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## Reactive Oxygen Species and Selenium in Epilepsy and in Other Neurological Disorders

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### Abstract

Oxidative stress has been implicated in epilepsy and various neurodegenerative disorders. In this review, we elaborate oxidative stress-mediated neuronal loss and assess the role of selenium in some neurological disorders including epilepsy. Selenium as an essential trace element has attracted the attention of many researchers because of its potentialities in human health. It has an important role in the brain, immune response, defense against tissue damage, and thyroid function. Selenium forms part of the active site of the peroxide-destroying enzyme glutathione peroxidase (GSHPx), and it also has other functions, for example in biotransformation and detoxification. Functional and clinical consequences of selenium deficiency states in neurological diseases have been described, and the selenium requirement, which is influenced by various processes, has been discussed. Wide variations have been found in selenium status in different parts of the world, and populations or groups of patients exposed to marginal deficiency are more numerous than was previously thought. Chronic diseases, such as neurological disorders, heart disease, diabetes, cancer, aging, and others, are reported to associate with markers of oxidative damage. It is, therefore, not unreasonable to suggest that antioxidants would alleviate the oxidative damage, resulting in health improvements. In recent years, accumulated evidence in nutrigenomics, laboratory experiments, clinical trials, and epidemiological data have established the role of selenium in a number of conditions. Most of these effects are related to the function of selenium in the antioxidant enzyme systems. Current research activities in the field of human medicine and nutrition are devoted to the possibilities of using selenium as an adjuvant for the treatment of degenerative or free radical diseases such as neurological disorders, inflammatory diseases, and cancer.

**Keywords:** selenium, antioxidants, oxidative stress, pathogenesis of neurological disorders

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## 1. Introduction

Selenium is a trace mineral essential to human health, which has an important role in the immune response, defense against tissue damage, and thyroid function. Improving selenium status could help protect against overwhelming tissue damage and infection in critically ill adults [1–4]. Selenium is incorporated into proteins to make selenoproteins, which are important antioxidant enzymes. The antioxidant properties of selenoproteins help prevent cellular damage from free radicals. Free radicals are natural by-products of oxygen metabolism that may contribute to the development of chronic diseases such as cancer and heart disease [5, 6]. There is evidence that selenium deficiency may contribute to development of a form of hypothyroidism and a weakened immune system. Specific diseases have been associated with selenium deficiency such as Keshan and Kashin-Beck disease, which results in osteoarthropathy and myxedematous endemic cretinism, which results in mental retardation [7, 8].

In recent years, considerable evidence has emerged implicating a role for oxygen free radicals in the initiation of cellular injury which can lead to the development of several neurological disorders. The neonatal brain, with its high concentrations of unsaturated fatty acids (lipid content), high rate of oxygen consumption, and low concentrations of antioxidants, is particularly vulnerable to oxidative damage. Thus, increased oxidative stress has been implicated in various neurological disorders such as seizures, ischemia-reperfusion injury, and neurodegenerative diseases [9, 10] such as Alzheimer's, Parkinson's, and Lou Gehrig's disease. Free radical damage has been implicated in the initiation and propagation of seizure activity as well as the accompanying seizure-induced neuronal damage [11]. Therefore, antioxidants could play an important role in modulating susceptibility to seizure activity and seizure-induced neuronal injury.

The use of selenium as a supplement in neurological disorders has been reported. The rationale for selenium supplementation comes from the nutrient's role as an antioxidant [12], working primarily as a component of glutathione peroxidase, an important cellular protector against free radical damage. Furthermore, selenium deficiency is known to result in neuromuscular disease. Attempts have been taken to relate selenium to different neurological disorders as epilepsy, phenylketonuria and maple syrup urine disease, Parkinson's disease, amyotrophic lateral sclerosis, neuronal ceroid lipofuscinoses, myotonic dystrophy, multiple sclerosis, Down syndrome (DS), and Alzheimer's disease [13, 14]. The relevant connection between selenium and the majority of these disorders rests on clinical observations during selenium supplementation alone or in combination with other antioxidants.

## 2. Selenium distribution in humans

Due to the uneven geographic distribution of selenium in soil, the amount of whole-body selenium in adult humans was reported to differ in different countries [15–18]. At normal dietary levels, the highest selenium concentration was detected in reindeer liver and kidney, followed

by the spleen, pancreas, heart, brain, lung, bone, and skeletal muscle. Selenium concentration in the human body was also found to vary with age. For instance, selenium concentration in fetal brain decreased with age but increased with age postnatally. Blood selenium levels were negatively correlated with age in healthy adults, and the same was documented for 40 patients with dementia of the Alzheimer type (DAT). Furthermore, Ejima et al. [19] reported that selenium concentrations varied in different adult human brain regions.

