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Physiopathological Role of Selenium and Selenoprotein in Neuropsychiatric Disease

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Selenium is widely distributed throughout the body, but it is particularly well maintained in the brain, even upon prolonged dietary selenium deficiency. Increased oxidative stress has been proposed as a pathomechanism in brain diseases and disorders including, among others, epilepsy, obsessive-compulsive disorders, Parkinson's disease, stroke and depression. Glutathione peroxidases and thioredoxin reductases are selenium-dependent enzymes involved in antioxidant defense and intracellular redox regulation and modulation. Selenium depletion in animals is associated with decreased activities of selenium-dependent enzymes and leads to enhanced cell loss in models of neurodegenerative disease. Genetic inactivation of cellular glutathione peroxidases increases the sensitivity towards neurotoxins and brain ischemia. Conversely, increased glutathione peroxidases activity as a result of increased selenium supply or overexpression ameliorates the outcome in the same models of disease. Genetic inactivation of selenoprotein P leads to a marked reduction of brain selenium content, which has not been achieved by dietary selenium depletion and to a movement disorder and spontaneous seizures. Here we review the role of selenium for the neuropsychiatric disorders under physiopathological conditions.

Key words: Antioxidant, brain functions, glutathione peroxidase, selenium, selenoprotein

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INTRODUCTION

The requirement of the trace element selenium (Se) for life and its beneficial role in human health has been known for several decades. Se is known primarily for its antioxidant activity and, in therapeutic aspects, for its chemopreventive properties (Papp *et al*., 2007; Rayman, 2000). Much of its beneficial influence on human health is attributed to its presence within at least 25 proteins (Kryukov *et al*., 2003). The essentiality of this trace element is due to the requirement for the 21st amino acid, selenocysteine (Sec), in a small number of selenoproteins (Low and Berry, 1996). Sec is co-translationally incorporated into selenoproteins at UGA codons, which typically function as stop codons. Most selenoprotein mRNAs contain a single UGA codon encoding a single selenocysteine residue per polypeptide chain and a single specific RNA secondary structure, termed a selenocysteine insertion sequence (SECIS) element, directing incorporation of this amino acid. This rare amino acid is found in the active site of all selenoenzymes characterized to date, e.g. Sec is critical to the catalytic activities of the glutathione peroxidases (GPx), iodothyronine deiodinases, thioredoxin reductases (TrxR) and methionine sulfoxide reductases (Pappas *et al*., 2008).

In addition to these enzymes are a growing number of selenoproteins whose functions are uncertain, including selenoprotein P (Sepp1), selenoprotein W (SelW), a 15-kDa selenoprotein identified by biochemical methods and selenoproteins H, I, K, M, N, O, S, T, U and V, identified through genomics (Castellano *et al*., 2001). In addition to incorporation as Sec, selenium can replace sulfur in methionine, forming selenomethionine. Consequently, Se can be tightly bound by some proteins, known as selenium-binding proteins, to distinguish them from true selenoproteins.

Selenium's physiological role has remained obscure in brain. Recently, the introduction of transgenics into the Se field has put new emphasis on a long debated and largely unrecognized relationship between the essential trace element Se and brain physiology. Here, we will review recent findings on Se biology and we will try to unite these findings to shape a new view on the role of Se for brain function.

SELENIUM

Selenium metabolism: The entry point of Se in animals is via plants, which absorb the element in its inorganic form from the soil. On a global scale, Se availability in the soil varies between areas. Low Se content is observed in volcanic regions (Mushak, 1985). The presence of other elements, such as sulphur, aluminium and iron, also negatively affects the uptake of Se by plants (Jonnalagadda and Roa, 1993). Consequently, selenium deficiency-linked disorders in animals and humans have been documented in such areas and where the food is produced mainly locally. In plants, Se becomes converted to organic forms such as methylated low-molecular-weight Se compounds and the amino acids selenomethionine (SeMet) and Sec. SeMet is the major selenocompound in cereal grains, legumes and soybeans and although it serves as a major precursor for Sec synthesis in animals, additional Se metabolites also are available for this process (Whanger, 2002).

Selenium and health: Se is essential for life and no doubt exists that adequate amounts of this element are required for optimal human health. Prenatal Se supplementation provides an effective antioxidant system that is already in place at the time of birth and postnatal Se supplementation becomes the main determinant of progeny Se status after the first few days of progeny life (Pappas *et al*., 2008).

