j.jtemb.2012.03.003

[91] Kryscio, R.J.; Abner, E.L.; Schmitt, F.A.; Goodman, P.J.; Mendiondo, M.; Caban-Holt, A.; Dennis, B.C.; Mathews, M.; Klein, E.A.; Crowley, J.J. A randomized controlled Alzheimer's disease prevention trial's evolution into an exposure trial: the PREADViSE Trial. *J. Nutr. Health Aging*, **2013**, *17*(1), 72-75. http://dx.doi.org/10.1007/s12603-013-0004-0

[92] Kryukov, G.V.; Castellano, S.; Novoselov, S.V.; Lobanov, A.V.; Zehtab, O.; Guigo, R.; Gladyshev, V.N. Characterization of mammalian selenoproteomes. *Science*, **2003**, *300*(5624), 1439-1443. http://dx.doi.org/10.1126/science.1083516

[93] Ksiazek J.; Sitarz K.; Anuszewska E.; Dudkiewicz Wilczanska J.; Roslon M.; Koroniewicz M.; P., S. Toxicity studies of selol-an organic selenium (IV) compound-*in vitro* research. *Int. J. Pharm. Pharm. Sci.*, **2014**, *6*(5, 2014).

[94] Kurokawa, S.; Berry, M.J. Selenium. Role of the essential metalloid in health. *Met. Ions Life Sci.*, **2013**, *13*, 499-534. http://dx.doi.org/10.1007/978-94-007-7500-8_16

[95] Lakshmi, B.V.; Sudhakar, M.; Prakash, K.S. Protective Effect of Selenium Against Aluminum Chloride-Induced Alzheimer's Disease: Behavioral and Biochemical Alterations in Rats. *Biol. Trace Elem. Res.*, **2015**. http://dx.doi.org/10.1007/s12011-015-0229-3

[96] Li, X.; Zhao, W.; Yang, H.; Zhang, J.; Ma, J. S14G-humanin restored cellular homeostasis disturbed by amyloid-beta protein. *Neural Regen. Res.*, **2013**, *8*(27), 2573-2580.

[97] Liang, L.P.; Patel, M. Seizure-induced changes in mitochondrial redox status. *Free Radic. Biol. Med.*, **2006**, *40*(2), 316-322. http://dx.doi.org/10.1016/j.freeradbiomed.2005.08.026

[98] Lillig, C.H.; Holmgren, A. Thioredoxin and related molecules--from biology to health and disease. *Antioxid. Redox Signal.*, **2007**, *9*(1), 25-47. http://dx.doi.org/10.1089/ars.2007.9.25

[99] Lippman, S.M.; Klein, E.A.; Goodman, P.J.; Lucia, M.S.; Thompson, I.M.; Ford, L.G.; Parnes, H.L.; Minasian, L.M.; Gaziano, J.M.; Hartline, J.A.; Parsons, J.K.; Bearden, J.D., 3rd; Crawford, E.D.; Goodman, G.E.; Claudio, J.; Winquist, E.; Cook, E.D.; Karp, D.D.; Walther, P.; Lieber, M.M.; Kristal, A.R.; Darke, A.K.; Arnold, K.B.; Ganz, P.A.; Santella, R.M.; Albanes, D.; Taylor, P.R.; Probstfield, J.L.; Jagpal, T.J.; Crowley, J.J.; Meyskens, F.L., Jr.; Baker, L.H.; Coltman, C.A., Jr. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *J. Am. Med. Assoc.*, **2009**, *301*(1), 39-51. http://dx.doi.org/10.1001/jama.2008.864

[100] Loef, M.; Schrauzer, G.N.; Walach, H. Selenium and Alzheimer's disease: a systematic review. *J. Alzheimers Dis.*, **2011**, *26*(1), 81-104.

[101] Loflin, J.; Lopez, N.; Whanger, P.D.; Kioussi, C. Selenoprotein W during development and oxidative stress. *J. Inorg. Biochem.*, **2006**, *100*(10), 1679-1684.

[102] Lovell, M.A.; Ehmann, W.D.; Butler, S.M.; Markesbery, W.R. Elevated thiobarbituric acid-reactive substances and antioxidant enzyme activity in the brain in Alzheimer's disease. *Neurology*, **1995**, *45*(8), 1594-1601. http://dx.doi.org/10.1016/j.jinorgbio.2006.05.018

[103] Lovell, M.A.; Xie, C.; Gabbita, S.P.; Markesbery, W.R. Decreased thioredoxin and increased thioredoxin reductase levels in Alzheimer's disease brain. *Free Radic. Biol. Med.*, **2000**, *28*(3), 418-427. http://dx.doi.org/10.1016/S0891-5849(99)00258-0

[104] Lubos, E.; Loscalzo, J.; Handy, D.E. Glutathione peroxidase-1 in health and disease: from molecular mechanisms to therapeutic opportunities. *Antioxid. Redox Signal.*, **2011**, *15*(7), 1957-1997. http://dx.doi.org/10.1089/ars.2010.3586

[105] Luchsinger, J.A.; Tang, M.X.; Shea, S.; Mayeux, R. Antioxidant vitamin intake and risk of Alzheimer disease. *Arch. Neurol.*, **2003**, *60*(2), 203-208. http://dx.doi.org/10.1001/archneur.60.2.203

[106] Luo, Z.; Liang, L.; Sheng, J.; Pang, Y.; Li, J.; Huang, L.; Li, X. Synthesis and biological evaluation of a new series of ebselen derivatives as glutathione peroxidase (GPx) mimics and cholinesterase inhibitors against Alzheimer's disease. *Bioorg. Med. Chem.*, **2014**, *22*(4), 1355-1361. http://dx.doi.org/10.1016/j.bmc.2013.12.066