### 3. Selenium in the brain

Neurochemical aspects of selenium have been widely reported. In this approach to the etio-pathogenetic role of selenium in CNS diseases, teleological ideas are explicitly correlated to the paradigm of oxygen toxicity. The brain differs from many other tissues, being a highly aerobic and totally oxygen-dependent tissue. Oxygen reduction produces reactive radical intermediates, i.e., singlet oxygen, a superoxide radical which is thought to be a major agent of oxygen toxicity. Hydrogen peroxide,  $H_2O_2$ , is formed through dismutation of a singlet oxygen catalyzed by Cu-Zn and Mn forms of superoxide dismutase, both found in CNS tissues. Other hydrogen peroxide-generating enzymes are associated with D- and L-amino acid oxidase, monoamine oxidase,  $\alpha$ -hydroxyacid oxidase, xanthine oxidase, and cytochrome P-450 system.

Unlike charged oxygen radicals being a rather unreactive and stable,  $H_2O_2$  rapidly crosses cell membranes. Cellular damage is accomplished when  $H_2O_2$  decomposes to the highly reactive hydroxyl radical in iron(II) or copper(I) catalyzed reactions. Scavenging of  $H_2O_2$  and contemporaneous prevention of hydroxyl radical formation occurs predominantly at two cellular sites, in the peroxisomes and in the cytoplasm by catalase and GSHPx (GSHPx, glutathione/hydrogen peroxide oxidoreductase, EC 1.11.1.9), respectively. If this is not done, the hydroxyl radical may attack the fatty acid side chains and start a chain reaction of lipid peroxidation. Lipid peroxidation causes gradual loss of membrane fluidity and membrane potential and increases membrane permeability to ions. Radical attack may also destroy membrane-bound enzymes and receptors, e.g., the binding of serotonin is decreased. Oxidative degradation and polymerization of lipids leads to the accumulation of lipofuscin, the age pigment. The presence of catalytic iron and copper complexes in human CSF, and the high iron content of brain, suggests that they are very sensitive to oxygen radical generation.

The crucial role of selenium as a trace element in the nervous tissue has been associated with a selenoenzyme glutathione peroxidase. Selenium is thought to be present at the active site of GSHPx in its selenolate form as selenocysteine [20]. The fairly homogenous distribution of selenium in the human brain corresponds well with the regions of the highest and lowest GSHPx activity found in the rat brain. However, estimates of the amounts of selenium in rat brain have indicated that GSHPx may account for only 1/5 of the total Se found in the brain [21]. Most of the selenium is bound to proteins and not to amino acids or nucleic acids [22]. Selenoproteins, other than GSHPx, found in the brain and the reproductive and the endocrine organs seem to serve as a priority pathway of the element during inadequate selenium intake. The function of selenium in proteins has been explained in

terms of semiconduction [23]. It is possible although not yet proven that selenium may have this or some other special functions outside of GSHPx too.

Observations suggest that free radical intermediates may be involved in the coupling between depolarization of the plasma membrane,  $\text{Ca}^{2+}$  fluxes, and neurotransmitter release [24]. In general, cellular redox adjustments regulate functional sulfhydryl groups of proteins. Therefore, cellular prooxidant states may be involved in the generation of physiological responses. This means that the adjustment of redox equilibrium in CNS is a far more delicate phenomenon than just a tendency to a normal balance.

The regulation of GSH level (GSH/GSSG) through pentose phosphate pathway producing NADPH, GSH-reductase, and GSHPx contributes to the overall redox state of cells in the brain [25]. The brain tends to need radical reactions as well as to possess specific or high endogenous levels of free radical scavengers such as dopamine, norepinephrine, and catechol estrogens, taurine and carnosine [26], in neurons. Carnosine is involved with GSBA activity in the brain, and a study by Takahashi [27] demonstrated that homocarnosine levels were high in patients who responded to antiepileptic drugs. The functional balance between various free radical scavenger systems in the brain seems reasonable. Significant positive correlations between catalase and SOD levels have been reported in tissues of normal subjects excluding erythrocytes. Factors concomitantly influencing the variation of the activities of SOD, catalase, and GSHPx have been reported. Enzymes frequently called a protective should rather be envisaged as being regulatory, controlling the levels of different states of oxygen reduction.

#### 4. Brain antioxidant homeostasy in relation to selenium and GSHPx

As a trace element in nature, the availability of selenium may be limited. GSHPx activity has been shown to reflect selenium status in deficient and adequate states [6]. On the other hand, protection against toxicity is likely to involve the alterations in GSH metabolism that occur in nutritional Se deficiency. High concentrations of erythrocyte glutathione in patients with neurological disorders have been reported [28]. However, regulatory mechanisms apparently exist which ensure that during periods of insufficient selenium intake, the content of the element is kept up above all in the brain and the reproductive and endocrine organs.