Many of its physiologic roles are directly attributed to its presence within selenoproteins. For example, one of the most fundamental cellular processes, DNA synthesis, depends on the presence of Se within the catalytic site of thioredoxin reductases (Arner and Holmgren, 2000). Moderate Se deficiency has been linked to many conditions, such as increased cancer and infection risk, male infertility, decrease in immune and thyroid function and several neurologic conditions, including Alzheimer's and Parkinson's disease (Rayman, 2000).

Selenium in neuropsychiatric disease and disorders: The metabolism of Se by the brain differs from other organs in that at times of deficiency the brain retains Se to a greater extent. The preferential retention of Se in the brain suggests that it plays important functions. To date mood is the clearest example of an aspect of psychological functioning that is modified by Se intake. Numerous studies (Benton and Cook, 1991; Benton, 2002) have reported that a low Se intake was associated with poorer mood. The underlying mechanism is unclear although a response to supplementation was found with doses greater than those needed to produce maximal activity of the selenoprotein glutathione peroxidase. Although the functions of many selenoproteins are unknown some play important roles in anti-oxidant mechanisms. As there are suggestions that oxidative injury plays a role in normal aging, schizophrenia, Parkinson's and Alzheimer's disease (PD and AD), the possible role of Se is considered. Although there is evidence that supplementation with

anti-oxidant vitamins shown some promise with Alzheimer's patients and in preventing the development of tardive dyskinesia in schizophrenics taking neuroleptics, a role for selenium has been little considered.

Reactive Oxygen Species (ROS) and oxidative stress are strongly implicated in a number of neuropsychiatric disease and disorders, including stroke and cerebrovascular disease, AD, PD, Obsessive-Compulsive Disorders (OCD), familial amyotrophic lateral sclerosis, Duchenne muscular dystrophy and epilepsy (Dexter *et al*., 1989; Kutluhan *et al*., 2009; Ozdemir *et al*., 2009; Ragusa *et al*., 1997; Smith *et al*., 1991). Se is known to provide protection from ROS-induced cell damage and the proposed mechanisms mainly invoke the functions of glutathione peroxidases (GPxs) and Sepp1. However, Se pre-treatment protects the brain against restraint stress-induced oxidative damage in hippocampus, striatum and frontal cortex (Atif *et al*., 2008). Considerable evidence exists linking heavy metals to neurodegenerative diseases (Ely, 2001). Heavy metals trigger the conversion of hydrogen peroxide to hydroxyl radical through Fenton reaction. Among the selenoproteins, Sepp1 has been reported in several studies to possess metal-binding function. The GPxs might also detoxify heavy metals through their well-known function of eliminating peroxides. Recently, we showed that serum Se levels and GPxs activities were significantly lower in patients with OCD (Ozdemir *et al*., 2009).

Selenium in human brain: It has been reported that Se concentrations were in different human brain regions. Two trends can be summarized from the results. Firstly, regions containing more gray matter tended to have higher Se levels: an early report documented the highest Se concentration in putamen (1093 ng g^{-1} dry wt.), but much lower level for white matters (for example, 283 ng g^{-1} in corpus callosum). Se was 115-155 ng g^{-1} wet wt in brain cortex and white matter and 206-222 ng g^{-1} in putamen (Ejima *et al*., 1996). Secondly, Se appeared to concentrate in glandular parts in brain: in a subsequent report, 111 ng g^{-1} wet wt of non-Hg-bound Se observed in cerebrum cortex, compared with 545 ng g^{-1} in pituitary gland (Drasch *et al*., 2000).

The changes of Se concentration in brain and blood in patients with AD, PD, brain tumors, obsessive-compulsive disorders, depression, Multiple Sclerosis (MS) and Batten's disease are shown in Table 1. Significant changes were found in most cases, but it would be preliminary to draw firm conclusion from these studies. Two children with severe neurodevelopmental retardation and elevated liver function tests developed intractable seizures during the first years of life. They were found systemically Se deficient. Oral substitution with Se supplements in both children (3-5 μg kg^{-1} b. wt.) resulted in reduction of seizures, improvement of the electroencephalogram recordings and return of normal liver function after 2 weeks (Ramaekers *et al*., 1994). It is unknown if Se deficiency is a direct factor for the neurodevelopmental retardation or it affected the brain via abnormal liver function.

