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Review

Nanoparticles as potential clinical therapeutic agents in Alzheimer's disease: Focus on selenium nanoparticles

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List of Abbreviations

AD, Alzheimer's Disease

Ag, silver

BBA, blood-brain barrier

GSH, glutathione

GSH-Px, glutathione peroxidase

GSSG, oxidized glutathione

NAC, N acetyl cysteine

NO, nitric oxide

NOS, nitric oxide synthase

PARP, poly (ADP-ribose) polymerase

QDs, quantum dots

RNS, reactive nitrogen species

ROS; reactive oxygen species

Se, selenium

SiO₂, silica dioxide

SOD, superoxide dismutase

TiO₂, titanium dioxide

Trx1, thioredoxin reductase 1

ZnO, zinc oxide
TRP, transient receptor potential
TRPM2, transient receptor potential melastatin
TRPV1, transient receptor potential vanilloid 1
VGCC, voltage gated calcium channels

Abstract

Introduction: In etiology of Alzheimer's disease (AD), involvement of amyloid β ($A\beta$) plaque accumulation and oxidative stress in the brain have important roles. Several nanoparticles such as titanium dioxide, silica dioxide, silver and zinc oxide have been experimentally using for treatment of neurological disease. In the last decade, there has been a great interest on combination of antioxidant bioactive compounds such as selenium (Se) and flavonoids with the oxidant nanoparticles in AD. We evaluated the most current data available on the physiological effects of oxidant and antioxidant nanoparticles.

Areas covered: Oxidative nanoparticles decreased the activities of reactive oxygen species (ROS) scavenging enzymes such as glutathione peroxidase (GSH-Px), superoxide dismutase (SOD) and catalase in the brain of rats and mice. However, Se-rich nanoparticles in small size (5-15 nm) depleted $A\beta$ formation through decreasing ROS production. Reports on low levels of Se in blood and tissue samples and the low activities of GSH-Px, catalase and SOD enzymes in AD patients and animal models support the proposed crucial role of oxidative stress in the pathogenesis of AD.

Expert Commentary: In conclusion, present literature suggests that Se-rich nanoparticles appeared to be a potential therapeutic compound for the treatment of AD.

KEYWORDS: Alzheimer's disease, brain, nanoparticles, selenium, oxidative stress.

1. Introduction

Metal-rich nanoparticles are between 1 and 200 nm in size and they possess special physicochemical characteristics [1]. In the last decade, the effects of nanoparticles on human diseases including neurological diseases such as Alzheimer's disease (AD) and dementia has been extensively studied. The experimental animals were treated with metal-rich nanoparticles via inhalation [2], oral supplementation [3], intratracheal [4], intravenous and intraperitoneal injection [5]. The metal-rich nanoparticles such as titanium dioxide (TiO_2), silica dioxide (SiO_2), silver and zinc oxide (ZnO) are absorbed into the body via the digestive tract, skin and also through inhalation (Table 1). These absorbed particles are stored in different organs but the brain is the most vulnerable to their oxidative toxic effects [6].

Brain and neurons are particularly vulnerable to oxidative stress-induced damage due to the following three reasons: (1) their high amount of oxygen consumption (The brain utilizes approximately 25% of the body's total oxygen consumption), (2) the presence of high amount of polyunsaturated fatty acids, and (3) low levels of enzymatic antioxidant activity [7,8]. Metal-rich nanoparticles enhance the production of reactive oxygen species (ROS). The main targets of reactive oxygen species (ROS) are the lipids (lipid peroxidation), proteins (protein-carbonyl formation) and nucleic acids (RNA and DNA oxidation, double- and single strand break of DNA). The ROS are scavenged by enzymatic and non-enzymatic antioxidants. Enzymatic antioxidant glutathione peroxidase (GSH-Px) contains selenium as co-factor. Hydrogen peroxide (H_2O_2) is converted to water by the catalytic effects of GSH-Px. Selenium can also have direct antioxidant effect on brain and neurons [8]. Selenium forms several allotropes (red, black and gray) that interconvert with temperature changes. It has two opposite physiological features. Concentration-dependently selenium can exert either its therapeutic or toxic effects. High doses of selenium

