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PATHOGENIC AND IMMUNOMODULATING PROPERTIES OF TITANIUM DIOXIDE

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Annotation. In chronic experiments on rats, a study was carried out of the biological effect of nano- or microparticles of titanium dioxide (TiO2) upon physiological intake through the gastrointestinal tract. It has been established that after the physiological intake of TiO2 nanoparticles (δ50 12 nm, Ssp 95 m2/g) at a dose of 250 mg/kg body weight through the gastrointestinal tract, disturbances in the processes of formation and degradation of the parietal mucous layer of the stomach and increased erosive damage to the gastric mucosa are observed. , increased pro- and antioxidant activity parietal mucus. This may be a manifestation of the body's compensatory reaction to the intake of TiO2 nanoparticles. Biochemical parameters in the blood of rats treated with nano- or microparticles of TiO2 demonstrate the absence of significant disturbances in the studied body systems under the conditions of our experiment.

Keywords: titanium dioxide nanoparticles; rats; stomach; pro- and antioxidant activity; biochemical blood parameters.

Relevance. Titanium can be found in trace amounts in normal tissues of animals and humans [19]. There is no evidence that it is an essential element for life. The concentration of Ti compounds in drinking water is generally low. It is generally accepted that TiO2 is a poorly soluble, low-toxic substance [1], insoluble in water, as well as in dilute mineral acids (with the exception of hydrofluoric acid).

The oral route of TiO2 intake is mainly through food products and drugs containing E171. In an experiment, after dissolving foods high in TiO2 in nitric acid and hydrogen peroxide followed by heating to 110°C, only 3.9% of particles from a chewing gum sample passed through a 0.45-μm filter. More Ti particles passed through the 0.7 μm filter, indicating that the chemical sample preparation method used was likely not completely degrading the food [1,21,22,23,24,25,26,27,28]. Knowledge is being accumulated on the interaction of TiO2 with proteins and cells of the body. When taken orally, TiO2 interacts with aggressive environments of the gastrointestinal tract, binds to proteins and enzymes and can significantly change

their properties. Additional studies simulating digestion are needed to study changes in the properties of protein molecules and enzymes under the influence of TiO2 supplied in different ways.

The important role of human serum albumin (HSA) in binding titanium in vivo has been shown [20]. Samples of TiO2 solutions with the addition of 0.1% and 1% HSA had a 2-3 orders of magnitude higher solute concentration and at all time intervals up to 8 days than control solutions without HSA [21].

Chronic (90 days) intragastric intake of TiO2 NPs leads to damage to the spleen in mice, the number of platelets, hemoglobin, immunoglobulins and CD3, CD4, CD8 lymphocytes, B cells and natural killer cells decreases, the levels of NF-kb, TNF-a, MMIF significantly increase , IL-2,4,6,8,10,18,1b, TGF-b, IFNg, Hsp70 and Bcl-2 [22]; in another study, a dose of 10 mg/kg causes severe kidney damage and nephron apoptosis in parallel with oxidative stress due to the expression of pro-inflammatory genes, apoptosis genes, immune regulation, etc. [23].Considering the size of TiO2 NPs, its entry is possible both through M-cells and transepithelial [24]. Enteral administration of NP (66 nm) and OC (260 nm) TiO2 to mice in an amount of 100 mg/kg body weight for 10 days revealed an increase in CD4 lymphocytes in all parts of the intestine, as well as increased secretion of the cytokines IL-12, IL-4, IL-23, TNF-a, IFN-g, TGF-b, especially in the wall of the large intestine [1,29,30,31,32].

A large number of studies have been devoted to studying the effect of TiO2 on the human and animal body when exposed through the lungs due to inhalation in the workplace. A carcinogenic effect has been shown—the development of lung tumors in rats—after two years of exposure to high concentrations of TiO2 NPs [26].

Nano-sized TiO2 delivered intratracheally causes damage to the cellular structure and dysfunction of alveolar macrophages, reducing their chemotactic ability and the expression of Fc receptors and MHC II molecules on the cell surface. The phagocytic ability of macrophages increases when exposed to low doses and decreases when exposed to high doses of TiO2 NPs [1,15,16 ,17,18,19,20].

Numerous studies describe the controversial effects of TiO2 exposure: the development of cytotoxicity, toxicity to the body as a whole or individual systems [1,8,9,10,11,12,13,14], or no or very slight toxicity [6–8] of TiO2 nanoparticles has been demonstrated. It has also been shown that, once ingested, nanoparticles may accumulate in individual organs or systems [9] or perhaps not, so a detailed study of the functioning of many systems is required in order to come closer to assessing the nature of their biological action.

One of the main routes, and often uncontrolled, is through the gastrointestinal tract. Nano- and microparticles of titanium dioxide (TiO2) enter the body through the gastrointestinal tract in different ways: with food (as a food additive E 171), with medicinal substances (as an auxiliary substance), from the surrounding air, etc. [1,2,3,4,5,6,7]. However, to date there is practically no data on how, under conditions of the whole organism, TiO2 particles of varying degrees of dispersion interact with the structural elements of the stomach, primarily the parietal mucous layer and mucous membrane, which are mandatory stages in the transport of substances into the internal environment of the body. At the same time, the state of the parietal mucous layer and the mucous membrane of the stomach largely determines its functional activity, the state of the barrier function, the efficiency of absorption, the consistency of intramural regulatory processes and other functions of the digestive system as a whole [14].

The purpose of this study was to study the condition of the stomach and its protective barrier, as well as biochemical blood parameters characterizing the state of the main body systems during the physiological intake of TiO2 nanoparticles through the gastrointestinal tract of rats.

