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Neurological Disorders and Oxidative Toxic Stress: A Role of Metal Nanoparticles

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Abstract

Context: Oxidative stress is a hallmark of many types of neuropathology disorders and underlying mechanism in several neurodegenerative diseases and brain injuries. The CNS is particularly susceptible to oxidative toxic stress (OTS). Reactive oxygen spices are the basic inflammation and neurotoxicity mediators in ischemia/reperfusion injuries. The purpose of the present review is to provide an overview of some nanoparticles (NPs) in developing OTS conditions and neurological disorders.

Evidence Acquisition: Here, a nanotechnology approach is evaluated using NPs in human neuronal protection against OTS. It may be wide therapeutic applications in the case of acute and/or chronic neurodegenerative disorders related to OTS.

Results: In the brain of mice treated with nanosize TiO_2, a significant association was found between the ability to induce the production of ROS and metabolic stress in intracellular environments and inflammatory responses in mice brai. The large surface area of AgNPs may efficiently facilitate the radicals generation including ROS in various organs. The production of ROS may cause DNA damage, cellular apoptosis, and activation of the mitogen activated protein kinase (MAPK) pathways which is responsible for regulating many cellular processes. Prolonged and excessive OTS may contribute to the activation of transcription factors and genes responsible for inflammation responses such as NF-κB and AP-1. Furthermore, OTS may contribute to the onset of neurodegenerative diseases. The ability of CuONPs to generate OTS in vitro studies has been demonstrated; however, information on the neurotoxicity of the CuONPs in vivo is low.

Conclusions: The NPs-induced OTS may increase the pro-inflammatory responses. On the other hand, administration of antioxidants such as NAC and vitamin C and E prior to exposure to metal NPs significantly decreases OTS conditions.

Keywords: Nanoparticles, Oxidative Toxic Stress, Neurzological Disorders

1. Context

Nanotechnology is the science of the manipulation of materials and their utilization in different fields, including medicine, pharmacology, electronics, and etc. However, the advent of nanotechnology resulted in human exposures to engineered nanomaterials which in turn may cause adverse health effects in exposed subjects in both environmental and occupational settings. Thus, the evaluation of potential human health effects of this type of technology before the sematerials be fully exploited is important. Nanoparticles (NPs) are an ultrafine (< 100 nm) class of substances with characteristics including large surface area, surface activity and shape (1). There are two main classes of NPs; combustion-derived NPs and manufactured NPs. Diesel exhaust particles and welding fumes are the examples of the first class. However, metal oxides NPs such as titanium dioxide, cerium oxide, and silver oxide are manufactured NPs (2). Recently, the health effects of NPs are considered as an occupational and environmental problem (3). Many studies have been conducted to assess the role of oxidative toxic stress (OTS) in pathogenesis of NPs-induced neurotoxicity (4). The objective of the present review is to summarize existing knowledge on the relevance of exposure to metal NPs and the role of OTS in metal NPs-induced neurotoxicity.

2. Evidence Acquisition

Here, a nanotechnology approach is evaluated using NPs in human neuronal protection against OTS. It may be wide therapeutic applications in the case of acute and/or chronic neurodegenerative disorders related to OTS.

2.1. Oxidative Toxic Stress and Nanoparticles Neurotoxicity

Reactive oxygen species (ROS) and reactive nitrogen

species (RNS) are the most important classes of free radicals that continuously produced due to cellular metabolism, particularly during the mitochondrial respiration (5). Reactive species are normally maintained at low but given levels regulating through a balance between oxidants' generation and their scavenging rate by various antioxidants (6). Mitochondria as the main sites for the metabolism of oxygen, accounting for about 85% - 90% of the oxygen consumption of cells (7) are a potential endogenous source of ROS.