[107] Maarouf, C.L.; Beach, T.G.; Adler, C.H.; Shill, H.A.; Sabbagh, M.N.; Wu, T.; Walker, D.G.; Kokjohn, T.A.; Roher, A.E. Cerebrospinal fluid biomarkers of neuropathologically diagnosed Parkinson's disease subjects. *Neurol. Res.*, **2012**, *34*(7), 669-676. http://dx.doi.org/10.1179/1743132812Y.0000000063

[108] Maraldi, T.; Riccio, M.; Zambonin, L.; Vinceti, M.; De Pol, A.; Hakim, G. Low levels of selenium compounds are selectively toxic for a human neuron cell line through ROS/RNS increase and apoptotic process activation. *Neurotoxicology*, **2011**, *32*(2), 180-187. http://dx.doi.org/10.1016/j.neuro.2010.10.008

[109] Martini, F.; Bruning, C.A.; Soares, S.M.; Nogueira, C.W.; Zeni, G. Inhibitory effect of ebselen on cerebral acetylcholinesterase activity *in vitro*: kinetics and reversibility of inhibition. *Curr. Pharm. Des.*, **2015**, *21*(7), 920-924. http://dx.doi.org/10.2174/1381612820666141014124319

[110] Matsui, M.; Oshima, M.; Oshima, H.; Takaku, K.; Maruyama, T.; Yodoi, J.; Taketo, M.M. Early embryonic lethality caused by targeted disruption of the mouse thioredoxin gene. *Dev. Biol.*, **1996**, *178*(1), 179-185. http://dx.doi.org/10.1006/dbio.1996.0208

[111] McClung, J.P.; Roneker, C.A.; Mu, W.; Lisk, D.J.; Langlais, P.; Liu, F.; Lei, X.G. Development of insulin resistance and obesity in mice overexpressing cellular glutathione peroxidase. *Proc. Natl. Acad. Sci. U. S. A.*, **2004**, *101*(24), 8852-8857. http://dx.doi.org/10.1073/pnas.0308096101

[112] Mehta, S.L.; Kumari, S.; Mendelev, N.; Li, P.A. Selenium preserves mitochondrial function, stimulates mitochondrial biogenesis, and reduces infarct volume after focal cerebral ischemia. *BMC Neurosci.*, **2012**, *13*, 79. http://dx.doi.org/10.1186/1471-2202-13-79

[113] Mehta, S.L.; Mendelev, N.; Kumari, S.; Andy Li, P. Overexpression of human selenoprotein H in neuronal cells enhances mitochondrial biogenesis and function through activation of protein kinase A, protein kinase B, and cyclic adenosine monophosphate response element-binding protein pathway. *Int. J. Biochem. Cell Biol.*, **2013**, *45*(3), 604-611. http://dx.doi.org/10.1016/j.biocel.2012.11.022

[114] Mendelev, N.; Mehta, S.L.; Idris, H.; Kumari, S.; Li, P.A. Selenite stimulates mitochondrial biogenesis signaling and enhances mitochondrial functional performance in murine hippocampal neuronal cells. *PLoS One*, **2012**, *7*(10), e47910. http://dx.doi.org/10.1371/journal.pone.0047910

[115] Mendelev, N.; Mehta, S.L.; Witherspoon, S.; He, Q.; Sexton, J.Z.; Li, P.A. Upregulation of human selenoprotein H in murine hippocampal neuronal cells promotes mitochondrial biogenesis and functional performance. *Mitochondrion*, **2011**, *11*(1), 76-82. http://dx.doi.org/10.1016/j.mito.2010.07.007

[116] Menon, B.; Ramalingam, K.; Kumar, R.V. Oxidative stress in patients with epilepsy is independent of antiepileptic drugs. *Seizure*, **2012**, *21*(10), 780-784. http://dx.doi.org/10.1016/j.seizure.2012.09.003

[117] Meseguer, M.; Garrido, N.; Simon, C.; Pellicer, A.; Remohi, J. Concentration of glutathione and expression of glutathione peroxidases 1 and 4 in fresh sperm provide a forecast of the outcome of cryopreservation of human spermatozoa. *J. Androl.*, **2004**, *25*(5), 773-780. http://dx.doi.org/10.1002/j.1939-4640.2004.tb02855.x

[118] Miller, J.A.; Oldham, M.C.; Geschwind, D.H. A systems level analysis of transcriptional changes in Alzheimer's disease and normal aging. *J .Neurosci.*, **2008**, *28*(6), 1410-1420. http://dx.doi.org/10.1523/JNEUROSCI.4098-07.2008

[119] Moussaoui, S.; Obinu, M.C.; Daniel, N.; Reibaud, M.; Blanchard, V.; Imperato, A. The antioxidant ebselen prevents neurotoxicity and clinical symptoms in a primate model of Parkinson's disease. *Exp. Neurol.*, **2000**, *166*(2), 235-245. http://dx.doi.org/10.1006/exnr.2000.7516

[120] Muller, A.; Cadenas, E.; Graf, P.; Sies, H. A novel biologically active seleno-organic compound--I. Glutathione peroxidase-like activity *in vitro* and antioxidant capacity of PZ 51 (Ebselen). *Biochem. Pharmacol.*, **1984**, *33*(20), 3235-3239.

[121] Musiani, F.; Ciurli, S.; Dikiy, A. Interaction of selenoprotein W with 14-3-3 proteins: a computational approach. *J.Proteome. Res.*, **2011**, *10*(3), 968-976. http://dx.doi.org/10.1021/pr101178k

[122] Nakayama, A.; Hill, K.E.; Austin, L.M.; Motley, A.K.; Burk, R.F. All regions of mouse brain are dependent on selenoprotein P for maintenance of selenium. *J. Nutr.*, **2007**, *137*(3), 690-693.