promotes the proliferation of cancer cells and has neurotoxic effects, although low and intermediate doses inhibit cancer cell proliferation and has a therapeutic effects on neurological diseases including AD. Antioxidant and anti-inflammatory effects of selenium were observed *in vitro* using cell lines and *in vivo* in animal models [9]. In addition, there is direct relationship between the evoked effect and the type of selenium compounds administered [10]. However, the results on the effects of selenium and selenium nanoparticles for the treatment of neuronal diseases are conflicting. These conflicting results can be in part attributed to the different concentrations used in experiments, and to the different cell lines used in *in vitro* assays. Oxidative stress is one of the main factors involved in the pathogenesis of many neurological diseases. Therefore, therapies using natural antioxidants compounds have been developed to cure several neurodegenerative diseases [11,12]. However, the success rate of treatments with natural antioxidants is low. Therefore, there is an urgent need for development of new nanoparticles with diagnostic and/or therapeutic properties to improve the detection and treatment of neurological diseases. Accumulating evidences indicate that there is a direct relationship between deficiency of selenium in serum and hair samples and memory deficit in patients with AD [13-16]. It has been reported that selenium treatment may decrease the risk of memory deficits in animal models and in AD patients [17,18]. Recently, high interest emerged to study the role of selenium and selenoproteins in neurodegenerative diseases including AD (Table 2). Selenoproteins are proteins containing selenium in the form of amino acid, selenocysteine. Selenoproteins are mainly expressed in the human brain and most likely involved in antioxidant processes, which are the key factor in preventing the onset and progression of AD [19]. In addition, there are some newly synthesized selenoproteins and selenium nanoparticles possessing remarkable physiological properties [20,21]. Due to the high potency and low systemic toxicity of these particles, they might serve as alternatives for conventional therapeutic drugs for the treatment of neurological diseases including AD.

In this review, we aimed to summarize the oxidant and antioxidant effects of nanoparticles in the brain. We also reviewed the potential therapeutic application of selenium nanoparticles for the treatment of AD. This review is expected to be a useful resource for the scientists working in the field of neurodegenerative diseases, oxidative brain injury or selenium-based drug development.

2. Role of selenium on oxidative stress in Alzheimer disease (AD)

There are two major types of free radical species: ROS and reactive nitrogen species (RNS). ROS are chemically reactive species containing oxygen. Examples include peroxides, superoxide, hydroxyl radical, and singlet oxygen. They are produced during the physiological processes. For example, engulfed bacteria and viruses in the neutrophils are killed by the ROS. Both ROS and RNS are produced in brain as a result of exposure to environmental factors such as electromagnetic radiation and industrial element pollution [22,23]. Toxic nanoparticles, for example aluminum or manganese oxide nanoparticles, from air pollution can induce excessive ROS production and oxidative stress in the brain. They can accelerate the progression of neurodegenerative diseases such as AD, amyloid lateral sclerosis and Parkinson's disease [23]. If the amount of ROS will not be controlled by antioxidants, they will cause significant reversible or irreversible damage to a wide range of biological molecules, including nucleic acids, lipids and proteins or any nearby molecule causing a cascade of chain reactions [24]. There is considerable interest in the ROS-induced reactions, and their relationship in the physiology and pathology of AD [10].

Oxidative stress was considered to be one of the main factors in the etiology of AD. AD is the world's most common form of dementia. Incidence of AD is still increasing in the world and the development of new strategies is needed for the treatment of AD. Despite the high number of studies, the molecular mechanisms responsible for the initiation of AD have not been elucidated yet. There are many theories to explain the cause of Alzheimer's disease. i.) accumulation of amyloid precursor protein forming amyloid- β ($A\beta$) plaques, ii) hyperphosphorylation of tau protein, iii) oxidative stress, iv) alterations in cholinergic neurotransmission v) environmental pollution vi) genetic factors including mutations of amyloid precursor protein (APP) and presenilin (PSEN)

genes, vi) immune system dysfunction, etc. [17,25,26]. Pathologically, the extracellular depositions of A β proteins and the presence of intraneuronal neurofibrillary tangles are important markers for posthumous diagnosis of AD. A β is the main protein component of senile plaques in the AD brain and it is composed of spontaneously aggregating peptides of 39-43 amino acids [17,27]. It is also known that microglia is the main source of neuroinflammatory factors and neuroinflammatory factors affect the nature of AD [17]. Inflammatory processes are associated with ROS production. Both ROS and RNS are considered to play important roles in induction of AD [11,28]. Moreover, A β fragment 25-35 (A β 25–35) induces activation of inducible nitric oxide (NO) synthase [29] and protein oxidation in hippocampal fibroblasts derived from AD patients [30] and they are appeared to be responsible for ROS and RNS-induced hippocampal damage. In addition, the ROS and RNS initiate other injury processes such as neuroinflammation and protein misfolding in the AD brain [31,32]. There are some reports showing that sulfur atoms are also involved in the oxidation process. For example, the oxidative stress-inducing properties of A β -peptide (1-42) are totally abolished by substitution of the sulfur atom of methionin at position 35 with a methylene group [33].

Selenium is an essential trace element in our body. One of the most important selenium-dependent detoxifying processes is associated with the activity of GSH-Px enzyme. GSH-Px protein contains a selenocysteine (Se-Cys) moiety in its active site. GSH-Px, catalase and SOD enzymes have synergistic functions in the removal of H₂O₂ and organic peroxides [8]. GSH-Px catalyzes a reaction, in which 2 reduced monomeric glutathione (GSH) react with H₂O₂, and form oxidized glutathione (GS-SG) and H₂O. GSH contains thiol groups in its structure. GS-SG is reduced back to its thiol form (GSH) by the glutathione reductase enzyme [19].