The selenium binding protein 1 gene (SELENBP1) activity in brain: The identification of biomarkers for brain disorders would provide a significant advance in the diagnostic procedure, which is currently dependent only on the presentation of clinical symptoms over an extended period of time. Since disorders such as schizophrenia and bipolar disorder are also highly heritable disorders, current pursuits of biomarkers for these disorders have focused on gene-based biomarkers, such as mRNA expression levels. Previous gene expression biomarker studies have identified candidate genes now implicated in the etiology of schizophrenia and bipolar disorder. While some of these candidates are in keeping with previous cellular and molecular studies of psychiatric disorders, novel candidates are also being identified (Chen and Chen, 2005; Kanazawa *et al*., 2008). For example, using microarray analysis Kanazawa *et al*. (2008) recently demonstrated that the expression of the SELENBP1 was increased in the blood and brain of patients with schizophrenia and bipolar disorder. Although the functional role of SELENBP1 is not well understood in the brain, Se-binding proteins have been shown to co-localize with g-actin at the growing neuroblastoma cells, which indicates the potential for SELENBP1 to be associated with the growth and

Table 1: Changes of selenium concentration in human brain in diseases and disorders

Brain disease and disorders	Brain region or blood fraction	Change (Se)	Reference
Obsessive-compulsive disorder	Serum	↓	Ozdemir *et al*. (2009)
Depression	Serum	↓	Cornett *et al*. (1998)
Epilepsy	Plasma	↓	Wenstrup *et al*. (1990)
Alzheimer's disease	Temporal lobe	↓	Angelova *et al*. (2008)
Parkinson's disease	Cerebrospinal fluid	-	Ramaekers *et al*. (1994)
Ischaemic stroke	Serum	↓	Basun *et al*. (1991)
Brain tumors	Cerebrospinal fluid	-	Sher (2008)
Cognitive disorder	Plasma	↓	Clausen *et al*. (1988)
Multiple sclerosis	Hematogenous cells	↓	Philipov and Tzatchev (1988)
Batten's disease	Hematogenous cells	↓	Philipov and Tzatchev (1988)

remodeling of neurites (Miyaguchi, 2004). These results are of interest in light of alterations in dendritic and synaptic proteins noted in both bipolar disorder and schizophrenia (Harrison, 2002).

SELENOPROTEINS

Selenoproteins in physiology and pathology: Only a few of the 25 identified mammalian selenoproteins have so far been functionally characterized. Most of these selenoproteins exhibit enzymatic redox function via Sec, which confers their catalytic or antioxidant activities. Cellular processes so far demonstrated to require selenoproteins include biosynthesis of dNTPs for DNA, removal of damaging or signaling peroxides, reduction of oxidized proteins and membranes, regulation of redox signaling, thyroid hormone metabolism, Se transport and storage and potentially protein folding. An overview of the human selenoproteins and their functions is presented in Table 2.

Based on the location of the Sec residue, selenoproteins can be divided into two groups. In one group, which includes all thioredoxin reductases, Sel S, Sel R, Sel O and Sel I, Sec is located in the C-terminal region, only a few amino acids from the stop UGA codon. The second group, including the rest of selenoproteins, are characterized by the presence of Sec in the N-terminal region, in between a β-strand and an α-helix, as part of a redox-active thioredoxin-like selenylsulfide/selenolthiol motif (Fomenko *et al*., 2007). Thus, human diseases associated with Se deficiency may be attributed to increased oxidative stress and alterations in redox signaling.

Glutathione peroxidases: The neurons produce endogenous hydrogen peroxide, which induces oxidative stress within the cells. These deteriorative reactions can be prevented by the GPxs, a selenoenzyme family capable of eliminating peroxides by reducing them to H_2O or alcohols, with GSH as reducing substrate. In addition, GPx are involved in such physiological events as differentiation, signal transduction and regulation of pro-inflammatory cytokine production (Moghadaszadeh and Beggs, 2006).

Cytoplasmic GPx (cGPx) is ubiquitously expressed in all types of cells. Mice deficient in cGPx were apparently healthy and fertile and showed no increased sensitivity to hyperoxia, but showed high sensitivity to the oxidant, paraquat, which can make its way to nerve terminals, causing death of dopamine neurons by oxidative injury (Ho *et al*., 1997). cGPx knockout mice also exhibited increased vulnerability to other neurotoxins, including hydrogen peroxide, malonate and 3-nitropropionic acid (De Haan *et al*., 1998). The brain of cGPx knockout mouse under ischemia/reperfusion injury showed increased infarct size and exacerbated apoptosis (Crack *et al*., 2003). Studies of GPx knockout mice also revealed that cGPx contributed to the neuroprotection seen in the superoxide dismutase-1 transgenic mouse in response to ischemia/reperfusion injury (Crack *et al*., 2003).