[123] Navarro-Alarcon, M.; Cabrera-Vique, C. Selenium in food and the human body: a review. *Sci. Total Environ.*, **2008**, *400*(1-3), 115-141. http://dx.doi.org/10.1016/j.scitotenv.2008.06.024

[124] Naziroglu, M. Role of selenium on calcium signaling and oxidative stress-induced molecular pathways in epilepsy. *Neurochem. Res.*, **2009**, *34*(12), 2181-2191. http://dx.doi.org/10.1007/s11064-009-0015-8

[125] Naziroglu, M.; Kutluhan, S.; Yilmaz, M. Selenium and topiramate modulates brain microsomal oxidative stress values, Ca2+-ATPase activity, and EEG records in pentylentetrazol-induced seizures in rats. *J. Membr. Biol.*, **2008**, *225*(1-3), 39-49. http://dx.doi.org/10.1007/s00232-008-9132-6

[126] Nonn, L.; Williams, R.R.; Erickson, R.P.; Powis, G. The absence of mitochondrial thioredoxin 2 causes massive apoptosis, exencephaly, and early embryonic lethality in homozygous mice. *Mol. Cell Biol.*, **2003**, *23*(3), 916-922. http://dx.doi.org/10.1128/MCB.23.3.916-922.2003

[127] O'Collins, V.E.; Macleod, M.R.; Donnan, G.A.; Horky, L.L.; van der Worp, B.H.; Howells, D.W. 1, 026 experimental treatments in acute stroke. *Ann. Neurol.*, **2006**, *59*(3), 467-477. http://dx.doi.org/10.1002/ana.20741

[128] Ogawa, A.; Yoshimoto, T.; Kikuchi, H.; Sano, K.; Saito, I.; Yamaguchi, T.; Yasuhara, H. Ebselen in acute middle cerebral artery occlusion: a placebo-controlled, double-blind clinical trial. *Cerebrovasc. Dis.*, **1999**, *9*(2), 112-118. http://dx.doi.org/10.1159/000015908

[129] Olde Rikkert, M.G.; Verhey, F.R.; Sijben, J.W.; Bouwman, F.H.; Dautzenberg, P.L.; Lansink, M.; Sipers, W.M.; van Asselt, D.Z.; van Hees, A.M.; Stevens, M.; Vellas, B.; Scheltens, P. Differences in nutritional status between very mild Alzheimer's disease patients and healthy controls. *J. Alzheimers Dis.*, **2014**, *41*(1), 261-271.

[130] Olm, E.; Fernandes, A.P.; Hebert, C.; Rundlof, A.K.; Larsen, E.H.; Danielsson, O.; Bjornstedt, M. Extracellular thiol-assisted selenium uptake dependent on the x(c)- cystine transporter explains the cancer-specific cytotoxicity of selenite. *Proc. Natl. Acad. Sci. U.S.A.*, **2009**, *106*(27), 11400-11405. http://dx.doi.org/10.1073/pnas.0902204106

[131] Ozbal, S.; Erbil, G.; Kocdor, H.; Tugyan, K.; Pekcetin, C.; Ozogul, C. The effects of selenium against cerebral ischemia-reperfusion injury in rats. *Neurosci. Lett.*, **2008**, *438*(3), 265-269. http://dx.doi.org/10.1016/j.neulet.2008.03.091

[132] Papp, L.V.; Lu, J.; Holmgren, A.; Khanna, K.K. From selenium to selenoproteins: synthesis, identity, and their role in human health. *Antioxid Redox Signal*, **2007**, *9*(7), 775-806. http://dx.doi.org/10.1089/ars.2007.1528

[133] Park, J.Y.; Seong, J.K.; Paik, Y.K. Proteomic analysis of diet-induced hypercholesterolemic mice. *Proteomics*, **2004**, *4*(2), 514-523. http://dx.doi.org/10.1002/pmic.200300623

[134] Persson, T.; Popescu, B.O. Oxidative stress in Alzheimer's disease: why did antioxidant therapy fail? *Oxid. Med. Cell. Longev*., **2014**, *2014*, 427318.

[135] Peters, M.M.; Hill, K.E.; Burk, R.F.; Weeber, E.J. Altered hippocampus synaptic function in selenoprotein P deficient mice. *Mol. Neurodegener.*, **2006**, *1*, 12. http://dx.doi.org/10.1186/1750-1326-1-12

[136] Pinton, S.; Bruning, C.A.; Sartori Oliveira, C.E.; Prigol, M.; Nogueira, C.W. Therapeutic effect of organoselenium dietary supplementation in a sporadic dementia of Alzheimer's type model in rats. *J. Nutr. Biochem.*, **2013**, *24*(1), 311-317. http://dx.doi.org/10.1016/j.jnutbio.2012.06.012

[137] Pocernich, C.B.; Butterfield, D.A. Elevation of glutathione as a therapeutic strategy in Alzheimer disease. *Biochim. Biophys. Acta*, **2012**, *1822*(5), 625-630. http://dx.doi.org/10.1016/j.bbadis.2011.10.003

[138] Popa-Wagner, A.; Mitran, S.; Sivanesan, S.; Chang, E.; Buga, A.M. ROS and brain diseases: the good, the bad, and the ugly. *Oxid. Med. Cell. Longev.*, **2013**, *2013*, 963520.