Yoshida et al. [29] reported a comprehensive method for identifying the selenium-binding proteins using PenSSeSPen as a model of the selenium metabolite, selenotrisulfide ( $\text{RSSeSR}$ , STS), which was applied to a complex cell lysate generated from the rat brain. The authors stated that a thiol-containing protein at  $m/z$  15155 in the brain cell lysate was identified as the cystatin-12 precursor (CST12) from a rat protein database search and a tryptic fragmentation experiment. CST12 belongs to the cysteine proteinase inhibitors of the cystatin superfamily that are of interest in mechanisms regulating the protein turnover and polypeptide production in the central nervous system and other tissues. Consequently, CST12 is suggested to be one of the cytosolic proteins responsible for the selenium metabolism in the brain [29].



Selenium seems to be somehow involved in the regulation of oxygen metabolism through its influence on a variety of enzymes. In concentrations of  $6 \times 10^{-7}$  to  $10^{-6}$  M, selenite induces a 30-fold increase of GSHPx activity in neuroblast cells in vitro. Other studies with the rat liver have suggested that Se status regulates the level of GSHPx mRNA as well as regulates GSHPx protein concentration and GSHPx activity [30]. In concentrations of  $0.7\text{--}2 \times 10^{-5}$  M, Se in rat liver increases the activities of g-glutamylcysteine synthetase, the first rate-limiting enzyme in GSH biosynthesis, and GSSG-reductase, which catalyzes the reduction of GSSG to GSH [31]. In some species the induction of GSH-S-transferase has been shown to occur as a result of Se deficiency.  $\text{H}_2\text{O}_2$  as the most stable and diffusible of the oxygen reduction intermediates may exert an influence on the expression of SOD, catalase, and GSHPx activities. GSHPx, which exists in several forms that differ in their primary structure and localization, catalyzes the reduction of hydrogen peroxide and organic hydroperoxide by glutathione and functions in the protection of cells against oxidative damage [32]. The homeostasy in the oxidative metabolism and oxygen reduction may be distorted by different means, either inherent or acquired. Depending on the spatial and temporal occurrence of the distortion, various neurological states are expressed.

The developing brain is particularly susceptible to oxidative stress, more so than the mature brain [33].  $\text{H}_2\text{O}_2$  accumulation has also been associated with increased injury in superoxide dismutase-overexpressing neonatal murine brain, and greater cell death is seen when immature neurons are exposed to  $\text{H}_2\text{O}_2$  than mature neurons. Increased  $\text{H}_2\text{O}_2$  accumulation may be the result of relative insufficiency of the endogenous enzyme GSHPx.

Under physiologic circumstances, the brain has efficient antioxidant defense mechanisms, including GSHPx, which converts potentially harmful  $\text{H}_2\text{O}_2$  to oxygen and water at the expense of reduced GSH. Under oxidative stress, in the immature brain, endogenous levels of GSHPx may be inadequate for converting excess  $\text{H}_2\text{O}_2$ . Transgenic mice that overexpress GSHPx (hGPx-tg), when subjected to hypoxic-ischemic (HI), have less histologic brain injury than their Wt littermates [25]. In addition, the cortex exhibits increased GSHPx enzyme activity at 24 h, whereas GSHPx activity remains unaltered in the Wt brain. In addition, neurons cultured from GSHPx-tg brain are resistant to injury from exogenously applied  $\text{H}_2\text{O}_2$  [34]. Neurons cultured from the hippocampus and cortex that are transfected (transfection describes the introduction of foreign material into eukaryotic cells) with genes for catalase and GSHPx also show protection from neurotoxic insults and a corresponding decrease in  $\text{H}_2\text{O}_2$  accumulation [35]. These findings indicate that adequate GSHPx activity can ameliorate injury to the immature brain from oxidative stress due to  $\text{H}_2\text{O}_2$ .

It is well established that previous stress to the brain can induce tolerance to subsequent injury, a phenomenon called personality change (PC). In neonatal rodents, protection against HI brain injury has been induced by PC with a period of hypoxia before the induction of HI [36]. The mechanisms of this protection have yet to be fully determined, but it has been established that a large number of genes are induced in response to hypoxia [37]. Several of these genes are regulated by the transcription factor hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ) and perhaps most importantly vascular endothelial growth factor (VEGF) and erythropoietin (EPO). VEGF is upregulated after focal ischemic injury in the neonatal rat, in parallel with induction of HIF-1 $\alpha$  [38, 39].

## 5. Aging, dementia, and Alzheimer's disease

Major interest in CNS selenium is related to aspects of oxidative stress and aging. The decrease in cerebral blood flow, glucose utilization, and oxygen consumption common to many dementias results from abnormalities of brain structure with a high oxidative capacity. During mental activity, regional cerebral oxidative metabolism and regional cerebral blood flow increase in several areas of the brain. In dementia of the Alzheimer type, brain blood flow and oxidative metabolism are reduced. This situation may lead to loss of balance between prooxidants and antioxidants [40]. The role of  $H_2O_2$  in the etiology of Alzheimer's disease has been reported [41, 42]. Furthermore, the activities of catalase and GSHPx decrease with aging in intact animals. Some reports suggest that the SOD activity is significantly greater in Alzheimer cell fibroblasts. Both GSHPx and SOD activities in the erythrocytes of AD have been reported to be normal, while other studies show significantly higher erythrocyte SOD level in AD [43]. It remains to be seen whether oxidative damage will still be related to the accumulation of aluminum silicates in the brain as well as to that of the senile plaques and tangles. Experiments have indicated that aluminum salts may not only accelerate Fe(II)-induced peroxidation of membrane lipids but do this especially in the brain [44, 45].

