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Correction of the Development of Periodontal Syndrome with Nanocerium in Rats under Conditions of Obesity and Stress

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Abstract: We have previously shown that the administration of nanocrystalline cerium dioxide to rats with obesity induced by neonatal administration of sodium glutamate led to a decrease in total proteolytic activity, and prevented oxidative stress and biopolymer degradation of the periodontal connective tissue. The aim of the study was to substantiate the protective effect of nanocerium on rat periodontal tissues in the development of isolated and combined effects of obesity induced by neonatal administration of sodium glutamate and chronic stress. The obesity modeling was reproduced by postnatal subcutaneous injection of newborn rats with sodium glutamate. The animals were kept on the normal vivarium diet for 4 months. Weight, BMI, and Lee index were monitored throughout the experiment. Nanocerium prevents the increased catabolism of fucoproteins and proteoglycans of periodontal connective tissue in rats with obesity against the background of chronic stress, which is evidenced by a significant decrease in the content of free fucose and glycosaminoglycans in the periodontium of rats compared to animals that simulated the combined effect of obesity and stress without correction. Nanocerium in periodontal tissues of rats prevents the development of oxidative stress, as evidenced by a significant decrease in TBA-reagents and oxidatively modified proteins against the background of a significant increase in catalase activity in obese and stressed animals. The introduction of cerium nanoparticles in conditions of chronic stress and obesity significantly reduces the risk of gastric ulcers, reduces their multiplicity and severity, and has a positive effect on the relative mass of the thymus, a marker of the severity of stress syndrome. Nanocerium prevents damage to the periodontal tissues of rats under conditions of chronic stress against the background of obesity, which is evidenced by the prevention of depolymerization of non-collagenous proteins of the extracellular matrix and suppression of the development of oxidative stress. Taken together, our investigation highlights the potential of nanoceria for future research in the treatment of periodontal tissue disease in overweight or obese individuals with chronic stress. Therefore, CeO_2 nanoparticles have great prospects in the clinical treatment of periodontal syndrome in obese patients with chronic stress.

Keywords: obesity; stress; nanocerium; periodontal tissues; monosodium glutamate; cerium oxide; oxidative stress; fucoproteins; proteoglycans.

1. Introduction

The incidence of periodontal disease is known to be associated with patients' body mass index (BMI). In the new 2017 Classification of Periodontal and Peri-implant Diseases and Conditions (World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions), obesity is classified in chapter three (other conditions affecting the periodontium) as a risk factor for periodontal pathology. However, it is noted that the true mechanisms of periodontal disease in obesity are not fully clarified. Given the current literature, the occurrence mechanisms of digestive lesions (including oral organs and structures) caused by obesity are poorly understood. It requires a detailed study of their pathogenesis, which will allow the correct choice of therapeutic tactics.

Considering the current state of the problem, in particular, in Ukraine, which is associated with long-term chronic emotional stress in connection with the war, the combined effect of overweight and obesity against the background of chronic stress is extremely relevant.

We have previously shown that the administration of nanocrystalline cerium dioxide [1,2] to rats with obesity induced by neonatal administration of sodium glutamate led to a decrease in total proteolytic activity, prevented oxidative stress and biopolymer degradation of the periodontal connective tissue [3].

Modern biomedical nanotechnology is gaining interest in cerium oxide or nanocerium nanoparticles [4,5]. The vacant-oxygen stoichiometry of nanocerium facilitates the redox process and catalytic activity and increases antioxidant capabilities through self-reduction and reuse in the redox system. Inorganic nanoparticle-based nanocerium nanozyme [6] has been shown to achieve anti-inflammatory effects [7] and effectively mimic catalytic activities [8] such as superoxide dismutase [9,10], catalase [11,12], phosphatase [13,14], peroxidase [15,16], oxidase [17] and other activities.