[139] Porat, A.; Sagiv, Y.; Elazar, Z. A 56-kDa selenium-binding protein participates in intra-Golgi protein transport. *J.Biol .Chem.*, **2000**, *275*(19), 14457-14465. http://dx.doi.org/10.1074/jbc.275.19.14457

[140] Power, J.H.; Blumbergs, P.C. Cellular glutathione peroxidase in human brain: cellular distribution, and its potential role in the degradation of Lewy bodies in Parkinson's disease and dementia with Lewy bodies. *Acta Neuropathol.*, **2009**, *117*(1), 63-73. http://dx.doi.org/10.1007/s00401-008-0438-3

[141] Pratico, D. Evidence of oxidative stress in Alzheimer's disease brain and antioxidant therapy: lights and shadows. *Ann. N. Y. Acad. Sci.*, **2008**, *1147*, 70-78. http://dx.doi.org/10.1196/annals.1427.010

[142] Prohaska, J.R.; Ganther, H.E. Selenium and glutathione peroxidase in developing rat brain. *J. Neurochem.*, **1976**, *27*(6), 1379-1387. http://dx.doi.org/10.1111/j.1471-4159.1976.tb02619.x

[143] Pumford, N.R.; Martin, B.M.; Hinson, J.A. A metabolite of acetaminophen covalently binds to the 56 kDa selenium binding protein. *Biochem. Biophys. Res. Commun.*, **1992**, *182*(3), 1348-1355. http://dx.doi.org/10.1016/0006-291X(92)91881-P

[144] Qiao, X.; Tian, J.; Chen, P.; Wang, C.; Ni, J.; Liu, Q. Galectin-1 is an interactive protein of selenoprotein M in the brain. *Int. J. Mol. Sci.*, **2013**, *14*(11), 22233-22245. http://dx.doi.org/10.3390/ijms141122233

[145] Rahden-Staron, I.; Suchocki, P.; Czeczot, H. Evaluation of mutagenic activity of the organo-selenium compound Selol by use of the *Salmonella typhimurium* mutagenicity assay. *Mutat. Res.*, **2010**, *699*(1-2), 44-46. http://dx.doi.org/10.1016/j.mrgentox.2010.04.018

[146] Ramaekers, V.T.; Calomme, M.; Vanden Berghe, D.; Makropoulos, W. Selenium deficiency triggering intractable seizures. *Neuropediatrics*, **1994**, *25*(4), 217-223. http://dx.doi.org/10.1055/s-2008-1073025

[147] Raman, A.V.; Pitts, M.W.; Seyedali, A.; Hashimoto, A.C.; Bellinger, F.P.; Berry, M.J. Selenoprotein W expression and regulation in mouse brain and neurons. *Brain Behav.*, **2013**, *3*(5), 562-574. http://dx.doi.org/10.1002/brb3.159

[148] Ramos, P.; Santos, A.; Pinto, N.R.; Mendes, R.; Magalhaes, T.; Almeida, A. Anatomical regional differences in selenium levels in the human brain. *Biol. Trace Elem. Res.*, **2015**, *163*(1-2), 89-96. http://dx.doi.org/10.1007/s12011-014-0160-z

[149] Rayman, M.P. Selenium and human health. *Lancet*, **2012**, *379*(9822), 1256-1268. http://dx.doi.org/10.1016/S0140-6736(11)61452-9

[150] Reddy, P.H.; Reddy, T.P. Mitochondria as a therapeutic target for aging and neurodegenerative diseases. *Curr. Alzheimer Res.*, **2011**, *8*(4), 393-409. http://dx.doi.org/10.2174/156720511795745401

[151] Reeves, M.A.; Bellinger, F.P.; Berry, M.J. The neuroprotective functions of selenoprotein M and its role in cytosolic calcium regulation. *Antioxid. Redox Signal.*, **2010**, *12*(7), 809-818. http://dx.doi.org/10.1089/ars.2009.2883

[152] Rehni, A.K.; Singh, T.G. Selenium induced anticonvulsant effect: a potential role of prostaglandin E(1) receptor activation linked mechanism. *J. Trace Elem. Med. Biol.*, **2013**, *27*(1), 31-39. http://dx.doi.org/10.1016/j.jtemb.2012.05.001

[153] Reitz, C.; Brayne, C.; Mayeux, R. Epidemiology of Alzheimer disease. *Nat. Rev. Neurol.*, **2011**, *7*(3), 137-152. http://dx.doi.org/10.1038/nrneurol.2011.2

[154] Resende, R.; Moreira, P.I.; Proenca, T.; Deshpande, A.; Busciglio, J.; Pereira, C.; Oliveira, C.R. Brain oxidative stress in a triple-transgenic mouse model of Alzheimer disease. *Free Radic. Biol. Med.*, **2008**, *44*(12), 2051-2057. http://dx.doi.org/10.1016/j.freeradbiomed.2008.03.012

[155] Ridet, J.L.; Bensadoun, J.C.; Deglon, N.; Aebischer, P.; Zurn, A.D. Lentivirus-mediated expression of glutathione peroxidase: neuroprotection in murine models of Parkinson's disease. *Neurobiol. Dis.*, **2006**, *21*(1), 29-34. http://dx.doi.org/10.1016/j.nbd.2005.06.003

[156] Rigsby, C.S.; Pollock, D.M.; Dorrance, A.M. Dietary potassium supplementation improves vascular structure and ameliorates the damage caused by cerebral ischemia in normotensive rats. *Nutr. Metab .(Lond)*, **2008**, *5*, 3.

[157] Rita Cardoso, B.; Silva Bandeira, V.; Jacob-Filho, W.; Franciscato Cozzolino, S.M. Selenium status in elderly: Relation to cognitive decline. *J. Trace Elem. Med. Biol.*, **2014**. http://dx.doi.org/10.1016/j.jtemb.2014.08.009

[158] Rueli, R.H.; Parubrub, A.C.; Dewing, A.S.; Hashimoto, A.C.; Bellinger, M.T.; Weeber, E.J.; Uyehara-Lock, J.H.; White, L.R.; Berry, M.J.; Bellinger, F.P. Increased Selenoprotein P in Choroid Plexus and Cerebrospinal Fluid in Alzheimer's Disease Brain. *J. Alzheimers Dis.*, **2014**.