Selenoprotein P: Selenoprotein P (Sepp1) is the second major selenoprotein in plasma after GPx and is estimated to contain 50% of the plasma Se (Akesson *et al*., 1994). Sepp 1 is secreted to the plasma by the liver in a glycosylated form; however, its expression is detected in all tissues (Burk and Hill, 1994).

Table 2: More significant selenoproteins and corresponding biological function

Selenoproteins	Biological function
Glutathione peroxidases [GPx1 (in erythrocytes or cystolic), Gpx2 (gastro intestinal), GPx3 (in plasma or extracellular) and Gpx4 (phospholipid hydroperoxide or intracellular)]	Antioxidant enzymes that protect against the oxidative stress by scavenging of hydrogen peroxide and lipid and phospolipidic hydroperoxides. Finally, H202 and a wide range of organic hydroperoxides are transformed to water and corresponding alcohols, respectively.
Iodothyronine deidodinases (three isoforms: type I in liver, kidney and thyroid gland; type II in encephalon; and type III inactivant)	Synthesis and metabolic regulation of thyroid sulphated hormones (T2, T3 and T4)
Thioredoxin reductases (also three isoforms)	Reduction of intracellular substrates like dehydroascorbic being related with anticancer effects. Specifically it participates in the reduction of nucleotides in the DNA synthesis as well as in the regulation of gene expression by redox control of binding of transcription factors to DNA
Selenoprotein N	Cell proliferation and regeneration
Selenoprotein P	Extracellular antioxidant associated to the vascular endothelium that protects endothelial cells against damage from peroxynitrite
Selenoprotein W	Although it is necessary for muscle function its biological function is still unknown
Selenophosphate synthetase (two isoforms)	Necessary for the biosynthesis of selenophosphate and, consequently, for that of S-Cys necessary for the selenoprotein synthesis
Mitochondrial capsule selenoprotein	GPx4 form that shields developing sperm cells from oxidative damage
Prostate epithelial selenoprotein	It is a 15 kDa selenoprotein that seems to have redox function that resembles that of Gpx4 in the epithelial cells of ventral prostate
DNA-bound spermatid selenoprotein	It is a 34 kDa selenoprotein with a biological activity like the GPx
18 kDa selenoprotein	Essential selenoprotein preserved in selenium deficiency
Selenoprotein I, O, H, K, S and V	Unknown

The main proposed role of Sepp1 since its identification has been in the transport and delivery of Se to remote tissues. This has been clearly confirmed in several studies by using the Sepp1 knockout mouse models. This studies demonstrate reduced Se distribution to several tissues including the brain, testes and the fetus, with consequential neurologic defects such as axon enlargement and degeneration, alteration in synaptic transmission in the hippocampus, impaired spatial learning, as well as growth defects (Peters *et al*., 2006; Schomburg *et al*., 2004).

In both Sepp1 gene knockout reports, a relationship between Sepp1 and motor co-ordination of mice was pointed out. In one study, the Sepp1 gene knockout mice developed ataxia with a wide clumsy gait at their third week of life (Schomburg *et al*., 2004). In the other study, only mice fed a Se deficient diet lost motor co-ordination. This was prevented by feeding diets containing sufficient amount of Se (Hill *et al*., 2003). Thus, an essential role of Se was indicated in maintaining the motor co-ordination of mice; Sepp1 can contribute to this function, but sufficient dietary selenium compensates for the loss of Sepp1.

Selenoprotein W: Selenoprotein W (SelW) is a small, 9.5-kDa protein (Gu *et al*., 1999). SelW is ubiquitously expressed in tissues and its expression is regulated by selenium levels. Selenium deficiency causes reduction of SelW in skeletal muscles, heart, intestine, prostate, esophagus and skin; however, its expression in the brain remains preserved during selenium deficiency (Whanger, 2001). SelW binds glutathione with very high affinity, which in early studies suggested a potential antioxidant function (Beilstein *et al*., 1996). Overexpression of SelW in cell cultures indeed protects cells against oxidative stress and its levels are upregulated in response to exogenous oxidants in muscle cells.