At low levels, ROS acts as signaling molecule in many physiological processes including cell proliferation (8), cellular aging (9), or cell death (10, 11) dependent on cell types. Under normal conditions, free radicals are eliminated rapidly by some body's defense mechanisms including enzymatic (superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase and non-enzymatic (glutathione, coenzyme Q, β-carotene, and vitamins E and C) antioxidant systems that scavenge free radicals to nontoxic forms. Imbalance between generation of free oxidative radicals and antioxidant defenses results in the cumulative production of ROS/RNS leading to a negative condition termed OTS (12-14). When particles deposited, oxidative damage of such macromolecules as lipids, nucleic acids, and proteins may occur. The brain is particularly susceptible to OTS because of its need to high levels of energy, low level of antioxidants as well as a high cellular content of lipids and proteins (15). Experimental studies have implicitly shown the role of ROS and OTS in pathogenesis of neurodegenerative disorders (16). After entering the human body via different routes such as inhalation, skin, and ingestion NPs may then be distributed in the body and reach various tissues even the brain (17). However, direct disruption of neuronal cell membranes would allow NPs to reach the brain (18, 19). For instance, intravenous, intraperitoneal, or intracerebral administration of silver (Ag), copper (Cu), or aluminium (Al) NPs (50 - 60 nm) has been reported to disrupt the blood brain barrier (BBB) and neurodegenerative systems (20, 21).

Functionality on the NPs surface can cause OTS leading to inflammation in tissues where NPs are deposited (22). Functionality, NPs such as C60 fullerenes and ultrafine particles generate ROS especially when they are exposed to ultraviolet (UV) wavelengths or transition metals (23). For instance, NPs of silver produced ROS may result in oxidative DNA damage in the brain (24). Additionally, enhanced levels of OTS have been reported in the mice brain with apolipoprotein E deficiency exposed to concentrated ambient NPs (25). High prevalence of neurodegenerative diseases such as Alzheimer's disease and primary brain tumors has been reported, however, the exact etiology of them is not clear yet and OTS has been reported as a possible mechanism of such diseases (26-29).

3. Results

3.1. Nanoparticles and Oxidative Toxic Stress

3.1.1. Titanium Dioxide Nanoparticles

Titanium dioxide (TiO_2) NPs are produced in large quantities because of their stronger catalytic activity than TiO_2 fine particles, they have been widely used in both industrial and consumer products (30). Titanium dioxide NPs have larger surface area because of their smaller size resulting in higher exposures that raises concerns about the potential adverse health effects of TiO_2 NPs (31, 32). In the brain of mice treated with nanosize TiO_2, a significant association was found between the ability to induce the production of ROS and metabolic stress in intracellular environments and inflammatory responses in mice brain (33, 34). Titanium dioxide NPs may cross the BBB and concentrate in the mice brain resulted in inflammatory cell infiltration and apoptosis of hippocampus cells leading to a decrement in cognitive function in the brain (35). As ROS generation would damage cell membranes, thereby facilitating the entry of TiO_2 NPs may activate the upstream signaling pathway involved in OTS, it is necessary to investigate the P38-nuclear factor-E2-related factor-2 (Nrf-2) pathway. The association between the Mitogen Activated Protein (MAP) kinase cascades (i.e. p38 and c-Jun Nterminal kinase (JNK)) and the upstream signaling mechanism responsible for regulating OTS is well-known as well as OTS can activate JNKs and p38 MAP kinases involving MAP kinase cascades (34, 36). Furthermore, TiO_2 NPs significantly alter the immune response, apoptosis and act as second messengers in intracellular signaling cascades. The increased ROS generation due to TiO_2 NPs exposures may be related to activation of the P38-Nrf-2 signaling pathway in brain injury (37).

3.1.2. Silver Nanoparticles

Silver NPs (AgNPs) have been used in antimicrobial, optical, conductive in chemical applications as well as in cosmetic production, household appliances, and medicine which resulted in daily human exposure to the silver NPs (38, 39). Because of their antimicrobial properties, AgNPs has the most frequent application in commercial products. However, these NPs are known to induce toxicity in different species and argyria or argyrosis due to chronic human exposure to silver is well-known (40-42). Chemical composition, surface charge, solubility, size, shape, and their ability to bind biological sites are important factors in NPs toxicity (3). It is suggested that toxicity of AgNPs is independent of silver ions and oxidative stress is the main mechanism of toxicity (43, 44). The large surface area of AgNPs may efficiently facilitate the radicals generation including ROS in various organs (45). Furthermore, AgNPs may deplete the antioxidant defense mechanism and resulted in ROS accumulation, (22) initiating an

inflammatory response and perturbation and destruction of mitochondria (46) leading to release cytochrome C and apoptosis as final consequences. In addition to mitochondria destruction, cell membrane damage seems to be another part of AgNPs mechanism of cytotoxicity preceding mitochondrial perturbation (38, 47).