[159] Rumia, J.; Marmol, F.; Sanchez, J.; Gimenez-Crouseilles, J.; Carreno, M.; Bargallo, N.; Boget, T.; Pintor, L.; Setoain, X.; Donaire, A.; Saez, G.T.; Ribalta, T.; Ferrer, E.; Puig-Parellada, P. Oxidative stress markers in the neocortex of drug-resistant epilepsy patients submitted to epilepsy surgery. *Epilepsy Res.*, **2013**, *107*(1-2), 75-81. http://dx.doi.org/10.1016/j.eplepsyres.2013.08.020

[160] Rundlof, A.K.; Arner, E.S. Regulation of the mammalian selenoprotein thioredoxin reductase 1 in relation to cellular phenotype, growth, and signaling events. *Antioxid. Redox Signal.*, **2004**, *6*(1), 41-52. http://dx.doi.org/10.1089/152308604771978336

[161] Saad, K.; Hammad, E.; Hassan, A.F.; Badry, R. Trace element, oxidant, and antioxidant enzyme values in blood of children with refractory epilepsy. *Int. J. Neurosci.*, **2014**, *124*(3), 181-186. http://dx.doi.org/10.3109/00207454.2013.831851

[162] Saito, I.; Asano, T.; Sano, K.; Takakura, K.; Abe, H.; Yoshimoto, T.; Kikuchi, H.; Ohta, T.; Ishibashi, S. Neuroprotective effect of an antioxidant, ebselen, in patients with delayed neurological deficits after aneurysmal subarachnoid hemorrhage. *Neurosurgery*, **1998**, *42*(2), 269-277; discussion 277-268.

[163] Sanmartin, C.; Plano, D.; Font, M.; Palop, J.A. Selenium and clinical trials: new therapeutic evidence for multiple diseases. *Curr. Med. Chem.*, **2011**, *18*(30), 4635-4650. http://dx.doi.org/10.2174/092986711797379249

[164] Saute, R.; Dabbs, K.; Jones, J.E.; Jackson, D.C.; Seidenberg, M.; Hermann, B.P. Brain morphology in children with epilepsy and ADHD. *PLoS One*, **2014**, *9*(4), e95269. http://dx.doi.org/10.1371/journal.pone.0095269

[165] Savaskan, N.E.; Borchert, A.; Brauer, A.U.; Kuhn, H. Role for glutathione peroxidase-4 in brain development and neuronal apoptosis: specific induction of enzyme expression in reactive astrocytes following brain injury. *Free Radic. Biol. Med.*, **2007**, *43*(2), 191-201. http://dx.doi.org/10.1016/j.freeradbiomed.2007.03.033

[166] Savaskan, N.E.; Brauer, A.U.; Kuhbacher, M.; Eyupoglu, I.Y.; Kyriakopoulos, A.; Ninnemann, O.; Behne, D.; Nitsch, R. Selenium deficiency increases susceptibility to glutamate-induced excitotoxicity. *FASEBJ.*, **2003**, *17*(1), 112-114.

[167] Savaskan, N.E.; Ufer, C.; Kuhn, H.; Borchert, A. Molecular biology of glutathione peroxidase 4: from genomic structure to developmental expression and neural function. *Biol. Chem.***2007**, *388*(10), 1007-1017. http://dx.doi.org/10.1515/BC.2007.126

[168] Schomburg, L.; Schweizer, U.; Holtmann, B.; Flohe, L.; Sendtner, M.; Kohrle, J. Gene disruption discloses role of selenoprotein P in selenium delivery to target tissues. *Biochem. J.*, **2003**, *370*(Pt 2), 397-402. http://dx.doi.org/10.1042/bj20021853

[169] Schweizer, U.; Brauer, A.U.; Kohrle, J.; Nitsch, R.; Savaskan, N.E. Selenium and brain function: a poorly recognized liaison. *Brain Res. Brain Res. Rev.,* **2004**, *45*(3), 164-178. http://dx.doi.org/10.1016/j.brainresrev.2004.03.004

[170] Schweizer, U.; Michaelis, M.; Kohrle, J.; Schomburg, L. Efficient selenium transfer from mother to offspring in selenoprotein-P-deficient mice enables dose-dependent rescue of phenotypes associated with selenium deficiency. *Biochem. J.*, **2004**, *378*(Pt 1), 21-26. http://dx.doi.org/10.1042/bj20031795

[171] Schweizer, U.; Schomburg, L.; Savaskan, N.E. The neurobiology of selenium: lessons from transgenic mice. *J. Nutr.*, **2004**, *134*(4), 707-710.

[172] Schweizer, U.; Streckfuss, F.; Pelt, P.; Carlson, B.A.; Hatfield, D.L.; Kohrle, J.; Schomburg, L. Hepatically derived selenoprotein P is a key factor for kidney but not for brain selenium supply. *Biochem. J.*, **2005**, *386*(Pt 2), 221-226. http://dx.doi.org/10.1042/BJ20041973

[173] Seo, J.Y.; Lee, C.H.; Cho, J.H.; Choi, J.H.; Yoo, K.Y.; Kim, D.W.; Park, O.K.; Li, H.; Choi, S.Y.; Hwang, I.K.; Won, M.H. Neuroprotection of ebselen against ischemia/reperfusion injury involves GABA shunt enzymes. *J. Neurol. Sci.*, **2009**, *285*(1-2), 88-94. http://dx.doi.org/10.1016/j.jns.2009.05.029

[174] Seyfried, J.; Wullner, U. Inhibition of thioredoxin reductase induces apoptosis in neuronal cell lines: role of glutathione and the MKK4/JNK pathway. *Biochem .Biophys. Res. Commun.*, **2007**, *359*(3), 759-764. http://dx.doi.org/10.1016/j.bbrc.2007.05.176