Purpose of the study: To evaluate the influence of TiO2 NPs on the morpho-biochemical parameters of the rat body.

Research methods. The studies were carried out in the experimental biological clinic of the Bukhara State University named after Abu Ali Ibn Sina on 30 white male Wistar rats weighing 150-180 g, kept under standard vivarium conditions and a diet for laboratory animals, in accordance with the rules of laboratory practice when conducting preclinical studies in UzR (GOST 3 51000.3-96 and GOST 51000.4-96).

Experimental studies on animals were carried out in accordance with the instructions recommended by the Uzbek Regulations, 1987 and “The Guide for the Care and Use of Laboratory Animals (National Academy Press Washington, D.C. 1996).” Efforts were made during the research to minimize animal suffering and reduce the number of samples used.

Experimental design. All experimental animals were divided into three groups (n=10). Animals of experimental groups I and II were administered a single dose of TiO2 NPs at a dose of 13.3 mg/kg and 133.3 mg/kg. The control group of animals was administered an isotonic solution of sodium chloride 0.9% in an equivalent volume. The selected concentrations of nanoparticles did not exceed the maximum

tolerated dose (MTD) for a given metal. On the first, seventh and fourteenth days, blood was taken from the tail vein for morphological and biochemical studies.

Results. Mass of parietal mucus of the stomach. In control animals, the mass of parietal gastric mucus was 0.058±0.005 g, in animals receiving TiO2 nanoparticles - 0.045±0.007 g ($p < 0.05$ compared to control), in animals receiving TiO2 microparticles - 0.063±0.011 g ($p < 0.05$ compared with animals treated with nanoparticles). Consequently, the mass of parietal gastric mucus in rats receiving TiO2 nanoparticles was the lowest relative to the comparison groups. A decrease in the mass of parietal mucus indicates disturbances in the processes of synthesis and degradation of glycoproteins of the parietal mucous layer, the most important protective mechanism of the stomach [1].

As a result of disturbances in the biosynthesis of glycoproteins in the parietal mucous layer (changes in transferase activity), so-called immature glycoproteins are formed, which are characterized by incompletely formed oligosaccharide chains, therefore they do not provide the required level of intermolecular interactions and gelation.

These biosynthetic disorders cause failure of the protective function of the parietal mucous layer, disruption of the integrity of the gastric mucosa and provoke the development of an acute ulcer, which is a symptomatic lesion and can develop, among other things, as a result of exposure to toxic substances [1]. Therefore, a decrease in the mass of parietal gastric mucus in rats treated with TiO2 nanoparticles is an important characteristic of the toxic effect of TiO2 nanoparticles on the body.

Area of erosive damage to the gastric mucosa. During a macroscopic examination of the gastric mucosa, it was found that erosive damage was found in all three studied groups of animals: in the control group this figure was 5.44 ± 4.1 mm2 per one animal, in rats receiving TiO2 nanoparticles - 13.91 ± 2.6 mm2 per animal ($p < 0.05$ compared to control), in rats receiving TiO2 microparticles - 10.99 ± 4.2 mm2 per animal. Consequently, in animals receiving TiO2 nanoparticles, the area of erosive damage under the conditions of our experiments was maximum. Three sequential types of damage to the mucous membrane of the digestive system are described: hemorrhages into the mucous membrane, which can vary from small petechiae to the formation of drain fields; erosions characterized by superficial destruction of the mucous membrane without penetration into the submucosal layer; acute ulcers, in which a round, “stamped” defect penetrates to the submucosal and even muscular layer of the wall of the organs of the digestive system [2]. Typically, acute ulcers of the digestive system do not last long and, with a favorable course of the underlying disease or, as in our case, after eliminating stress factors, they heal

quite quickly, within 1–2 weeks, almost without a trace. If the toxic effect becomes protracted, then the course of acute ulcers in 10–12% of patients is complicated by bleeding and perforation, and in contrast to chronic ulcers, a combination of these complications is much more common. The significant size of the area of erosive damage to the gastric mucosa of rats treated with TiO2 nanoparticles, compared to the control, indicates the toxic nature of the effect of these nanoparticles on the gastric mucosa of rats when they enter the body through the gastrointestinal tract.

Pro- and antioxidant activity of gastric parietal mucus. The study of induced chemiluminescence of gastric parietal mucus shows the level of free radicals in a given object. Under our experimental conditions, the maximum level of induced chemiluminescence of gastric parietal mucus (and, consequently, free radicals) in animals treated with TiO2 nanoparticles was significantly different from the control (Fig. 1). The level of induced chemiluminescence of the parietal mucus of rats receiving TiO2 microparticles was intermediate between the control and the level of induced chemiluminescence of rats receiving TiO2 nanoparticles.

The antioxidant activity of the parietal gastric mucus upon intake of TiO2 nano- and microparticles through the gastrointestinal tract changed according to the state of induced chemiluminescence in the comparison groups. In animals receiving TiO2 nanoparticles, this indicator was the highest, and starting from the 4th minute of the reaction, it was significantly different from the control. In animals receiving TiO2 microparticles, the level of antioxidant activity of the parietal mucus was almost no different from the control values.

Conclusion. Thus, the studies have shown that after the physiological intake of TiO2 nanoparticles (δ50 12 nm, Ssp 95 m2/g) at a dose of 250 mg/kg body weight through the gastrointestinal tract, disturbances in the processes of formation and degradation of the parietal mucous layer of the stomach are observed, increased erosive damage to the gastric mucosa, increased pro- and antioxidant activity of parietal mucus.

These processes lead to the development of a toxic effect of TiO2 nanoparticles on the functional activity of the protective mucous barrier and affect the functioning of the stomach and digestive tract as a whole.

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