Thioredoxins are small peptides in the cytosol and mitochondria and also play an important role in maintaining a reduced environment in the cells through thiol-disulfide exchange reactions and protects cells and tissues from oxidative stress [34]. Reduction of thioredoxin is catalyzed by thioredoxin reductase-1 (Trx1) and most radicals such as hydrogen peroxide (H₂O₂) and nitric oxide (NO) are scavenged by Trx1 (Figure 1).

Besides of the neuronal injury evoked by hyperphosphorylated tau and A β plaques, accumulating evidences indicate the involvement of oxidative stress in apoptotic neuronal loss observed in the AD brain [35]. Since antioxidants are able to inhibit of A β aggregation pathways, new therapies have been developed for the treatment of AD. As it was mentioned above, thioredoxin (Trx) and glutathione (GSH) are the two major systems which play an important role in the maintenance of cellular redox homeostasis (Figure 1). It was reported that the inhibition of GSH synthesis resulted in an increase in A β -induced cell death and intracellular A β accumulation [36]. Decreased levels of selenium, GSH and GSH-Px were observed in model animals and in AD patients [37]. Correlation between the loss of cognitive function and plasma selenium levels was also observed in patients with AD. Therefore, the relevance of selenium and GSH redox system in patients with AD indicates their important roles in redox regulation [38]. Reduced selenium contents in plasma and hair were reported in the patients with AD and it was found a negative correlation between the selenium content in plasma and incidence of AD [39]. Moreover, selenium treatments decreased the levels of oxidative stress and A β formation in the brain of experimental animal models for AD [40,41]. Positive correlations between plasma and hair selenium deficiency and cognitive decline were reported in patients with AD [15,16]. Recently, selenium, total tau, A β 42, GSH, lipid peroxidation and antioxidant enzyme values were analyzed in the blood samples from AD patients in South India. No correlations were reported between the levels of selenium, total tau and A β 42 [42]. On the contrary, decreased GSH-Px enzyme activity and reduced levels of selenium were reported in erythrocytes [13] of patients with dementia and AD.

2.1. Size dependent effects of metal-rich nanoparticles in brain and AD

It is well known that the brain is the most vulnerable organ in body for oxidative stress-induced neurodegenerative injuries such as cerebral ischemia [42,43] and traumatic brain injury [44]. In most neurodegenerative diseases, these injuries are irreversible. The nanoparticles are mostly oxidant and they could induce neuronal injury and impair brain cognitive functions in AD

[39,45-48]. Recent *in vivo* studies in the experimental animals treated intraperitoneal or oral with nanoparticles have shown that metal-rich oxidative nanoparticles such as TiO₂, ZnO, iron oxide, SiO₂, silver and gold can pass the blood-brain barrier (BBA) and accumulate in the brain [23,49,50] (Table 1). For example, high transport rate of Ag nanoparticles from blood to brain via BBA was reported in brain of rats after injection a dose 5 mg/kg silver nanoparticles (20 and 200 nm) for 28 days. In addition, there is low rate of excretion from the brain and this leads to a gradual accumulation of nanoparticles in the brain. Contrary to intraperitoneal and oral applications, no accumulation of TiO₂ nanoparticles in the brain area via nasal application was reported in mice [51].

Apart from the oxidant nanoparticles, there are nanoparticles with antioxidant properties, for instance selenium. Metabolism of selenium nanoparticles in cells were reported in a recent paper [52] and it was also summarized in Figure 1. Mitochondria are physiologically the main source of ROS such as superoxide and hydroxyl radicals in mammalian cells during normal energy metabolisms [53].

Selenium consumed in foods and supplements exists in a number of forms including selenomethionine, selenocysteine, selenate and selenite. Reduced form of sodium selenite is selenide and it is produced in cytosol by catalytic effects of the GSH and superoxide radicals [54]. Then, the selenide is transformed to methylselenol and it is further transformed to methylated metabolites [55]. In addition, the selenide in cytosol serves as a source for selenoproteins, selenium-sugar, and elemental selenium. In a recent study, high amount of elemental selenium was indicated in human lung cancer cell line treated with sodium selenite [56].

Oxidative properties of nanoparticles are affected by physicochemical and biochemical factors such as surface properties, charge, and the adsorption rate of the nanoparticles [57]. In addition to these factors, the size of nanoparticles is an important factor which influences their biological activity. The large size of nanoparticle decreases its transport into brain and it is also constantly clearing foreign materials from the brain [45-48]. Redox regulatory and ROS scavenging