[175] Sharma, A.K.; Amin, S. Post SELECT: selenium on trial. *Future Med Chem*, **2013**, *5*(2), 163-174. http://dx.doi.org/10.4155/fmc.12.203

[176] Sheng, P.F.; Jiang, Y.; Zhang, Z.W.; Zhang, J.L.; Li, S.; Zhang, Z.Q.; Xu, S.W. The effect of Se-deficient diet on gene expression of inflammatory cytokines in chicken brain. *Biometals*, **2014**, *27*(1), 33-43. http://dx.doi.org/10.1007/s10534-013-9682-7

[177] Shi, M.; Bradner, J.; Bammler, T.K.; Eaton, D.L.; Zhang, J.; Ye, Z.; Wilson, A.M.; Montine, T.J.; Pan, C.; Zhang, J. Identification of glutathione S-transferase pi as a protein involved in Parkinson disease progression. *Am. J. Pathol.*, **2009**, *175*(1), 54-65. http://dx.doi.org/10.2353/ajpath.2009.081019

[178] Shivakumar, B.R.; Kolluri, S.V.; Ravindranath, V. Glutathione and protein thiol homeostasis in brain during reperfusion after cerebral ischemia. *J. Pharmacol. Exp. Ther.*, **1995**, *274*(3), 1167-1173.

[179] Shrivastava, S. Combined effect of HEDTA and selenium against aluminum induced oxidative stress in rat brain. *J. Trace Elem. Med .Biol.*, **2012**, *26*(2-3), 210-214. http://dx.doi.org/10.1016/j.jtemb.2012.04.014

[180] Shultz, S.R.; Wright, D.K.; Zheng, P.; Stuchbery, R.; Liu, S.J.; Sashindranath, M.; Medcalf, R.L.; Johnston, L.A.; Hovens, C.M.; Jones, N.C.; O'Brien, T.J. Sodium selenate reduces hyper-phosphorylated tau and improves outcomes after traumatic brain injury. *Brain*, **2015**, *138*(Pt 5), 1297-1313. http://dx.doi.org/10.1093/brain/awv053

[181] Singh, N.; Halliday, A.C.; Thomas, J.M.; Kuznetsova, O.V.; Baldwin, R.; Woon, E.C.; Aley, P.K.; Antoniadou, I.; Sharp, T.; Vasudevan, S.R.; Churchill, G.C. A safe lithium mimetic for bipolar disorder. *Nat. Commun.*, **2013**, *4*, 1332. http://dx.doi.org/10.1038/ncomms2320

[182] Smeyne, M.; Smeyne, R.J. Glutathione metabolism and Parkinson's disease. *Free Radic. Biol. Med.*, **2013**, *62*, 13-25. http://dx.doi.org/10.1016/j.freeradbiomed.2013.05.001

[183] Smorgon, C.; Mari, E.; Atti, A.R.; Dalla Nora, E.; Zamboni, P.F.; Calzoni, F.; Passaro, A.; Fellin, R. Trace elements and cognitive impairment: an elderly cohort study. *Arch .Gerontol. Geriatr. Suppl.*, **2004**, (9), 393-402. http://dx.doi.org/10.1016/j.archger.2004.04.050

[184] Sochacka, M.; Giebultowicz, J.; Remiszewska, M.; Suchocki, P.; Wroczynski, P. Effects of Selol 5% supplementation on the activity or concentration of antioxidants and malondialdehyde level in the blood of healthy mice. *Pharmacol. Rep.*, **2014**, *66*(2), 301-310. http://dx.doi.org/10.1016/j.pharep.2013.10.004

[185] Soerensen, J.; Jakupoglu, C.; Beck, H.; Forster, H.; Schmidt, J.; Schmahl, W.; Schweizer, U.; Conrad, M.; Brielmeier, M. The role of thioredoxin reductases in brain development. *PLoS One*, **2008**, *3*(3), e1813.

[186] Song, G.; Zhang, Z.; Wen, L.; Chen, C.; Shi, Q.; Zhang, Y.; Ni, J.; Liu, Q. Selenomethionine ameliorates cognitive decline, reduces tau hyperphosphorylation, and reverses synaptic deficit in the triple transgenic mouse model of Alzheimer's disease. *J. Alzheimers Dis.*, **2014**, *41*(1), 85-99.

[187] Spencer, S.S.; Kim, J.; deLanerolle, N.; Spencer, D.D. Differential neuronal and glial relations with parameters of ictal discharge in mesial temporal lobe epilepsy. *Epilepsia*, **1999**, *40*(6), 708-712. http://dx.doi.org/10.1111/j.1528-1157.1999.tb00767.x

[188] Stańczyk, M.; M., J.; Wilk, M.; Suchocki, P.; E., A. The effect of selenium on redox state and thiols changes in lung tissue after Selol, a new organoselenium (IV) compound, administration. *Centr. Eur. J. Immunol.*, **2010**, *7*(35), 115-122.

[189] Steinbrenner, H.; Sies, H. Selenium homeostasis and antioxidant selenoproteins in brain: implications for disorders in the central nervous system. *Arch. Biochem. Biophys.*, **2013**, *536*(2), 152-157. http://dx.doi.org/10.1016/j.abb.2013.02.021

[190] Storch, A.; Jost, W.H.; Vieregge, P.; Spiegel, J.; Greulich, W.; Durner, J.; Muller, T.; Kupsch, A.; Henningsen, H.; Oertel, W.H.; Fuchs, G.; Kuhn, W.; Niklowitz, P.; Koch, R.; Herting, B.; Reichmann, H. Randomized, double-blind, placebo-controlled trial on symptomatic effects of coenzyme Q(10) in Parkinson disease. *Arch. Neurol.*, **2007**, *64*(7), 938-944. http://dx.doi.org/10.1001/archneur.64.7.nct60005

[191] Sun, Y.; Butler, J.A.; Whanger, P.D. Glutathione peroxidase activity and selenoprotein W levels in different brain regions of selenium-depleted rats(1). *J. Nutr. Biochem.*, **2001**, *12*(2), 88-94. http://dx.doi.org/10.1016/S0955-2863(00)00130-3

[192] Takagi, Y.; Gon, Y.; Todaka, T.; Nozaki, K.; Nishiyama, A.; Sono, H.; Hashimoto, N.; Kikuchi, H.; Yodoi, J. Expression of thioredoxin is enhanced in atherosclerotic plaques and during neointima formation in rat arteries. *Lab. Invest.*, **1998**, *78*(8), 957-966.