3.1.3. Zinc Oxide Nanoparticles

Zinc oxide (ZnO) NPs are widely used in production of cosmetics and sunscreens for protection against UV-induced skin damage (48). As an antimicrobial agent, ZnO NPs have been used as food additives and as packaging materials (2, 3). Other applications of these NPs are their potential use as fungicides in agriculture (4), anticancer drugs and biomedical imaging (49). Toxicity of NPs on bacterial systems, vertebrates, and mammalian systems has been reported in previous studies (50). The production of ROS has been recommended as one of the primary mechanisms in NPs toxicity leading to oxidative stress, inflammation, as well as protein and DNA damage (51). Regarding ZnO NPs, the potential mechanisms of toxicity are thought to be oxidative stress and DNA damages through lipid peroxidation as well as apoptosis via p53 and p38 pathways (52). The production of ROS may cause DNA damage, cellular apoptosis, and activation of the mitogen activated protein kinase (MAPK) pathways which is responsible for regulating many cellular processes (53, 54).

3.1.4. Iron Oxide Nanoparticles

Iron oxide nanoparticles (IONPs) have many biomedical applications including cell labeling, drug targeting, gene delivery, hyperthermia therapy and as a contrast agent in magnetic resonance imaging (55, 56). Iron oxide NPs can cause a variety of tissue responses from cell activation and ROS generation to cell death (57). Moreover, IONPs might induce mitochondrial damage even if they are not localized into it (58).

Because of the ability of IONPs in passing through the BBB and entering the brain (59), the health consequences of IONP applications, particularly in the brain, are especially interested. Since IONPs have a large content of iron, they can potentially damage the cells (60). Iron-dependent formation of ROS by the Fenton reaction has been considered because of many NPs (61). However, these conditions may be accelerated because of liberating irons from deposited IONPs, since iron promotes the production of ROS in the brain (61, 62).

Iron is a transition metal and because of its catalytic action in Fenton-type reactions may be resulted in ROS generation (particularly hydroxyl radicals). Besides Adenosine triphosphate (ATP) generation, mitochondria are a major source of ROS production in an intracellular region. Thus, the investigation on activities of mitochondrial respiratory chain complexes is interesting (63).

Iron oxide NPs can reach the brain via the olfactory nerve resulted in OTS and ultra-structural alterations in the cells of the olfactory bulb (64). Although, there is little information about the health consequences of accumulation and retention of IONPs in the brain (59, 65), including the striatum and hippocampus (25, 66) it appears that iron-dependent processes are especially important for oligodendrocytes because of their highest content of iron compared to the other types of brain cells (67). Because of their highly oxidative energy metabolism, oligodendrocytes are vulnerable to excess levels of iron which enhance OTS through the Fenton reaction (68). The high surface activity of NPs concentrated in the brain, during long-term exposures, may be related to cellular interactions and free radical formation leading to brain damage and increased risk of neurodegenerative conditions (25). Because of the high level of a metabolic rate, low endogenous scavenger levels, and extensive networks of neurons, the brain is more vulnerable to OTS than many other tissues (28). It has been reported that excessive accumulation of ROS resulted in irreversible neuronal death in the brain which may progress to develop neurodegenerative disorders (69). Prolonged and excessive OTS may contribute to the activation of transcription factors and genes responsible for inflammation responses such as NF-κB and AP-1. Furthermore, OTS may contribute to the onset of neurodegenerative diseases. Therefore, it is recommended to carefully monitor the accumulation and retention of IONPs in the striatum (70).