There are various studies that prove the antibacterial efficacy of nanocerium and demonstrate their significant inhibition of both Gram-negative and Gram-positive bacteria [18–20]. Nanocerium has been demonstrated to directly or indirectly affect the signal transduction pathways involved in neuronal death and neuroprotection [21], reducing microglia activation and migration [22].

Based on the aforementioned, the study aimed to substantiate the protective effect of nanocerium on rat periodontal tissues in the development of isolated and combined effects of obesity induced by neonatal administration of sodium glutamate and chronic stress.

2. Materials and Methods

Experimental studies were performed on 103 white nonlinear rats of both sexes in accordance with the bioethical principles of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1986), the Council of Europe Directive 2010/63/EU (2010), the Law of Ukraine "On the Protection of Animals from Cruelty" (No. 3447-IV dated 21.02.2006, Article 26), and the General Ethical Principles of Animal Experiments (Kyiv, 2001-2019), as certified by the Bioethics Committee of Poltava State Medical University (Protocol No. 181 dated 26.03.2020, No. 225 dated 21.03.2024), in which glutamate-induced obesity and chronic stress were simulated. The obesity modeling was reproduced by postnatal subcutaneous injection of newborn rats with sodium glutamate [23] at 4 mg/g doses at 2, 4, 6, 8, and 10 days after birth. Rats of the control group were injected subcutaneously with a physiological solution at a dose of 8 µl/g. The

animals were kept on the normal vivarium diet for 4 months. Throughout the entire experiment, the animals were housed in the vivarium of Poltava State Medical University in accordance with zoo hygiene regulations and maintained under a 12/12 hour light-dark cycle with constant aeration, an air temperature of 26°C, and humidity of (43±2)%. The rats were provided ad libitum with a mixed grain-vegetable diet and water. Weight, body mass index (BMI) and Lee index (the ratio of the cube root of body mass in grams to body length in centimeters) were monitored throughout the experiment. Chronic stress was modeled according to G. Sellier by immobilizing the animals on their backs for 5 hours during the last week before slaughter, which was performed 2 hours after immobilization stress under thiopental anesthesia by bloodletting. Starting 1 month from birth and for the next three months, experimental rats were administered orally with nanocrystalline cerium dioxide (2-7 nm cerium dioxide nanoparticles stabilized by sodium citrate) at a dose of 1 mg/kg dissolved in water for injection, the volume of which was 2.9 ml/kg at 2-week intervals (2 weeks enter, 2 weeks break). For biochemical studies, a 1% homogenate was used. After removing the soft periodontal tissues, they were minced in a Petri dish. A sample was weighed and homogenized in a 10 mM Tris(2-amino-2-hydroxymethyl-propane-1,3-diol)-HCl buffer with a pH of 7.4. The supernatant was used for biochemical studies. All manipulations were performed at temperatures ranging from 0°C to +4°C (on an ice bath).

The test objects were rat periodontal soft tissues in whose homogenate total proteolytic activity (Veremeenko K.N.), total antitryptic activity (Veremeenko K.N.), content of TBC-active products (Stalennaya I.D., Garishvili T.G.), content of oxidatively modified proteins (Dubinina E.E.) and catalase activity (Korolyuk M.A.), content of free fucose and glycosaminoglycans (GAG) (Sharaev P.N.) were determined.

The results were statistically processed using the IBM SPSS Statistics 26 software package in 2019. The Kruskal-Wallis test was used to determine a statistically significant difference between the groups. The difference was considered statistically significant at $p<0.05$.

3. Results and Discussion

The experimental effectiveness of nanocerium was proved based on the analysis of indicators reflecting the severity of stress, namely, the development of ulcerations of the gastric mucosa: complete absence in rats with obesity against the background of correction, and a decrease in the frequency, severity, and multiplicity of ulcers in animals with stress, obesity with stress on background correction in comparison with the corresponding control (Table 1).

Table 1. Indicators of stress syndrome severity in animal groups.