activities of the selenium nanoparticles with different sizes has been reported [58]. ROS scavenging effects of red selenium nanoparticles with small (5-15 nm), medium (20-60 nm) and large (80-200 nm) sizes were investigated in an *in vitro* model and the highest ROS scavenging effect was observed in the case of small-size red selenium nanoparticles [58]. Red elemental selenium nanoparticles with 20-60 nm sizes are produced from sodium selenite by the activated GSH redox system and they induced the proliferation rate of human hepatic cancer cells *in vitro*. They induced an increased activity of GSH-Px and Trx1 enzymes compared to sodium selenite [20]. On the contrary, Zhang and colleagues [59] reported that GSH-Px and Trx1 activities were affected neither in human hepatoma HepG2 cells nor in the mice liver by administration of selenium-rich nanoparticles in a size range of 5 to 200 nm. Similarly, chitosan nanoparticles with small size (40 and 70 nm) were more active and toxic tested on cancer cells [60]. In addition, size dependent protective effect of selenium nanoparticles against ROS production and DNA damage has been found [61]. More recently, the protective role of dextrin coated selenium nanoparticles (64 nm)-treated rats were investigated in the rat model of chronic inflammatory arthritis [56]. Increased SOD, GSH-Px and catalase activities were reported in liver, kidney and spleen of rats treated with dextrin-coated selenium nanoparticles [63,64]. According to the present literature, it seems that the small size range of selenium will ensure longer circulation time and increased accumulation in the brain of patients with AD

3. Role of nanoparticles in the brain

The presence of metals in the brain can be physiologically a necessity as well as a poison. Accumulation of the metals in brain tissues occur not only in the form of free ions, but also in the form of metalloproteins [23]. Abnormal homeostasis of metal ions in brain may induce neuronal damage if their levels move out of the normal physiological range especially due to the lack of specific metal binding proteins [39]. Biometals play significant roles in the biological systems through regulating and participating in numerous cellular processes such as induction of action

potential and co-factor of enzymes [54]. In particular, homeostasis of these elements has been demonstrated to be critical in brain, because they are involved in enzymatic activities, mitochondrial function, myelination, and neurotransmitter release [19].

The well-known metal-rich nanoparticles such as TiO₂, ZnO, iron oxide, SiO₂, silver (Ag) and gold (Au) have mostly oxidative effect in the brain [23,39]. On the contrary, selenium rich nanoparticles with antioxidant properties such as red selenium and sodium selenite are used in treatment of brain diseases and they size-dependently improve cognitive functions. In the following sections we will review recent reports on metal-rich nanoparticles such as TiO₂, ZnO, SiO₂ and silver.

3.1. Effects of TiO₂ and silica nanoparticles on antioxidant enzyme activity in the brain: TiO₂ nanoparticles are of high stability and have anticorrosion properties. They have been used for the treatment of neurological disease in experimental animals. However, potential toxic effects of TiO₂ have not been clarified yet.

Decreased activities of GSH-Px, catalase and SOD in the mouse brain samples were reported after nasal application of TiO₂ nanoparticles [51]. Results of another study indicated that activities of SOD and GSH-Px are decreased in the brain cortex and hippocampus region after oral administration of TiO₂ with/without lead acetate [3] and the study concluded that TiO₂-induced oxidative toxicity is supported by lead acetate. Ze and colleagues [64] investigated brain injury by nasal administration of different doses of TiO₂ (2.5, 5, and 10 mg/kg) for 90 consecutive days. They performed oxidant and antioxidant analyses and analyzed the gene expression profile of the brain samples. They observed that the levels of malondialdehyde (MDA) and protein carbonyls as markers of oxidative stress in the mouse brain were higher in the three treated group than in the control. Another study reported that inhalation of silica nanoparticles decreased GSH-Px, catalase and SOD activities in the rat corpus striatum [55]. Microglia is the main phagocytic neuronal cells in the brain and they play an important role in the process of inflammation. Recently, positive role

of silica nanoparticles on excessive ROS, RNS and cytokine production, and increased expression level of proinflammatory genes were reported in primary rat microglia [66].

3.2. Effects of ZnO on the activity of antioxidant enzymes in the brain: ZnO nanoparticles are commonly used in many commercial products such as construction material, toothpaste, beauty material, and wall paints. The ZnO nanoparticles attract specific attention in medical area due to small size and high specific surface area. The toxic effect of ZnO nanoparticles has been well known in experimental animals and cell lines. ZnO nanoparticles are toxic for different tissues, including the brain [67].

There are limited reports on how ZnO influence GSH-Px enzyme activity in the brain or neuronal cell lines. In a study, the effects of ZnO on oxidative stress and inflammation were investigated on brain samples from adult and old male mice. Intraperitoneal injection of ZnO nanoparticles decreased the activities of SOD and GSH-Px enzymes but MDA levels were increased [68].

3.3. Effects of CuO and silver nanoparticles on the activity of antioxidant enzymes in the brain: Expression levels of antioxidant enzymes in neurons are differently affected by CuO, manganese and silver. For example, Wang et al. [69] reported that expression of Trx1 is increased in PC12 neuronal cell line by incubation with copper but not with manganese and silver. However, GSH-Px expression in the cell line was decreased by the copper and silver nanoparticles but its expression level was not affected by manganese.

Dziendzikowska et al. [70] reported that silver nanoparticles caused neuronal oxidative damage through excessive ROS production and directly interfered with calcium responses in primary neural cells. Moreover, oxidative stress-induced GSH gene expression levels changed in caudate nucleus of the striatum, frontal cortex and hippocampus after administration of 25 nm Ag nanoparticles to mice [71]. Similarly, Hritcu and colleagues [5] reported that SOD and GSH-Px activities in temporal cortex of rat brain were decreased by intraperitoneal treatments of two doses

(23 and 29 nm) of Ag nanoparticles for 7 days, although lipid peroxidation level as MDA were increased in the brain area.