3.1.5. Copper Oxide Nanoparticles

Copper oxide (CuO) is a semiconducting material with a monoclinic structure which exhibits useful chemical and physical properties (71). Because of its excellent thermal conductivity, the CuO suspension has been used in mechanical devices as a heat transfer fluid (72). It is showed that CuONPs could regulate the delayed rectifier potassium current in hippocampal CA1 pyramidal neurons of rats and alter the action potential of hippocampal CA1 neurons by impairing the functional properties of voltage-gated sodium channels (73). Additionally, CuONPs may cross the BBB and reach the central nervous system (CNS). Therefore, long-term exposure to CuONPs expected to be potentially neurotoxic (74).

The exposure to CuONPs may result in hippocampal dysfunction and further affect learning and memory abilities (25, 75). The toxicity of particles is often explained by oxidative damage mechanism (76). The ability of CuONPs to generate OTS in vitro studies has been demonstrated; however, information on the neurotoxicity of the CuONPs in vivo is low (77, 78). Furthermore, oxidative damage is associated with cognitive dysfunction and disorders in brain (79, 80).

3.1.6. Cerium Oxide Nanoparticles

Cerium oxide (CeO_2) has been used as a polishing agent for glass productions, ophthalmic lenses, and precision optics. Another application of this substance as an UV-ab-

sorber is for preventing solarization and discoloration of glass products. It is also used as a diesel fuel-borne catalyst to reduce particulate matter emissions in emission control systems of automobile engines (81-83). Studies on CeO_2NPs application to quench ROS in biological systems have shown that CeO_2NPs are able to confer neuronal, ocular, and radioprotection (84, 85). Protective effects of CeO_2NPs against oxidative and inflammatory injuries caused by cardiac-specific expression of monocyte chemotactic protein-1 have been reported (82). The antioxidative role of CeO_2NPs is primarily due to exchange between ROS and the high ratio of electrons on the NPs' larger surface area (86). Furthermore, inhibition of CSE-induced activation of NF-κB and inflammatory cytokines generation have been reported in cells treated with CeO2NPs (87).

3.2. Antioxidants

An antioxidant is a molecule that can reduce or prevent the oxidation of other molecules in the organism because of any chemical events such as ROS/RNS generation. The levels of ROS and RNS are balanced by two lines of cell defense including the enzymatic (as the first line) and nonenzymatic (as the second line) antioxidants providing maximal protection against OTS via ROS clearing and scavenging (88). Preventive and therapeutic features of antioxidants are well-known and they have been known to have a critical role in protecting biological sites from oxidative injuries (89-92). By now, many kinds of fruits, vegetables, plant food materials, and dietary supplementation have been investigated for their antioxidant capabilities (92-94). The association between specific oxidative damage and sites of injury in many different types of neurodegeneration conditions are not clear exactly. At present, a clear delineation of the cause-effect relationship cannot be concluded. However, a large number of studies indicates the role of oxidants in developing distinct pathological consequences promoting and propagating oxidative injuries leading to irreversible degeneration in brain (69).

Recently, nano-antioxidants, the substances which scavenge certain free radicals, have been investigated in many studies and it has been indicated to have effective antioxidant in treatment of diseases.

4. Conclusions

Although neurotoxicity of combustion-derived NPs are reported in both in vivo and in vitro studies, it is difficult to evaluate; it in environmental and occupational settings because, after generation, these NPs readily aggregated (3). Anti-inflammatory properties of some metal NPs have been indicated suggesting them to pose anti-inflammatory effects by down regulation of NF-κB signaling pathway in macrophages (95). However, several studies have shown a major role of ROS in cytotoxicity of nanoparticles. The NPs-induced OTS may increase the pro-inflammatory responses (22). On the other hand, administration of antioxidants such as NAC and vitamin C and E prior to exposure to metal NPs significantly decreases OTS conditions (96, 97). Further studies are required to improve existing knowledge on the mechanisms of NPs-induced neurodegenerations.

Footnote

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