Animal groups	Rate of gastric mucous ulcers, %	Multiplicity (Number of ulcers for 1 rat per group)	Severity, scores	Relative weight of thymus (mg/g)	Relative weight of the adrenal gland (mg/g)
1. Intact n=10	-	-	-	1,08±0,17	0,23±0,02
2. Obesity n=14	-	-	-	1,10±0,07	0,16±0,02
3. Obesity+stress n=17	60	0,93	5	0,99±0,07	0,17±0,02
4. Stress n=10	75	1,79	6	0,77±0,16	0,30±0,04
5. Nanocerium control n=10	-	-	-	0,89±0,13	0,20±0,04
6. Obesity+Nanocerium n=16	-	-	-	1,15±0,08	0,23±0,02
7. Obesity+stress+Nanocerium n=16	9	0,09	1	1,27±0,10*	0,31±0,06

Animal groups	Rate of gastric mucous ulcers, %	Multiplicity (Number of ulcers for 1 rat per group)	Severity, scores	Relative weight of thymus (mg/g)	Relative weight of the adrenal gland (mg/g)
8. Stress + Nanocerium n=10	10	0,4	2	0,79±0,06	0,29±0,04

Note: In this and the following tables, n is the number of animals. *P_{3-7}<0,05.

The thymus involution decreased in animals that modeled obesity against stress syndrome, as indicated by probable changes in relative thymus gland weight compared to animals' modeled obesity and stress without correction (Table 1).

The obtained data indicate a significant impact of stress and obesity on the development of gastric ulcers and the reduction of thymus weight, which may be associated with immunosuppression. The administration of nanoceria demonstrated a pronounced protective effect, reducing the multiplicity and severity of ulcers. In the group with the combined effects of obesity and stress with nanoceria administration (Group 7), the ulcer f multiplicity decreased to 9%, compared to the obesity and stress group (Group 3), where the ulcer multiplicity was 60%, and it also contributed to the recovery of thymus weight. This may suggest an anti-stress and immunomodulatory effect of cerium nanoparticles.

Table 2. Anthropometric characteristics of the animal groups studied.

Animal groups	Lee index ($\sqrt[3]{}$g/cm)	Visceral fat mass (g)	BMI (g/cm^2)
1. Intact n=10	0,254±0,003	0,50±0,26	0,35±0,01
2. Obesity n=14	0,268±0,003*	11,42±1,30*	0,43±0,01*
3. Obesity+stress n=17	0,263±0,002**	12,90±0,74**	0,39±0,01
4. Stress n=10	0,258±0,002	0,09±0,09#	0,37±0,01
5. Nanocerium control n=10	0,257±0,002	0,00±0,00	0,39±0,01
6. Obesity+Nanocerium n=16	0,258±0,002***	5,05±1,08***	0,37±0,01***
7.Obesity+stress+Nanocerium n=16	0,251±0,003^^,&&	1,59±0,47^^,&&	0,33±0,01&&
8. Stress + Nanocerium n=10	0,255±0,003&,^	0,71±0,38&,^	0,36±0,01
Statistics indicator	*P_{1-2}<0,05 **P_{1-3}<0,05 ***P_{2-6}<0,05 &P_{2-8}<0,05 &&P_{3-7}<0,05 ^P_{3-8}<0,05 #P_{2-4}<0,05 ^^P_{2-7}<0,05		

Postnatal administration of sodium glutamate to rats promoted the development of obesity after 4 months on a normal vivarium diet, as indicated by a probable increase in BMI, visceral fat mass, and Lee index compared with these indices in intact animals (Table 2). In the group of rats modeled with obesity and chronic stress, only the Lee index and visceral fat mass were significantly altered compared to controls (Table 2). In rats with glutamate-induced obesity and stress against the background of nanocerium administration, Lee index, visceral fat mass, and BMI significantly decreased 1.1 times, 8- times, and 1.2 times, respectively, compared to animals with glutamate-induced obesity under the condition of chronic stress without correction (Table 2).