In order to evaluate the peroxidative stress in dementias, autopsy brain samples should be studied for GSHPx, SOD, catalase, and selenium. A direct causal relationship between brain antioxidant defenses and dementia in aging and Alzheimer's disease is hard to demonstrate because of the extremely slow process. Interestingly a high proportion of Down syndrome patients develop the neuropathological and clinical changes of AD, suggesting a close pathogenetic relationship between these disorders. Thus, the correction of antioxidant balance in AD by Se supplementation should be demonstrated by other means so as to direct it preventatively to those with a high risk of developing AD.

In Alzheimer's disease the  $H_2O_2$  molecule should be considered a therapeutic target for treatment of the oxidative stress associated with the disease. The actions of  $H_2O_2$  include modification of DNA, proteins, and lipids, all of which are effects seen in an Alzheimer's disease brain, possibly contributing to the loss of synaptic function characteristic of the disease. Future research and development of agents that specifically target the  $H_2O_2$  molecule or enzymes involved in its metabolism may provide the future route to Alzheimer's disease therapy [42].

## 6. Down syndrome

Trisomy 21 (Down syndrome) is the most common genetic cause of learning disability in humans [46], occurring in about 1 per 1000 babies born each year [47]. Postmortem studies have reported neuronal depletion and structural abnormalities of the brain during late gestation and early postnatal life [48]. Down syndrome was found to have increased activity of superoxide dismutase without a compensatory increase in glutathione peroxidase activity [49]. However, there is no evidence to support the use of antioxidant or folic acid supplements in children with Down syndrome [50].

Increased primary gene products which may contribute to the pathology of DS include cytoplasmic CuZn-superoxide dismutase (SOD). Consistent with the gene dosage effect, SOD activity is increased by 50%, leading to noxious concentrations of  $H_2O_2$ , while brain GSHPx remains normal. The overall redox state in other tissues is corrected by an adaptive increase of GSHPx activity. This means that the brain is especially susceptible to oxygen free radical stress. Our primary survey of specific antioxidant therapy with selenium [51] rests on this theory.

The whole-body retention of 5–8 kBq  $^{75}Se$ -sodium selenite with 0.4 g Se as carrier/kg body weight in DS patients has been earlier estimated to be  $53.3 \pm 21.1\%$ . Stable Se supplementation increased  $^{75}Se$  elimination, indicating a saturated Se pool in the body. Twenty-four patients aged 1–41 years were either given selenium supplements of 0.025 mg Se/kg/d in the form of sodium selenite or given placebo or no preparation. The serum levels of selenium indicated no real deficiency as compared to the normal healthy population. However, the mean compensatory increase of erythrocyte GSHPx activity before supplementation was lower than expected. Because of difficulties in obtaining brain biopsies, variables found in the plasma and erythrocyte samples were used as indicators of antioxidant balance. Sinet et al. [52] have reported a high positive correlation between erythrocyte GSHPx values and the intelligence quotient in DS patients. Because of this and the difficulties in testing changes of IQ which is one of the most decisive clinical goals of therapy, we found it reasonable to follow changes of E-GSHPX. Selenium supplementation increased E-GSHPx activity by 28% (59.9% above normal). The correction is sensitive to adequate Se supplementation as indicated by SOD/GSHPx index which decreased by 23.9% ( $P < 0.01$ ) [51]. Interestingly the primarily high serum and blood mononuclear cell levels of cupric and ferrous ions decreased, and that of zinc ions increased during supplementation. In conclusion we believe that the patients have benefited from the selenium supplementation through optimization of their antioxidant protection by GSHPx.

## 7. Selenium and epilepsy

An epilepsy syndrome is a complex of signs and symptoms defining a unique condition [53]. Oxidative stress and generation of reactive oxygen species are strongly implicated in a number of neuronal and neuromuscular disorders, including epilepsy. The functions of selenium as an antioxidant trace element are believed to be carried out by selenoproteins that possess antioxidant activities and the ability to promote neuronal cell survival. Selenoproteins are important for normal brain function, and decreased function of selenoproteins may lead to impaired cognitive function and neurological disorders [54].