[193] Terasaki, Y.; Liu, Y.; Hayakawa, K.; Pham, L.D.; Lo, E.H.; Ji, X.; Arai, K. Mechanisms of neurovascular dysfunction in acute ischemic brain. *Curr. Med. Chem.*, **2014**, *21*(18), 2035-2042. http://dx.doi.org/10.2174/0929867321666131228223400

[194] Tofaris, G.K.; Kim, H.T.; Hourez, R.; Jung, J.W.; Kim, K.P.; Goldberg, A.L. Ubiquitin ligase Nedd4 promotes alpha-synuclein degradation by the endosomal-lysosomal pathway. *Proc. Natl. Acad. Sci. U.S.A.*, **2011**, *108*(41), 17004-17009. http://dx.doi.org/10.1073/pnas.1109356108

[195] Tolonen, M.; Halme, M.; Sarna, S. Vitamin E and selenium supplementation in geriatric patients : A double-blind preliminary clinical trial. *Biol. Trace Elem. Res.***1985**, *7*(3), 161-168. http://dx.doi.org/10.1007/BF02916538

[196] Trepanier, G.; Furling, D.; Puymirat, J.; Mirault, M.E. Immuno-cytochemical localization of seleno-glutathione peroxidase in the adult mouse brain. *Neuroscience*, **1996**, *75*(1), 231-243. http://dx.doi.org/10.1016/0306-4522(96)00222-9

[197] Turanov, A.A.; Lobanov, A.V.; Hatfield, D.L.; Gladyshev, V.N. UGA codon position-dependent incorporation of selenocysteine into mammalian selenoproteins. *Nucleic Acids Res.*, **2013**, *41*(14), 6952-6959. http://dx.doi.org/10.1093/nar/gkt409

[198] Turanov, A.A.; Xu, X.M.; Carlson, B.A.; Yoo, M.H.; Gladyshev, V.N.; Hatfield, D.L. Biosynthesis of selenocysteine, the 21st amino acid in the genetic code, and a novel pathway for cysteine biosynthesis. *Adv. Nutr.*, **2011**, *2*(2), 122-128. http://dx.doi.org/10.3945/an.110.000265

[199] Uguz, A.C.; Naziroglu, M. Effects of selenium on calcium signaling and apoptosis in rat dorsal root ganglion neurons induced by oxidative stress. *Neurochem. Res.*, **2012**, *37*(8), 1631-1638. http://dx.doi.org/10.1007/s11064-012-0758-5

[200] Unsal, C.; Oran, M.; Albayrak, Y.; Aktas, C.; Erboga, M.; Topcu, B.; Uygur, R.; Tulubas, F.; Yanartas, O.; Ates, O.; Ozen, O.A. Neuroprotective effect of ebselen against intracerebroventricular streptozotocin-induced neuronal apoptosis and oxidative stress in rats. *Toxicol. Ind. Health*, **2013**.

[201] Valentine, W.M.; Hill, K.E.; Austin, L.M.; Valentine, H.L.; Goldowitz, D.; Burk, R.F. Brainstem axonal degeneration in mice with deletion of selenoprotein p. *Toxicol. Pathol.*, **2005**, *33*(5), 570-576. http://dx.doi.org/10.1080/01926230500243045

[202] van Eersel, J.; Ke, Y.D.; Liu, X.; Delerue, F.; Kril, J.J.; Gotz, J.; Ittner, L.M. Sodium selenate mitigates tau pathology, neurodegeneration, and functional deficits in Alzheimer's disease models. *Proc. Natl. Acad. Sci. U.S.A.*, **2010**, *107*(31), 13888-13893. http://dx.doi.org/10.1073/pnas.1009038107

[203] Vinceti, M.; Mandrioli, J.; Borella, P.; Michalke, B.; Tsatsakis, A.; Finkelstein, Y. Selenium neurotoxicity in humans: bridging

laboratory and epidemiologic studies. *Toxicol. Lett.*, **2014**, *230*(2), 295-303. http://dx.doi.org/10.1016/j.toxlet.2013.11.016

[204] Vural, H.; Demirin, H.; Kara, Y.; Eren, I.; Delibas, N. Alterations of plasma magnesium, copper, zinc, iron and selenium concentrations and some related erythrocyte antioxidant enzyme activities in patients with Alzheimer's disease. *J. Trace Elem. Med. Biol.*, **2010**, *24*(3), 169-173. http://dx.doi.org/10.1016/j.jtemb.2010.02.002

[205] Whanger, P.D. Selenocompounds in plants and animals and their biological significance. *J. Am. Coll. Nutr.*, **2002**, *21*(3), 223-232. http://dx.doi.org/10.1080/07315724.2002.10719214

[206] Wilkaniec, A.; Strosznajder, J.B.; Adamczyk, A. Toxicity of extracellular secreted alpha-synuclein: Its role in nitrosative stress and neurodegeneration. *Neurochem. Int.*, **2013**, *62*(5), 776-783. http://dx.doi.org/10.1016/j.neuint.2013.02.004