Table 3. Free fucose and GAG content in periodontal tissues of the studied animal groups.

Animal groups	Free fucose content, μmol/g	GAG content, μmol/g
1. Intact n=10	2,98 ± 0,71	1,94 ± 0,37
2. Obesity n=14	2,53 ± 0,30	1,57 ± 0,35
3. Obesity+stress n=17	4,75 ± 2,32 *,&	3,29 ± 0,37*,&
4. Stress n=10	3,99 ± 0,42***	2,08 ± 0,15#
5. Nanocerium control n=10	2,47 ± 0,70	2,42 ± 0,57
6. Obesity+Nanocerium n=16	1,76± 0,41	1,49± 0,29
7. Obesity+stress+Nanocerium n=16	1,70 ± 0,57**	1,94 ± 0,13**
8. Stress + Nanocerium n=10	2,61 ± 0,53##	2,59 ± 0,32
Statistics indicator	*P_{1-3} <0,05 ** P_{3-7} <0,05 *** P_{1-4} <0,05 & P_{2-3} <0,05 # P_{3-4} <0,05 ##P_{4-8} <0,05	

We found that in rats with glutamate-induced obesity and stress, free fucose and GAG content in the periodontal tissues significantly increased compared to these indicators in control and in animals that simulated only obesity (Table 3). Nanocerium prevents the increased catabolism of fucoproteins and proteoglycans of periodontal connective tissue in rats with obesity against the background of chronic stress, which is evidenced by a significant decrease in the content of free fucose and GAG in the periodontium of rats compared to animals that simulated the combined effect of obesity and stress without correction (Table 3).

Table 4. Proteinase inhibitory potential of the periodontal tissue of the studied groups

Animal groups	Total antitrypsin activity (g/kg)	Total proteolytic activity (μmol/g×min)
1. Intact n=10	27,88 ± 4,52	1,61 ± 0,09
2. Obesity n=14	56,12 ± 11,09^	1,60 ± 0,07
3. Obesity+stress n=17	98,27 ± 14,95*,&	1,80 ± 0,06
4. Stress n=10	22,56 ± 2,23#	1,54 ± 0,08
5. Nanocerium control n=10	46,06 ± 4,52	1,66 ± 0,08
6. Obesity+Nanocerium n=16	48,91 ± 5,98	1,70 ± 0,07
7. Obesity+stress+Nanocerium n=16	56,17 ± 10,89**	1,73 ± 0,10
8. Stress + Nanocerium n=10	27,13 ± 1,84	1,53 ± 0,09
Statistics indicator	*P_{1-3} <0,05 ** P_{3-7} <0,05 & P_{2-3} <0,05 # P_{3-4} <0,05 ^ P_{1-2} <0,05	

Analyzing the total proteolytic and antitrypsin activity of the periodontal tissues of the studied animals, we established the absence of probable changes in the activity of proteinases and a significant increase in the total inhibitory activity by 2 times in animals with obesity and by 3.5 times in obesity on the background of stress compared to the control (Table 4).

Table 5. Oxidative stress indicators of periodontal tissues in the studied rats.