Free radicals and lipoperoxidation reactions seem to be involved in epileptic seizure developing after brain hemorrhage of different kinds. There is an association between hemosiderin deposition and post-traumatic epilepsy. An extravasation of blood and hemolysis of erythrocytes result in the decompartmentalization of free iron and accelerate the rates of lipoperoxidation and superoxide-dependent formation of OH radicals, which are propagated by reperfusion and reoxygenation in postischemic tissue injury. Simultaneously the activity of GSHPx in the ischemic tissue is decreasing. Selenium and other antioxidants have been



observed to prevent synergistically the lipoperoxidation in animals and in man. Pretreatment of rats with vitamin E and selenium prior to iron injections has been shown to prevent the development of seizures to a high degree in a large percentage of experimental rats [55]. There are also reports of the normalization of the EEG of patients with the juvenile type of neuronal ceroid lipofuscinosis (JNCL) after vitamin E and sodium selenite supplementation. In addition, the onset of epilepsy is significantly earlier among JNCL patients not given this antioxidant therapy (11.1 year) than patients receiving antioxidant therapy (13.6 year) [56].

Numerous evidences suggest that selenium may ameliorate some of the adverse metabolic consequences of valproic acid. Valproic acid therapy has been shown to deplete plasma selenium levels, a cofactor required for glutathione peroxidase activity. Selenium supplement may help lower ammonia level in patients with valproate-induced hyperammonemia over long-term treatment. Selenium deficiency may lead to the loss of seizure control, even when the patient is remained on the same dose of valproic acid [57, 58]. Furthermore, Ashrafi et al. [59] concluded that the measurement of serum selenium in patients with intractable epilepsy should be considered.

## 8. Juvenile type of neuronal ceroid lipofuscinosis

The neuronal ceroid lipofuscinoses (NCL) are a group of recessively inherited neurodegenerative-lysosomal storage diseases of infancy, with an estimated occurrence of 1 in 12,500 live births [60–62]. Characteristics of the diseases are deposits of ceroid and lipofuscin pigments in the tissues, particularly in the neural tissue, visual failure, and progressive mental retardation. Depending on the age of onset and clinical, electrophysiological, and neuropathological features, the NCLs can be subdivided into the infantile, the late infantile, the juvenile, and the adult type of NCL. The pathogenesis of NCL is unknown. The polyenic acid level with low levels of linoleic acid and an inverse relationship between GSHPx activity and the level of eicosatrienoic acid has been observed in JNCL [63].

The occurrence of the fluorescent pigments suggested the peroxidation of lipids in the etiology of NCL. It is likely that the diseased tissues peroxidize more rapidly than normal tissues and cytotoxic end products of lipoperoxidation cause secondary damage. On a weight basis, ceroid seen in JNCL patients binds five times more iron than the lipofuscin seen in normal elderly individuals. The increased levels of aluminum salts greatly enhance iron-dependent damage to membranes. Heiskala et al. [64] have confirmed the presence of complexable iron and copper in the CSF of patients with NCL and other neurological disorders, and when the pH value of the assay for iron was lowered, the NCL group had substantially more complexable iron in their CSFs. Interestingly aluminum has been observed in CSF and in ceroid lipofuscin pigments of the brain of NCL patients [65]. It is well established that damaged tissue releases metals from protein-bound sites and these metals stimulate peroxidative damage to lipids and other biomolecules.

One of the most essential enzymes counteracting lipoperoxidation is the selenium-containing GSHPx. Two independent reports have demonstrated that erythrocyte GSHPx activity is decreased in JNCL patients [66, 67]. This low GSHPx activity was reversed to normal level by selenium supplementation.

The evaluation of sodium selenite absorption and losses before supplementation of JNCL patients has been studied by using total body counting for  $^{75}\text{Se}$  detection. These studies showed that in three JNCL patients, about 55% of the administered  $^{75}\text{Se}$  was eliminated during the first 11 days in the feces and about 10% in the urine [68]. Compared to healthy controls ( $n = 2$ , percentages 42% and 7%, respectively), findings indicate a reduced absorption of selenium in JNCL patients contrary to a previous report. The low GSHPx activity in NCL patients may indeed reflect a low selenium intake, most probably due to a disturbed absorption of selenium and secondary phenomena due to an inborn error of metabolism. Apart from the low selenium status, also very low vitamin E levels are found in the serum of advanced and hospitalized NCL patients. This can be explained by the recent finding of a pronounced reduction of apoprotein B as well as the whole fraction of very low density lipoprotein (VLDL) in JNCL patients.

JNCL patients (genetically subgroups) have been given daily supplementation of sodium selenite (0.05–0.1 mg/Se/kg of b.w.), vitamin E ( $\alpha$ -tocopherol acetate 0.014–0.05 g/kg b.w.), vitamin B<sub>2</sub> (0.025–0.05 mg/kg b.w.), and vitamin B<sub>6</sub> (0.63–0.8 mg/kg b.w.). The benefits of the therapy are corroborated by the significant negative correlation of GSHPx activity with neurological dysfunction of motor performance, balance, coordination, and speech [69]. The mean age at death has been extended by 4 years as compared to that at the beginning of the century. As the best responders to antioxidant therapy show no neurological dysfunction at the age of over 20 years, there is no doubt that the life expectancy of JNCL patients receiving antioxidants, including selenium, will be significantly prolonged in the future [70]. Complications of the antioxidant therapy have been few and not severe. Six patients have experienced vomiting and nausea when the serum concentration of selenium reached the level of 4.5–5 M. Serum levels up to 4.0 M were usually well tolerated as well as when the sodium selenite was changed to EbselenR (2-Phenyl-1,2-benzoselenazol-3-one).