3.4. Effects of cerium dioxide (CeO₂) and on the activity of antioxidant enzymes in AD: CeO₂ nanoparticles as coating agent protecting from corrosion in mechanical polishing were extensively used in addition to its utilization as diesel fuel additive [72]. It was reported that activities of several antioxidant enzymes such as GSH-Px, catalase and SOD are generally increased by CeO₂ nanoparticle treatments although excessive production of ROS decreased [72]. Recent reports indicated potential catalytic antioxidant role of CeO₂ nanoparticles in AD [73,74]. Decreased level of A β plaque formation and oxidative stress in cortical neurons was reported by CeO₂ nanoparticles through regulation of mitochondrial function [74]. Result of a recent study indicated that Cu²⁺-induced A β aggregation and ROS production were decreased by CeNP@MnMoS₄ Core-Shell nanoparticles [75]. In addition, A β -mediated toxicity was also decreased by CeONP@POMD nanoparticles [76]. The antioxidant enzyme-mimetic activity of CeO₂ nanoparticles were attributed to the auto-regenerative cycle of Ce³⁺/Ce⁴⁺ and oxygen vacancies on the surface of CeO₂ [72]. Therefore, it seems that CeO₂ nanoparticles have protective effects against oxidative stress in AD supporting antioxidant enzyme activities.

4. Protective role of nanoparticles for treatment of AD

As it was mentioned above, AD is the world's most common form of dementia characterized by the A β plaque accumulation, tau protein hyperphosphorylation, oxidative stress, and cell apoptosis in the brain [17,77]. Accumulating evidences indicated that A β polymerization may be crucial to AD pathologies [27]. Hence, there is a considerable effort to develop new drugs that inhibit A β fibrillation. Recently, nanoparticles such as sialic acid-modified selenium nanoparticles [41] and silver [69] nanoparticles have been investigated and their effects on AD are summarized in the following sections.

4.1. Role of selenium nanoparticles in AD: As mentioned above, trace element selenium as an essential nutrient has important health effect in human biology [64]. Accumulating evidences indicate the important role of selenium in redox regulation because there are considerable data on positive correlation between increased cognitive decline and decreased selenium level [70]. The redox cycles of selenium (II), sodium selenate (VI) and sodium selenite (IV) forms are thought to be the most important mechanism linked to biological systems in brain by the inhibition of ROS [19]. Over the last decades, involvement of oxidative stress in neurological diseases such as dementia [18] and AD [10,41] have been extensively investigated. Different forms and sizes of selenium can influence its performance. The elemental selenium nanoparticles have size between 20 and 500 nm and they are also referred to as red or elemental selenium. However, the size of red elemental selenium formed was dependent on the amount of protein in the redox system. For example, it was reported in two recent studies that selenium nanoparticles between 20 and 60 nm in size has similar bioavailability to sodium selenite [20,21]. Over the last decade, other selenium containing antioxidant nanoparticles attracted high interest in human neurobiology due to their inhibitory effects on oxidative stress and their excellent low toxicity [20]. The effects of sialic acid-modified selenium nanoparticles in PC12 neuronal cell line were investigated by analyses of cytotoxicity, mitochondrial membrane depolarization-induced oxidative stress and apoptosis levels. The potential therapeutic application of sialic acid-modified selenium nanoparticles coated with B6 peptide has been reported. It inhibited A β aggregation and crossed the BBA [41]. Main phenol component of green tea is epigallocatechin-3-gallate and it has antioxidant role against oxidative stress in cells and protective role of epigallocatechin-3-gallate-stabilized selenium nanoparticles on A β aggregation and amyloid fibril disaggregation was reported in *in vitro* model [37]. Some tree species (i.e. *Oroxylum indicum*) and flowers produce a flavonoid chrysin (5,7- dihydroxyflavone). The protective role of chrysin loaded solid lipid nanoparticles against A β 25–35 induced oxidative stress was recently reported in rat hippocampal region [32]. Wang and colleagues [26] investigated involvement of selenium-containing clioquinol derivatives on Cu(II)-induced A β oxidation and they

were observed beneficial effects of the selenium containing clioquinol derivatives on hydrogen peroxide scavenging activity, intracellular ROS production and Cu²⁺-induced A β aggregation in SH-SY5Y neuroblastoma cell line. Gupta et al. [78] investigated potential therapeutic effects of water soluble biphenyl ethers-core shell CdSe/ZnS quantum dots on A β fiber in an *in vitro* model and they observed direct inhibitory effects of the dots on A β fiber formation.

4.2. Role of silver nanoparticles in AD: There is limited report on how Ag-rich nanoparticles influence redox status. Huang et al. [79] investigated the toxic effects of Ag-rich nanoparticles on induction and progression of AD in three neuronal cell lines (murine brain ALT astrocytes, murine microglial BV-2 cells and mouse neuroblastoma Neuro-2a). After the exposure, these neural cells had increased inflammatory cytokine secretion and signs of oxidative stress. Additionally, this study found A β plaque formation deposited in neural cells after Ag-rich nanoparticles treatment.