Animal groups	Content of TBA-reactants (μmol/g)	Content of POM, n.u.	Catalase activity (μkat/g)	The content of molecules of average weight, n.u.
1. Intact n=10	10,00 ± 2,13	0,036 ± 0,003	0,34 ± 0,02	0,042 ± 0,014
2. Obesity n=14	12,43 ± 3,03	0,076 ± 0,007^	0,37 ± 0,01	0,145 ± 0,017^
3. Obesity+stress n=17	22,77 ± 5,25*,&	0,082 ± 0,004*	0,16± 0,02*,&	0,086 ± 0,021*,&
4. Stress n=10	21,04 ±8,27***	0,108 ±0,005***	0,10±0,02***	0,042 ± 0,012
5. Nanocerium control n=10	12,74 ± 3,17	0,046 ± 0,003	0,37 ± 0,01	0,047 ± 0,034
6. Obesity+Nanocerium n=16	10,10 ± 1,02	0,031± 0,013^^	0,39 ± 0,01	0,084 ± 0,028
7. Obesity+stress+Nanocerium n=16	10,19 ± 1,73**	0,025 ± 0,009**	0,41 ± 0,01**	0,038 ± 0,031**
8. Stress + Nanocerium n=10	11,61 ± 1,61##	0,030 ± 0,012##	0,36 ± 0,02##	0,048 ± 0,016
Statistics indicator	*P_{1-3} <0,05 ** P_{3-7} <0,05 *** P_{1-4} <0,05 & P_{2-3} <0,05 # P_{3-4} <0,05 ##P_{4-8} <0,05 ^ P_{1-2} <0,05 ^^ P_{2-6} <0,05			

We found that under the conditions of the combined effect of experimental obesity against the background of stress syndrome, the content of secondary products of lipid peroxidation in the periodontal tissues of rats likely increases compared to the group of control animals (Table 5). Under these conditions, we observe the development of carbonyl-oxidative stress, evidenced by a significant increase in oxidatively modified proteins of periodontal tissues against the background of a probable decrease in catalase activity (Table 5). The development of oxidative stress contributes to the syndrome of endogenous intoxication, evidenced by a 2-times increase in the content of medium-weight molecules in the periodontal tissues of rats compared to the control under conditions of the combined effect of obesity and stress (Table 5). Analyzing the isolated effects of obesity and stress in comparison with animals with the combined effect of these factors on periodontal tissues, we obtained probable changes in the intensification of free-radical oxidation, namely, the content of TBA-reactants increased by 1.8 times and the activity of catalase decreased by 2.3 times compared to obese rats (Table 5). Therefore, glutamate-induced obesity against the background of chronic stress contributes

to more pronounced oxidative stress in periodontal tissues compared to isolated exposures. Administration of nanocerium to rats prevented activation of free-radical oxidation of lipids and proteins, as evidenced by the probable decrease of TBA, POM, and MMM, against the background of a significant 2.5-times increase in catalase activity in obese and stressed animals, which were simulated by the combined effect of factors without correction (Table 5).

Akhtar M. *et al*. demonstrated that the catalase activity of nanocerium can increase intracellular glutathione (GSH) in cells affected by H_2O_2, protecting cells from oxidative damage [24].

Renewable changes between Ce^{3+} and Ce^{4+} make nanocerium an effective therapeutic agent for oxidative stress-related diseases and inflammatory diseases. A review by Wu *et al*. discusses the antioxidant and anti-inflammatory mechanisms of the action of nanocerium [25].

CeO_2 nanoparticles can possess oxygen vacancies (lattice defects) that affect their catalytic activity. An oxygen vacancy forms when oxygen leaves the lattice, creating a vacancy that is compensated by the reduction of cerium ions' oxidation state from Ce^{4+} to Ce^{3+}:

$$CeO_2 \rightarrow \quad CeO_{2-x} + \quad X * O_2 \; CeO_2 \; \rightarrow \mathrm{Ce}O_{2-x} \; + 2x * O_2$$

Where x - represents the number of oxygen vacancies. This ability to lose and subsequently absorbance oxygen provides CeO_2 with its properties as an effective antioxidant.

When Ce^{4+} is reduced to Ce^{3+}, a decrease in the amount of oxygen in the structure occurs (oxygen vacancy), which influences the material's electrical and catalytic properties. This oxidation-reduction process, observable at high temperatures or in low-oxygen environments, indicates CeO_2's ability to reversibly change its oxidation state. This makes it effective in catalytic processes, particularly in emission control systems, and it is an antioxidant in biomedical applications. The reduction in stoichiometry (increase in the number of vacancies) allows CeO_2 to actively interact with free radicals and other reactive oxygen species (ROS), reducing them to stable forms [26].