## 9. Multiple sclerosis (MS)

Multiple sclerosis is a severe neurodegenerative disease of polygenic etiology affecting the central nervous system. Low levels of polyenic acids are involved in the pathogenesis of both MS and JNCL [71, 72]. In 1972 Thompson et al. found decreased levels of serum linoleate as well as unsaturated fatty acids of brain phospholipids in MS patients. It has also been shown that supplementation with essential fatty acids may improve the clinical status of young MS patients diagnosed early. As in NCL, the selenium may by activating GSHPx (scavenger of organic peroxides) regulate the metabolic transformation of essential fatty acids and biotransformation of these to prostaglandins, thromboxanes, and leukotrienes. Curiously decreased GSHPx activities in erythrocytes have been found in female but not in male MS patients [73].

Blood selenium levels have been reported to be lower in MS patients than in healthy controls [74–76]. However, selenium concentration has been shown to be normal in plasma and erythrocytes but lowered in platelets of MS patients. Impaired Se status has been found in MS largely in the connection of severe protein-calorie malnutrition. Treatment of MS with Se supplementation does not seem warranted in the absence of demonstrated deficiency. Thus, in the reported selenium-containing antioxidant treatments, the clinical benefit to the course of MS has remained open to speculation.

## 10. Neurotoxicity

### 10.1 Mercury intoxication

Mercury is well known for its severe toxicity especially by inhalation [77]. People exposure to Hg is mainly due to environmental pollution and the consumption of fish or other aquatic product [78]. Chronic mercury poisoning is characterized by neurological and psychological symptoms, such as tremor, restlessness, personality changes, anxiety, sleep disturbance, and depression. Symptoms are reversible after cessation of exposure. Because of the blood-brain barrier, there is no central nervous involvement related to inorganic mercury exposure [79]. Selenium interacts in the body with a wide range of toxic metals such as arsenic, cadmium, mercury, copper, silver, and lead. It has been shown to be highly effective in animals in preventing brain damage of organic and inorganic mercury. In postmortem brain samples from persons exposed to mercury vapors, mercury and selenium were found at a molar ratio of approximately 1. This indicates that the brain is the target organ in human exposure to mercury vapors. Mercury and selenium react in various ways. The role of brain selenium in inorganic heavy metal toxicity is thought to be minimal [80, 81]. Mercuric ion bound to selenium is proposed to form a biologically inert complex, leading to increased body burden of both elements. This reaction seems to take place only when a threshold of mercury exposure is exceeded. Selenium influences the oxidation rate of elemental mercury in cases of low GSHPx activity; decreased mercury oxidation may lead to increased brain uptake. Selenium may also together with vitamin E counteract mercury-induced lipid peroxidation.

## 11. Other CNS diseases related to selenium

### 11.1 Parkinson's disease

Parkinson's disease (PD) is a chronic and progressive movement disorder, meaning that symptoms continue and worsen over time. Oxidative stress is also thought to have a pathogenic role in Parkinson's disease [82, 83]. Selenium protects cellular elements from oxidative damage and may participate in redox-type reactions. Low plasma selenium concentrations are associated with subtle neurological impairments reflected in soft neurological signs [84, 85]. Plasma Se was the only statistically significant difference of up to 16 elements identified for PD patients [86] relative to Alzheimer's disease patients. Redox-active role is evidenced by an increased lipid peroxidation and reduced glutathione levels [87] and high concentration of iron and free radical generation via autocatalytic mechanisms within neuromelanin-containing catecholaminergic neurons in the substantia nigra. In addition, the observation that exogenous administration of cysteine, N-acetyl cysteine, or glutathione decreased the neurotoxic effects of 6-hydroxydopamine in vitro and in vivo reinforces this hypothesis [88].

### 11.2 Tardive dyskinesia

Tardive dystonia (TD), a rarer side effect after longer exposure to antipsychotics, is characterized by local or general, sustained, involuntary contraction of a muscle or muscle group, with

twisting movements, generally slow, which may affect the limbs, trunk, neck, or face [89, 90]. This condition is characterized by involuntary movements. These abnormal movements most often occur around the mouth. The disorder may range from mild to severe. For some people, it cannot be reversed, while others recover partially or completely. Tardive dyskinesia is seen most often after long-term treatment with antipsychotic medications. Other names for this specific disorder are linguofacial dyskinesia, oral-facial dyskinesia, tardive dystonia, tardive oral dyskinesia, and TD. Many preclinical and clinical studies have investigated the possible role of selenium and other antioxidants. These studies suggest that free radicals are probably involved in the pathogenesis of TD and that vitamin E and selenium could be efficacious in its treatment.

