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19) NANOSCALE CERIUM DIOXIDE AS A MYMETIC OF ANTIOXIDANT PROTECTION ENZYMES

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Abstract

The analysis of recent publications shows the widespread use in the biology and medicine of nanoscale compounds with biomimetic and antioxidant activity. Cerium dioxide nanoproducts are considered as a promising nanobiomaterial for biomedical applications because of their high biocompatibility, low toxicity and catalytic activity. The role of Ce^{3+} soluble salts as bacteriostatic, bactericidal, immunomodulatory and antitumor agents is characterized. The value of nanocrystalline cerium dioxide in protecting cells from oxidative stress is shown. The high efficiency of nano-dispersed cerium dioxide is associated with its oxygen non-stoichiometry, the ability to participate in redox processes in a living cell and its ability to auto-regenerate, which is its main difference from classical antioxidants. As a compound what is shown to have a UV-protective effect, different in efficiency for individual tissues, nano-cerium dioxide is shown for use in the treatment of tumor processes, it has a probiotic, antibacterial and antiviral effect. It has been shown that nanocerium can act as a mimetic of superoxide dismutase, catalase, some oxidases, oxidoreductases, and phosphatases, as well as being able to participate in the neutralization of reactive nitrogen. It has been found that, unlike natural enzymes, nanoceria has a more intense effect on the rate of reaction and does not require special environmental conditions, such as a particular temperature and reaction of the environment. The possibility of changing the catalytic activity of cerium dioxide nanoparticles can be achieved by varying their size, dispersion and ligand shell. The presence of more surface defects (surface oxygen vacancies), which stabilize the degree of oxidation of Ce^{3+}, allows cerium dioxide to accumulate and release oxygen from its crystal lattice depending on the environmental conditions. By changing the stoichiometry of nano-dispersed cerium dioxide, its antioxidant and pro-oxidant properties and enzyme activity can be regulated. The use of nanomaterial-based mimetics enzymes creates the ability to reduce the cost of their synthesis, increase catalytic activity and stability under harsh conditions.

Introduction

Cerium (Ce) is a rare earth element of the lanthanide family. Its uniqueness is due to its ability to exist in different oxidation states (Ce^{3+} and Ce^{4+}) (Ferraro et al., 2017, Pezzini et al., 2017). Ce^{3+} soluble salts are used for bacteriostatic, bactericidal, immunomodulating and antitumor purposes (Щербаков et al., 2014, Casals et al., 2017). Nanodispersed cerium dioxide (CeO_2NPs) has recently been widely used as a potential catalytic antioxidant in biology and medicine (Charbgoo et al., 2017, Zhang et al., 2017). The biological activity of cerium dioxide nanoparticles is determined by its oxygen non-stoichiometry, which depends on the size of the nanoparticle and the surface ligand (Pezzini et al., 2017), high degree of biocompatibility, low toxicity and catalytic activity (Gil et al., 2017, Singh, 2016, Sun et al., 2017, Walkey et al., 2015, Zhang et al., 2017). However, all possible mechanisms of its biological activity have not been studied.

Material and methods

The work is a fragment of the research work "Development of biotechnologies for the creation of new probiotics, biologically active substances and nanomaterials" State Registration No. 0116U005824. In this study, literature studies on the mimetic and antioxidant effects of nanocrystalline cerium dioxide were investigated and compared.

Results and discussion

There are numerous reports on the role of nanocrystalline cerium dioxide in protecting against oxidative stress (Щербаков et al., 2014, Tsekhmistrenko & Tsekhmistrenko, S., 2015). In case of disturbance of the protective (antioxidant) system of the body or with a significant increase in the level of exogenous ROSs, a third-party regulator is required, which is able to perform the function of an enzyme or antioxidant (Lushchak, 2017, Tsekhmistrenko et al., 2018, Tsekhmistrenko et al., 2018b). It has been proved that nanocrystalline cerium dioxide can act as oxidoreductases, enzymes, that regulate redox processes in biological systems (Dalapati et al.,2017). It is likely that the CeO_2NPs should protect cells from destruction by the effects of adverse factors that cause oxidative stress.

Oxygen non-stoichiometry and the associated ability of CeO_2NPs to participate in redox processes in living cells, as well as the ability to autoregenerate, ensures its high efficiency (Pezzini et al., 2017). For CeO_2NPs, UV-protective action was shown, different in efficiency for individual tissues, promising application in the treatment of tumor processes (Щербаков et al., 2014). CeO_2NPs has a probiotic, antibacterial (Цехмістренко et al., 2018, Tsekhmistrenko et al., 2018) and antiviral (Щербаков et al., 2014) effect.