[207] Xu, S.W.; Yao, H.D.; Zhang, J.; Zhang, Z.W.; Wang, J.T.; Zhang, J.L.; Jiang, Z.H. The oxidative damage and disbalance of calcium homeostasis in brain of chicken induced by selenium deficiency. *Biol. Trace Elem. Res.*, **2013**, *151*(2), 225-233. http://dx.doi.org/10.1007/s12011-012-9552-0

[208] Xu, X.M.; Carlson, B.A.; Mix, H.; Zhang, Y.; Saira, K.; Glass, R.S.; Berry, M.J.; Gladyshev, V.N.; Hatfield, D.L. Biosynthesis of selenocysteine on its tRNA in eukaryotes. *PLoS Biol*, **2007**, *5*(1), e4. http://dx.doi.org/10.1371/journal.pbio.0050004

[209] Yamaguchi, T.; Sano, K.; Takakura, K.; Saito, I.; Shinohara, Y.; Asano, T.; Yasuhara, H. Ebselen in acute ischemic stroke: a placebo-controlled, double-blind clinical trial. Ebselen Study Group. *Stroke*, **1998**, *29*(1), 12-17. http://dx.doi.org/10.1161/01.STR.29.1.12

[210] Yamashita, M.; Yamashita, Y.; Suzuki, T.; Kani, Y.; Mizusawa, N.; Imamura, S.; Takemoto, K.; Hara, T.; Hossain, M.A.; Yabu, T.; Touhata, K. Selenoneine, a novel selenium-containing compound, mediates detoxification mechanisms against methylmercury accumulation and toxicity in zebrafish embryo. *Mar. Biotechnol. (NY)*, **2013**, *15*(5), 559-570. http://dx.doi.org/10.1007/s10126-013-9508-1

[211] Yamashita, Y.; Yabu, T.; Yamashita, M. Discovery of the strong antioxidant selenoneine in tuna and selenium redox metabolism. *World J. Biol. Chem.*, **2010**, *1*(5), 144-150. http://dx.doi.org/10.4331/wjbc.v1.i5.144

[212] Yan, J.; Barrett, J.N. Purification from bovine serum of a survival-promoting factor for cultured central neurons and its identification as selenoprotein-P. *J. Neurosci.*, **1998**, *18*(21), 8682-8691.

[213] Younes-Mhenni, S.; Aissi, M.; Mokni, N.; Boughammoura-Bouatay, A.; Chebel, S.; Frih-Ayed, M.; Kerkeni, A.; Bost, M.; Chazot, G.; Sfar, M.T.; Sfar, M.H. Serum copper, zinc and selenium levels in Tunisian patients with Parkinson's disease. *Tunis Med.*, **2013**, *91*(6), 402-405.

[214] Yousuf, S.; Atif, F.; Ahmad, M.; Hoda, M.N.; Khan, M.B.; Ishrat, T.; Islam, F. Selenium plays a modulatory role against cerebral ischemia-induced neuronal damage in rat hippocampus. *Brain Res.*, **2007**, *1147*, 218-225. http://dx.doi.org/10.1016/j.brainres.2007.01.143

[215] Yurekli, V.A.; Naziroglu, M. Selenium and topiramate attenuates blood oxidative toxicity in patients with epilepsy: a clinical pilot study. *Biol. Trace Elem. Res.*, **2013**, *152*(2), 180-186. http://dx.doi.org/10.1007/s12011-013-9616-9

[216] Zachara, B.A.; Pawluk, H.; Bloch-Boguslawska, E.; Sliwka, K.M.; Korenkiewicz, J.; Skok, Z.; Ryc, K. Tissue level, distribution, and total body selenium content in healthy and diseased humans in Poland. *Arch. Environ. Health*, **2001**, *56*(5), 461-466. http://dx.doi.org/10.1080/00039890109604483

[217] Zafar, K.S.; Siddiqui, A.; Sayeed, I.; Ahmad, M.; Salim, S.; Islam, F. Dose-dependent protective effect of selenium in rat model of Parkinson's disease: neurobehavioral and neurochemical evidences. *J. Neurochem.*, **2003**, *84*(3), 438-446. http://dx.doi.org/10.1046/j.1471-4159.2003.01531.x

[218] Zhang, G.; Nitteranon, V.; Guo, S.; Qiu, P.; Wu, X.; Li, F.; Xiao, H.; Hu, Q.; Parkin, K.L. Organoselenium compounds modulate extracellular redox by induction of extracellular cysteine and cell surface thioredoxin reductase. *Chem. Res. Toxicol.*, **2013**, *26*(3), 456-464. http://dx.doi.org/10.1021/tx300515j

[219] Zhang, S.; Rocourt, C.; Cheng, W.H. Selenoproteins and the aging brain. *Mech. Ageing Dev.*, **2010**, *131*(4), 253-260. http://dx.doi.org/10.1016/j.mad.2010.02.006

[220] Zhang, Y.; Zhou, Y.; Schweizer, U.; Savaskan, N.E.; Hua, D.; Kipnis, J.; Hatfield, D.L.; Gladyshev, V.N. Comparative analysis of selenocysteine machinery and selenoproteome gene expression in mouse brain identifies neurons as key functional sites of selenium in mammals. *J .Biol .Chem.*, **2008**, *283*(4), 2427-2438. http://dx.doi.org/10.1074/jbc.M707951200

[221] Zhong, L.; Holmgren, A. Essential role of selenium in the catalytic activities of mammalian thioredoxin reductase revealed by characterization of recombinant enzymes with selenocysteine mutations. *J. Biol. Chem.*, **2000**, *275*(24), 18121-18128. http://dx.doi.org/10.1074/jbc.M000690200

Received: May 01, 2015 Revised: August 20, 2015 Accepted: September 16, 2015