### 11.3 Duchenne muscular dystrophy

Muscular dystrophy (MD) is a group of genetic diseases involving progressive weakness and degeneration of the muscles that control movement. In some forms of MD, the heart muscles and other involuntary muscles, as well as other organs, are also affected. There are nine distinct types of MD, with myotonic the most common form among adults and Duchenne the most common form among children, primarily affecting males. MD is an incurable, often fatal disease. It is usually obvious by the age of 5 and evolves progressively until it causes disablement and death, around the age of 20. Death commonly results from involvement of the respiratory muscles. It is recessively inherited and linked to sex, and the gene determining DMD has been mapped in the Xp-21 locus. It has an incidence of 1/3000–1/3500 male births, and one third of the cases come from new mutation. Some affected individuals may develop intellectual disturbance due to unknown mechanism, so far. The sister of an affected individual has a 50% chance of carrying the defective gene. The result of the dystrophic locus on the gene is the absence of dystrophin, a rod-shaped protein that is part of the muscle cytoskeleton.

The genetic alteration produces abnormality in the membrane of the muscular fibers that consists of a disturbance in the calcium transport ( $\text{Ca}^{2+}$ ), inside the muscular fibers, which is the base mechanism of cellular degeneration and necrosis. There is fiber necrosis and replacement of fibers by fat. A nucleotide degradation, and decreased muscle ATP and ADP content, has been reported. The ATP is necessary to drive the  $\text{Na}^+/\text{K}^+$  pump, which maintains ionic gradients across the sarcolemma; re-sequester the  $\text{Ca}^{2+}$  into the cisternae; and have power contraction. The production of ATP can be the result of anaerobic respiration, which breaks glucose down into ATP and lactic acid, or aerobic respiration when ATP, carbon dioxide, and water are formed. A second immediate reserve of energy exists in the form of creatine phosphate, which can donate phosphate to ADP to form ATP, becoming itself creatine. In the resting muscle, glucose is stored as glycogen, and in such a muscle aerobic respiration synthesizes ATP from glucose or fatty acids.

Therapy of DMD has been an elusive goal. Studies with isolated myocytes have shown that lipid peroxidation with an enhanced free radical production can be activated by increasing Ca concentration. Low oxygen saturation in the muscle tissue may stimulate the IL-6 production, a cytokine, which is produced by contracting muscles and released into the blood. The blood circulation of the older Duchenne patients is particularly disturbed. Pedersen et al. [91] have demonstrated that IL-6 affects the metabolic genes, induction of lipolysis, inhibition of insulin resistance, and



stimulation of cortisol production. In addition, carbohydrate supplementation during exercise was shown to inhibit the release of IL-6 from contracting muscle. Thus carnitine supplementation is indicated to the Duchenne patients, to make sure that the energy supply will be good.

Johansson et al. [92] hypothesized that increased production of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha) may be important underlying mechanisms in myotonic dystrophy. Patients with high body fat mass had significantly increased insulin levels and decreased morning levels of cortisol, ACTH, and testosterone. IL-6 and TNF-alpha levels are increased, and adrenocortical hormone regulation is disturbed in MD. Adiposity may contribute to these disturbances, which may be of importance for decreased adrenal androgen hormone production and metabolic, muscular, and neuropsychiatric dysfunction in MD [92]. Henríquez-Olguín et al. [93] reported that IL-6 is a key metabolic modulator that is released by the skeletal muscle to coordinate a multisystemic response (liver, muscle, and adipocytes) during physical exercise; the alteration of this response in dystrophic muscles may contribute to an abnormal response to contraction and exercise.

Thus, several kinds of antioxidants have been proposed as a treatment since increased levels of thiobarbituric acid (TBA) reactive material have been found in the muscles and blood of DMD boys [94]. Increased amounts of pentane are expelled by the DMD patients [95]. We have previously reported that the biological half-life of  $^{75}\text{Se}$  in DMD patients was significantly shorter than in healthy controls [96]. We also reported that patients with myotonic muscular dystrophy, the most common form of muscular dystrophy in adults, show improvement in muscular force and function when treated with selenium and vitamin E [97].