5. Expert commentary

Selenium compounds are potent neuroprotective agents, with modest effect on normal tissues and clinically well tolerated. The exact mechanism of their neuroprotective action has not been solved completely, though numerous mechanisms have been proposed depending on compound and system examined. Low selenium levels in blood, hair and tissue samples from AD patients were reported. Diagnosis of AD is difficult because it can be confused with other neurological diseases. Therefore, there is need for new diagnostic markers and low selenium level and GSH-Px activity might serve as diagnostic markers of AD.

Apart from the diagnosis, there are six main future directions and expert's recommendation for this issue. There are only few reports on the application of selenium nanoparticles for the treatment of AD. Additional studies should be performed using nanoparticles as potential therapeutic neuroprotective agents in cell lines and experimental animals.

In addition, there are limited reports on interactions between selenium-rich nanoparticles and neuronal cells and the available reports are conflicting (Tables 1). Hence, effects of the selenium nanoparticles on the activity of GSH-Px should be investigated by further experiments.

Third, there are not enough reports on bio-distribution of oxidant and antioxidant nanoparticles in different brain areas. It is well known that each brain area is responsible for different physiological functions and hippocampus region is initially affected in AD. Therefore, clarifying the third subject is important to understand the etiopathogenesis of oxidative stress-induced neurological diseases.

Forth, changing the physicochemical structures of metal-rich nanoparticles may decrease their oxidative properties, resulting in their reduced oxidative toxicity in brain and neurological disease. The subject should be investigated in future studies by using different size of oxidant nanoparticles including ZnO and silver.

Fifth, the potential therapeutic effects of selenium nanoparticles on AD should be tested properly in animal models and in clinical trials.

Sixth, interactions between selenium nanoparticles and calcium ion (Ca^{2+}) homeostasis should be investigated in neurons. The Ca^{2+} plays a crucial physiological role in physiological and pathophysiological functions such as apoptosis and mitochondrial functions [53,81]. Alteration in the function of Ca^{2+} entry channels on the plasma membrane including voltage gated calcium channels (VGCC) and transient receptor potential (TRP) cation channels play also an important role in oxidative stress-induced apoptosis and mitochondrial overload of Ca^{2+} [82]. Some transient TRP channels such as TRP melastatin 2 (TRPM2) and TRP vanilloid 1 (TRPV1) are modulated by different stimuli, including altered extracellular ionic milieu and metal cations [83]. A growing amount of evidence has shown that increased levels of Ca^{2+} entry through TRPM2 and TRPV1 channels induces excessive ROS production via increased depolarization membrane rate of mitochondria [12]. Since neurons express higher levels of TRPV1 channels compared to epithelial or cancer cells, neurons are more vulnerable [84,85]. Recently, we observed a modulator role of

selenium on excessive ROS production and increased mitochondrial membrane depolarization via inhibition of TRPM2, TRPV1 channel activity in hippocampus of dementia and diabetes-induced rats [18,80]. Contrary to our reports, increased intracellular Ca^{2+} concentration was reported in primary cultures of rat hippocampal neurons by CdSe quantum dots (nanocrystals) through activation of VGCC [81]. In the conversion of selenide into elemental selenium, ROS plays an important role [52]. Overload Ca^{2+} entry via TRPM2, TRPV1 and VGCC may induce mitochondrial membrane depolarization and excessive ROS production increasing the levels of elemental selenium. This, in turn, may induce an increase in the production of GSH-Px enzyme leading to a decrease of ROS in neurons (negative feedback mechanism). This issue should be clarified by a study on neuronal cell lines or primary neuronal culture.

6. Five year review

ROS production occurs during the normal physiological function of our body. Physiological levels of ROS are not toxic if they are controlled by antioxidants enzymes and proteins such as GSH-Px. Etiology of AD has not been clarified although oxidative stress can be an important factor in this process. In addition, diagnosis of AD with continuous monitoring of dementia is not easy. Therefore, plasma selenium level and GSH-Px activity might be a diagnostic indicator of old patients with AD. Nanoparticles are used for commercial purposes such as leather production, cosmetics, microelectronics, and drug carriers and accumulating evidences indicated their environmental toxic effects [86]. In addition of their application in the commercial area, the nanoparticles are used in last decade for the treatment of diseases such as cancer and neurological diseases. Most metal-rich drug nanoparticles such as ZnO and TiO_2 have been extensively investigated in cancer research and they are used as a therapeutical agent for cancer treatment [87]. Some metal-rich nanoparticles are proposed to be used in the treatment of neurological diseases, including AD but they influence brain functions. The threatening effects of the nanoparticles are driven from their ability to stimulate of ROS production and generate inflammation. In addition, the