During recent years there had revealed the enzymatic activity of CeO_2NP due to its oxygen non-stoichiometry (Pezzini et al., 2017). The low energy of formation of oxygen defects in the crystalline lattice of cerium oxide makes it possible to easily engage in redox reactions and inactivate the active forms of oxygen and nitrogen (Щербаков et al., 2014). The main difference between CeO_2NP and classical antioxidants is its ability to regenerate itself (Pezzini et al., 2017, Singh, 2016). The change in the catalytic activity of cerium nanoparticles can be achieved by varying their size, dispersion and ligand shell (Щербаков et al., 2014).

Nanocerium acts as a mimetic of superoxide dismutase (SOD) and catalase, and its efficiency in radical scavenging is proportionally related to the concentration of Ce^{3+} ions on the particle surface (Singh, 2016). Treatment of CeO_2NP with hydrogen peroxide leads to a complete loss of SOD-like activity, but after a while the activity is restored, which confirms the process of autoregeneration of the nanoparticle surface (with respect to oxygen non-stoichiometry) and recovery to trivalent cerium (McCormack et al., 2014). The SOD-like activity of the nanoparticles depends on the size. Nanoparticles of 3–5 nm in size more intensively inactivate superoxide anion than nanoparticles of 5–8 nm. Addition of titanium ions to CeO_2NPs don't alter their oxidase activity, but at the same time SOD-like activity is reduced (Щербаков et al., 2014, Tsekhmistrenko et al., 2018). The SOD activity of cerium dioxide nanoparticles depends on the ionic composition of the solution (McCormack et al., 2014). Phosphate ions cause phosphorylation of the surface of the particles and lead to a decrease in their ability to perform the function of SOD and catalase. The use of stabilizers causes varying degrees of adsorption of phosphate groups by the surface of the nanoparticles, that is, the sensitivity to phosphating. SOD-like activity of CeO_2NP is comparable to the level of natural enzyme (Tsekhmistrenko & Tsekhmistrenko, S., 2015, Tsekhmistrenko et al., 2018, Tsekhmistrenko et al., 2018). CeO_2NPs on the surface of which are dominated by Ce^{3+} most clearly exhibit SOD-like activity (Щербаков et al., 2014, Tsekhmistrenko & Tsekhmistrenko, S., 2015, Tsekhmistrenko et al., 2018, Tsekhmistrenko et al., 2018).

Another active form of oxygen that can oxidize virtually all organic molecules is the hydroxyl radical (Щербаков et al., 2014, Lushchak, 2017, Singh, 2016). The CeO_2NP is capable of inactivating a highly active hydroxyl radical (Gil et al., 2017). The predicted mechanism of OH· inactivation in the presence of cerium dioxide nanoparticles is described in (Casals et al., 2017, Ferraro et al., 2017, Lushchak, 2017, McCormack et al., 2014, Tsekhmistrenko et al., 2018). Another ROS is hydrogen peroxide, which is metabolized by catalase. CeO_2NP effectively protects cells from exposure to hydrogen peroxide (Щербаков et al., 2014, Wang et al., 2017) and other peroxides (Tsekhmistrenko et al., 2018).

Nanodispersed cerium dioxide compounds exhibit oxidase properties (Dalapati et al.,2017). The pH-dependent peroxidase activity (Sun et al., 2017) with several transitions with the formation of intermediates was established (Gil et al., 2017). The intensity of the catalase action is associated with the number of Ce^{3+}

ions on the surface of the nanoparticles (McCormack et al., 2014, Pezzini et al., 2017, Walkey et al., 2015). The change in color of the CeO_2NPs after reaction with hydrogen peroxide is used to create different colorimetric tests and test strips. It has been established that the size and surface ligands influence the reaction activity of nanodispersed cerium dioxide with hydrogen peroxide (Walkey et al., 2015). The catalase activity of nanoparticles can be changed by modifying cerium dioxide nanoparticles with ions of different metals (Щербаков et al., 2014).

CeO_2NP is able to inactivate the active forms of nitrogen and nitrogen-free radicals (Singh, 2016). It is active against short-lived and stable nitroxyl radicals (Щербаков et al., 2014), with the rate of inactivation significantly increasing with decreasing size of nanoparticles. The ability of cerium dioxide nanoparticles to inactivate peroxynitrile has been demonstrated (Щербаков et al., 2014, Ferraro et al., 2017).

The catalytic activity of CeO_2NP is similar to phosphatase (Singh, 2016, Wang et al., 2017) and depends on the pH of the medium and the concentration of Ce^{3+} ions on the surface (Щербаков et al., 2014, Tsekhmistrenko et al., 2018). However, CeO_2NP cannot be called a complete analog of phosphatase, since the phosphate group binds to the surface of the nanoparticle irreversibly.

Conclusions and outlook

Thus, by altering the stoichiometry of nanodispersed cerium dioxide, its antioxidant and prooxidant properties and enzyme activity can be regulated. There is a need for further study of the functions, properties and role of NDCs in order to improve the integration of biomimetic nanomaterials into humans and animals, which is the basis for new scientific developments in the field of biology, chemistry, medicine for the prevention, diagnosis and treatment of various diseases.

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