Further studies by Khurana A. *et al*. demonstrated decreased NF-κB and increased expression of Nrf2 and SOD1 proteins in pancreatic tissues of nanocerium-treated diabetic mice, which proves the role of NF-κB/Nrf2 signaling pathway in mediating anti-inflammatory and antioxidant potential [26]. The authors substantiated the potential anti-diabetic role of nanocerium in mice with streptozotocin-induced type 1 diabetes mellitus.

Nanocerium's ability to repair tissue is attributed to its ROS uptake property and angiogenic potential. In addition, nanocerium can also induce stem cell differentiation, which promotes tissue regeneration [27]. In 2015, [28] used primary mouse bone marrow stromal cells and investigated the effects of nanocerium on osteogenic and adipogenic differentiation. They showed that nanocerium is non-toxic to bone marrow stromal cells when incubated within 24 and 72 hours. In addition, they showed that nanocerium demonstrates both dose- and time-dependent differentiation of bone marrow stromal cells into osteoblasts and adipocytes [29]. [30] investigated the effect of nanocerium on the behavior and function of human periodontal stem cells: in vitro, they proved that nanocerium promotes the differentiation of osteogenesis of human periodontal stem cells; in vivo, they demonstrated that fibrous membranes in incorporated nanocerium accelerate bone tissue regeneration compared to "empty" membranes. The authors believe that nanocerium has great potential in the treatment of periodontal tissue diseases, as evidenced by the findings of changes in alkaline phosphatase activity and increased expression of osteogenic genes, including bone morphogenetic protein gene, osteocalcin and osteopontin [31].

From a tissue engineering perspective, nanocerium offers outstanding biological properties to accelerate tissue repair and regeneration, including antioxidant, anti-inflammatory [32], antibacterial, angiogenic, and anti-apoptotic activity [33,34]. Li X. *et al*. [35] substantiated that among nanocerium nanoparticles, due to the formation of oxygen vacancies and low-valence states, they have a potential powerful antioxidant capacity in scavenging free radicals. Long-term studies have shown that nanocerium promotes angiogenesis and significantly restores impaired nerve function after ischemic stroke in mice, providing a new therapeutic approach for ischemia-reperfusion injury. In a review by Humaira, Bukhari S. *et al*. [36] highlight recent progress in the biosynthesis of CeO_2 nanoparticles and exploration of their medical use as biocompatible antitumor [37], antibacterial [38], antifungal, antioxidant, antidiabetic and wound healing agents. Based on a study of a ternary polycomplex of polyethylenimine, nanocerium, and DNA, substantiated a promising strategy for synergistic delivery therapy of genes encoding proteins that scavenge reactive oxygen species, transcription factors, growth factors, tumor suppressors, or anti-inflammatory cytokines [39].

Nanocrystalline cerium dioxide has a powerful protective effect against oxidative stress, manifested by the reduction of oxidative products, restoration of antioxidant enzyme activity (catalase), and reduction of inflammation markers. Its antioxidant and anti-inflammatory properties can be effectively used to protect the body from damage caused by stress and obesity.

4. Conclusions

The introduction of cerium nanoparticles in chronic stress and obesity significantly reduces the risk of gastric ulcers, reduces their multiplicity and severity, and has a positive effect on the relative mass of the thymus, a marker of the severity of stress syndrome. Nanocerium prevents damage to the periodontal tissues of rats under conditions of chronic stress against the background of obesity, which is evidenced by the prevention of depolymerization of non-collagenous proteins of the extracellular matrix and suppression of the development of oxidative stress.

Taken together, our study highlights the potential of nanocerium for future research in the treatment of periodontal tissue disease in overweight or obese individuals with chronic stress. Therefore, CeO_2 nanoparticles have great prospects in the clinical treatment of periodontal syndrome in obese patients with chronic stress.

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Conflicts of Interest

The author declares no conflict of interest, financial or otherwise.

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