excessive accumulation of cytosolic metal-rich nanoparticles in the brain is another problem originated from high transport rate of the nanoparticles via BB [88,89]. In order to inhibit the oxidant effects of nanoparticles, studies with antioxidant covered nanoparticles such as selenium and flavonoid-covered selenium nanoparticles have been already introduced for the treatments of AD [26,32]. Selenium-rich nanoparticles inhibited formation and oxidation of A β in experimental animals and cell lines with AD. Yet, there is no human study on A β -formation although there are several studies on other metal-rich nanoparticles such as ZnO and TiO₂. Hence, there is a need to study the effects of selenium-rich nanoparticles on human samples. The metal-rich nanoparticles have beneficial effects via excessive ROS production in cancer cells but selenium might have a therapeutic effect formation on *in vitro* models of AD via inhibition of excessive ROS production and A β formation. Hence, decreased activity of antioxidant enzymes such as GSH-Px, SOD and catalase are reported by the metal-rich nanoparticles, whereas the enzyme activities are increased by selenium rich nanoparticles treatments. It seems that selenium and flavonoid enriched nanoparticles are important candidates for drug development to treat AD [26,32]. However, results of the limited studies are not enough to clarify the role of selenium-rich nanoparticles. Therefore, the putative correlations between improvement in AD symptoms and treatment with selenium nanoparticles require further studies. Normally, sizes of selenium rich nanoparticles are between 1-200 nm. ROS-scavenging effectiveness of selenium-rich nanoparticles is affected by size and highest ROS-scavenging activity was found in the case of small size nanoparticles (5 and 15 nm).

7. Key issues

- Investigation of selenium rich nanoparticles is important for drug development in AD.
- There are serious unmet needs in the examination of the neuroprotective role of selenium-rich nanoparticles in biological samples from experimental animal models and patients with AD.

- The bio-distribution of selenium nanoparticles in brain areas should be investigated.
- Further experiments are needed to clarify the main role of GSH-Px in AD patients.
- Selenium nanoparticles differing in physicochemical properties and size should be tested focusing their inhibitory effect on oxidative stress.
- Interactions of oxidative stress-related TRP channels such as TRPM2 and TRPV1 and selenium- rich nanoparticles can be also an important topic.

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Declaration of Interest

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Table 1. Effects of nanoparticles on antioxidant enzymes in brain of experimental animals.

Nanoparticle	Administration route	Material	Value/Effect	Reference
Ag	Incubation	PC12 cell line	Trx1 and GSH-Px/Trx1 expression level unchanged but GSH-Px expression decreased	Wang et al. [69]
Ag	Intraperitoneal	Caudate, frontal cortex and hippocampus of mice brain	Glutathione gene expression	Rahman et al. [71]
Ag	Intraperitoneal	Temporal cortex of rat	SOD and GSH-Px/ Decreased	Hritcu et al. [5]
CuO	Incubation	PC12 cell line	Expression level of Trx1 increased but GSH-Px expression decreased	Wang et al. [69]
Mn	Incubation	PC12 cell line	Expression level of Trx1 and GSH-Px/unchanged	Wang et al. [69]
TiO ₂	Nasal	Mice brain	GSH-Px, catalase and SOD/ Decreased	Jeon et al. [51]
TiO ₂ with/without lead acetate	Oral	Brain cortex and hippocampus of mice	SOD and GSH-Px/ Decreased	Zhang et al. [3]

ZnO	Intraperitoneal	Brain of adult and old male	SOD and GSH-Px/ Decreased	Vedagiri and Thangarajan [32]
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CAT; Catalase, GSH-Px; glutathione peroxidase, SOD; superoxide dismutase, Trx1; thioredoxin reductase 1,

Table 2. In vivo and in vitro effects of nanoparticles on Alzheimer's disease (AD) in cell line, humans and animals.

Nanoparticle	Material	Value/Effect	Reference
Ag	Neuronal cell lines	Induction and progression of AD	Huang et al. [73]
Biphenyl ethers conjugated CdSe/ZnS core/shell quantum dots	In vitro A β model	A β fibril disruption	Gupta et al. [78]
Chrysin loaded solid lipid nanoparticles	Rat	Protective and antioxidant effect	Vedagiri and Thangarajan [32]
Epigallocatechin-3-gallate-stabilized selenium nanoparticles	A β peptides	A β aggregation and cytotoxicity/protective effect	Zhang et al. [37]
Sialic acid-modified Se	PC12 neuronal cell line	Crossing the blood-brain barrier and decreased level of A β aggregation and	Yin et al. [41]
Se-containing clioquinol derivatives	Neuroblastoma cell line	Cu(II)-induced A β oxidation and aggregation /protective effect	Wang et al. [26]