Shimomura et al. [98] observed a group of trained animals, part of which were coenzyme Q10 treated and had to exercise for 30 min on treadmill, in downhill position. CoQ10-treated animals had higher level of CoQ10 in their muscles, and the early rise in creatine kinase and lactic dehydrogenase plasma levels, due to the exercise, was evident at a remarkably significant lower extent, in the treated ones. Similar observations were also made in humans [99]. Therefore we have been treating the Duchenne patients with CoQ10. We have been given two siblings of whom the elder one got practically no antioxidants and the younger one whose antioxidant treatment started at the age of 6 years. Nutrient supplement protocol for DMD patients included sodium selenite  $0.05\text{--}0.1\text{ mg Se kg}^{-1}\text{ b.w. day}^{-1}$ ; alpha-tocopherol,  $10\text{--}20\text{ mg kg}^{-1}\text{ b.w. day}^{-1}$ ; vitamin B2,  $0.2\text{ mg kg}^{-1}\text{ b.w. day}^{-1}$ ; vitamin B6,  $5\text{ mg kg}^{-1}\text{ b.w. day}^{-1}$ ; L-carnitine  $10\text{--}20\text{ mg kg}^{-1}\text{ b.w. day}^{-1}$ ; ubiquinone-10 (coenzyme Q10)  $3\text{ mg kg}^{-1}\text{ b.w. day}^{-1}$  [100]. In the future the therapy may be by producing functional amounts of dystrophin by skipping the mutated exon like what has been done in the mdx dystrophic mouse [101].

## 12. Personalized gene therapy

The analytical power of modern methods for DNA analysis has outstripped our capability to interpret and understand the data generated. It is vital that we understand the mechanisms



through which mutations affect biochemical pathways and physiological systems [102]: major bcr-abl mRNA nucleic acid amplification assay, genetic analysis of progressive muscular dystrophy, genetic analysis of rearranged immunoglobulin gene, and genetic analysis of malignant tumor. The promise of personalized medicines is enormous, particularly for rare disease [103, 104]. The genetic diversity of Emery-Dreifuss muscular dystrophy (EDMD) predicts that a cure will ultimately depend upon the individual's defect at the gene level, making this an ideal candidate for a precision medicine approach [105]. Ataluren known as PTC124 is a drug for the treatment of Duchenne muscular dystrophy caused by a nonsense mutation (nmDMD) and cystic fibrosis caused by a nonsense mutation (nmCF). PTC124 can lead to restoration of some dystrophin expression in human Duchenne muscular dystrophy muscles with mutations resulting in premature stops [106]. Eteplirsen, a phosphoramidite morpholino sequence complementary to a portion of exon 51, is designed to force the exclusion of exon 51 from the mature DMD mRNA. Similar drugs targeting other DMD exons are under development and could theoretically restore reading frame in majority of patients. The fact that such drugs rely on specific sequence information and target the proximate cause of the disease makes these one of the first examples of precision genetic medicine [104, 107].

A common denominator to the spectrum of neurological disorders and selenium seems to be oxygen toxicity. Difficulties exist in giving proper weight to the interaction of the components of a complex system like the brain's antioxidant defense. The presence of multiple and contemporaneous control mechanisms means that a dysregulated system is impaired not only in one but more regulatory or homeostatic mechanism. Supplementation by a single factor like selenium or together with other antioxidants may to a limited extent sustain these mechanisms. However, much more basic research should be done before these complexities can be better understood. The neurological diseases reviewed above have provided the theoretical framework for the continued investigation of the efficacy of the pharmacological manipulation of glutathione concentration and synthesis in treatment of these diseases [108–110].

## Acknowledgements

### **In memoriam of Faik Atroshi (1949–2019)**

Our dear friend, collaborator in research and present coauthor Dr Faik Atroshi, PhD, born on September 22, 1949 in Mosul passed unexpectedly away on February 25, 2019. He was until his retirement docent in University of Helsinki, Senior Researcher in Pharmacology and Toxicology, Adjunct Professor in Clinical Genetics and Clinical Nutrition, and Visiting Professor at different international universities. He will be remembered as an exceptionally dedicated and respectable scientist as well as an inspirational mentor and collaborator. We will miss his enthusiasm, creativity, and desire to continuously learn and to integrate knowledge from various fields of biomedicine.

## Abbreviations

DAT	dementia of the Alzheimer type
LPO	lipid peroxides
SOD	superoxide dismutase
CAT	catalase
GSH	glutathione
GSHPx	glutathione peroxidase
Zn	zinc
Cu	copper
Cu-Zn SOD	copper zinc superoxide dismutase
ROS	reactive oxygen species
CNS	central nervous system
DHP	enzyme dehydropeptidase
TNF	tumor necrosis factor
GR	glutathione reductase
GSH	glutathione
ADC	arginine decarboxylase
ODC	ornithine decarboxylase
NADPH	nicotinamide adenine dinucleotide phosphate
GST	glutathione-S-transferases
GSSG	oxidized glutathione
AD	Alzheimer's disease
$\cdot\text{OH}$	hydroxyl radical
E-GSHPx	erythrocyte glutathione peroxidase
EEG	electroencephalogram activation: EEG is an essential component in the evaluation of epilepsy
CSF	cerebrospinal fluid
JNCL	juvenile neuronal ceroid lipofuscinosis
MS	multiple sclerosis

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