Other selenoproteins: Besides SelW, thioredoxin reductase (TrxR) was also detected in the brain. TrxR activity was maintained during Se deficiency, suggesting its important function in the brain (Whanger, 2001). Other report revealed that human and mouse 15 kDa selenoprotein genes manifested high levels of expression in the brain, human type 2 iodothyronine deiodinase mRNAwas expressed in the brain and selenophosphate synthetase, an enzyme required for the biosynthesis of selenophosphate, the precursor of selenocysteine, was detected by immunoblotting in the brain (Kumaraswamy *et al*., 2000).

Neuroprotection by selenium and selenoproteins: The brain is more susceptible to oxidative stress than most other organs due to its high oxygen consumption (Halliwell, 1992). In particular, high quantities of hydrogen peroxides are continuously generated in the brain. A rapid clearance of hydrogen peroxide has been reported for cultured astroglial cells as well as for neurons, requiring combined action of catalase and glutathione peroxidases (Dringen *et al*., 1999). Moreover, astroglial cells enhance the survival of neurons through degradation of extracellular ROS via the glutathione system (Drukarch *et al*., 1998). An additional antioxidant defense system is provided by hydroperoxide-detoxifying peroxiredoxins, which are subsequently reduced by thioredoxin, in turn relying on thioredoxin reductases for its recycling (Rhee *et al*., 2005). Thus, in the form of GPx and TrxR selenoenzymes, Se is involved in protection of astroglial and neuronal cells against oxidative stress. The vital importance of Se for the brain is illustrated by its extraordinary capacity to retain Se for prolonged periods of time under conditions of limited dietary Se supply (Behne *et al*., 1988).

Under physiological conditions, the brain is supplied with Se mainly through Sepp1 (Hill *et al*., 2007). Sepp1 was identified as survival-promoting factor for neurons in cell culture, supporting neuronal growth more efficiently than sodium selenite. Assumedly, neurons take up Sepp1 via the apolipoprotein E receptor-2 (ApoER-2), which is expressed in several isoforms in neurons throughout the brain (Burk *et al*., 2007). Knock-out mice with deletions of the genes for Sepp1 or its receptor ApoER-2 were reported to show decreased brain Se levels and to develop severe neurological dysfunction (Table 3) when fed a diet low in Se (Burk *et al*., 2007; Hill *et al*., 2004). However, brain Se levels in both these knock-out mice were restored and the neurological phenotype was normalized by a Se-supplemented diet, pointing to low

Table 3: Pathophysiological effects on the brain of deleting apoER2 and Sepp1

Effects	ApoER2 -/- mice (reference)	Sepp1-/- mice (reference)
Anxiety changes	- (Harrison, 2002)	- (Rhee *et al*., 2005)
Severe neurological dysfunction and death in the selenium deficient diet	+ (Dreher *et al*., 1997)	+ (Smith *et al*., 1991)
Migratory defects of neurons	+ (Burk *et al*., 2007)	- (Rhee *et al*., 2005)
Balance and coordination defects	- (Harrison, 2002)	+ (Rhee *et al*., 2005)
Long-term potentiation deficits in hippocampus	+ (Harrison, 2002)	+ (Rhee *et al*., 2005)
Associative learning defects	+ (Harrison, 2002)	- (Rhee *et al*., 2005)
Depression of brain selenium concentration	+ (Harrison, 2002)	+ (Hill *et al*., 2007)

molecular weight selenocompounds as additional Se transport forms besides Sepp1 (Schweizer *et al*., 2005; Burk *et al*., 2007).

CONCLUSIONS

The trace element Se plays a critical role in the maintenance of proper functioning of the nervous system. Se is a potent protective agent for neurons through the expression of selenoproteins, which are mostly involved in regulation of redox status under physiological conditions and in antioxidant defense. Furthermore, insufficient brain Se levels have potentially detrimental effects on brain function and may exacerbate neuronal loss and dysfunction subsequent to endogenous or exogenous stimuli, trauma and other neurodegenerative conditions. With most, if not all, selenoprotein encoding genes being identified, the stage is set to begin understanding more completely the Se-dependent effects on brain physiology at the molecular level, thus opening new avenues for the potential development of Se containing compounds as preventive or therapeutic agents in neurological conditions.

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