AD; Alzheimer's Disease; GSH-Px, glutathione peroxidase; Se, selenium

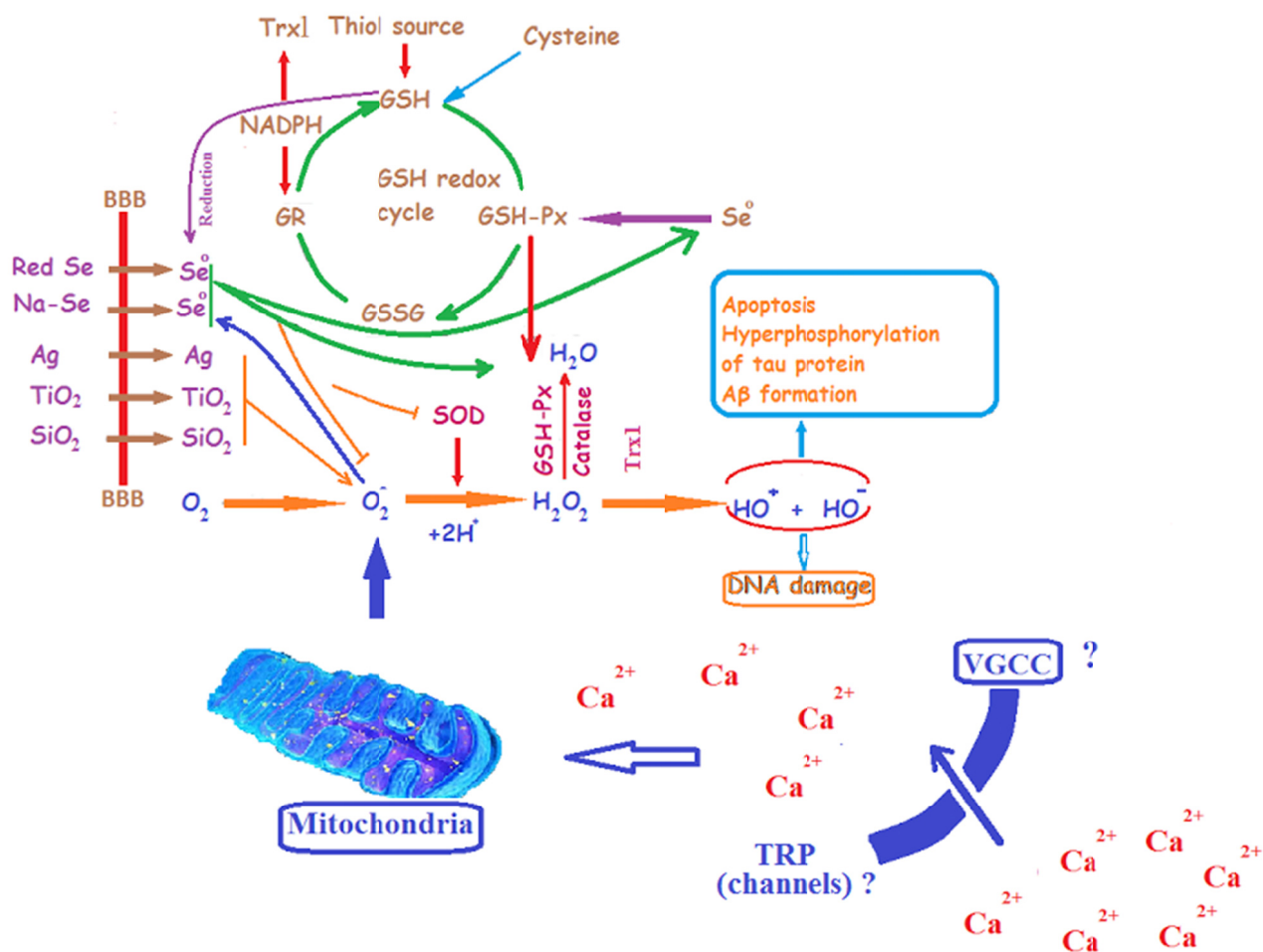


Figure 1. Possible pathways of nanoparticles on oxidative stress and amyloid beta (Aβ) plaque formation in brain of patients Alzheimer's disease (AD). Excessive production of reactive oxygen species (ROS) occurs in brain affected by AD. ROS have important roles in the pathophysiology of AD. Blood-brain barrier (BBA) permeable nanoparticles such as zinc oxide (ZnO), silver (Ag) and titanium dioxide (TiO₂) induces ROS production in brain. One of the most important selenium-dependent detoxifying processes is glutathione peroxidase (GSH-Px) system. The GSH-Px with catalase and superoxide dismutase (SOD) plays a central role in the removal of hydrogen peroxide (H₂O₂) and leads to the formation of oxidized glutathione (GS-SG). GSH-Px contains thiol groups in its structure and it is synthesized from GSH. GS-SG is reduced back to its thiol form (GSH) by the glutathione reductase (GR) enzyme. Reduction of thioredoxin is catalyzed

by thioredoxin reductase-1 enzyme (Trx1) and many radicals such as H_2O_2 and nitric oxide are scavenged by Trx. Elemental selenium (Se^0) from selenium rich nanoparticles is produced by catalytic effects of reduced GSH and mitochondrial ROS. Excessive Ca^{2+} entry through oxidative stress-activated TRP channels induce mitochondrial membrane depolarization and excessive ROS production. Interactions between TRP channel and selenium nanoparticles in AD should be investigated by future studies.

ACCEPTED MANUSCRIPT