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Review

Toxicity of titanium dioxide nanoparticles in central nervous system

Magdalena Czajka [a,*], Krzysztof Sawicki [a], Katarzyna Sikorska [b], Sylwia Popek [a], Marcin Kruszewski [a,b,c], Lucyna Kapka-Skrzypczak [a,c]

[a] Department of Molecular Biology and Translational Research, Institute of Rural Health, Lublin, Poland
[b] Institute of Nuclear Chemistry and Technology, Centre for Radiobiology and Biological Dosimetry, Warsaw, Poland
[c] Department of Medical Biology and Translational Research, Faculty of Medicine, University of Information Technology and Management, Rzeszów, Poland

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ABSTRACT

Titanium dioxide nanoparticles (TiO_2 NPs) have found many practical applications in industry and daily life. A widespread application of TiO_2 NPs rises the question about safety of their use in the context of potential occupational, environmental and intentional exposure of humans and biota. TiO_2 NPs easily enter the body through inhalation, cross blood–brain barrier and accumulate in the brain, especially in the cortex and hippocampus. Toxicity of these NPs and the molecular mechanisms of their action have been studied extensively in recent years. Studies showed that TiO_2 NPs exposure resulted in microglia activation, reactive oxygen species production, activation of signaling pathways involved in inflammation and cell death, both *in vitro* and *in vivo*. Consequently, such action led to neuroinflammation, further brain injury. A, spatial recognition memory and locomotor activity impairment has been also observed.

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Abbreviations: 5-HT, 5-hydroxytryptamine; AChE, acetylcholinesterase (EC 3.1.1.7); APx, L-ascorbate peroxidase (EC 1.11.1.11); ATPase, adenosinetriphosphatase (EC 3.6.1.3); CAT, catalase (EC 1.11.1.6); DA, dopamine; Glu, glutamate; GSH, glutathione; GSH-Px, glutathione peroxidase (EC 1.11.1.9); GST, glutathione transferase (EC 2.5.1.18); HDG, hippocampal denate gyrus; IL-1β, interleukin 1β; LPS, *lipopolysaccharide*; LTP, long-term synaptic plasticity; NE, norepinephrine; NOS, nitric-oxide synthase (NADPH dependent) (EC 1.14.13.39); NF-κB, nuclear factor kappa B; NPs, nanoparticles; Nrf-2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; SOD, superoxide dismutase (EC 1.15.1.1); SRXRF, synchrotron radiation X-ray fluorescence; TNF-α, tumor necrosis factor alpha.

* Corresponding author at: Department of Molecular Biology and Translational Research, Institute of Rural Health, Jaczewskiego 2, 20-090 Lublin, Poland. Tel.: +48 81 7184539.
E-mail address: czajka.magdalenaa@gmail.com (M. Czajka).

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1. Introduction

Fast development of nanoscience caused an increase in production and use of nanomaterials (NMs), including nanoparticles (NPs), nanomaterials that have all dimensions less than 100 nm. Physical, chemical and biological properties of NPs are different from those of individual atoms and molecules or bulky material, thus development of nanotechnology is foreseen to bring a significant benefit to the society. NPs are applied in many sector markets, such as health, defence, energy, agriculture or environment protection. With an increase of application of nanotechnology products, there is increasing need to evaluate risk associated with their use, due to the potential occupational and environmental exposure of humans and biota to NPs and their intentional use in diagnosis or therapy.

Titanium dioxide nanoparticles (TiO_2 NPs) are widely used in many applications, e.g. paints, lacquers, laminates, food wraps, foils, transparent plastics, papers, textiles, cosmetics, food products, medicines, pharmaceuticals and toothpaste. Due to their catalytic properties they are also used in self-cleaning tiles, windows, anti-fogging car mirrors, in the purification of water, sewage, combustion gases, as a antimicrobial material in decontamination, as catalyst in organic synthesis and as a photoactive material in solar cells (Shi et al., 2013).

Owing to the common use of TiO_2 NPs in everyday life, it is very important to gain the knowledge about their toxicity and their potential harmful influence on human health and environment. There are numerous experimental evidence, which suggest that TiO_2 NPs exposure could be harmful and cause negative health effects. Many *in vitro* studies showed that TiO_2 NPs was cyto- and genotoxic, led to apoptosis, inflammation, induced ROS, changed enzyme activities and gene expression. In concordance with *in vitro* experiments, many *in vivo* studies also showed that TiO_2 NPs, once entered the blood stream, could reach and accumulate in important organs and cause their injury. TiO_2 NPs induced damage in such organs as spleen, liver, kidney, lung, brain or heart (Chang et al., 2013; Shi et al., 2013). However, there are also studies showing lack of TiO_2 NPs toxicity, thus further study is necessary to univocally determine the possible impact of TiO_2 NPs on human health.

In this review we attempt to summarize the knowledge on the toxicity of TiO_2 NPs on central nervous system (CNS), both *in vivo* and *in vitro* experimental design.

2. Exposure routes and biodistribution of TiO_2 NP

TiO_2 NPs enter the body by different exposure routes and then are distributed to the important organs throughout the body. Gastrointestinal absorption seems a prevalent exposure route, as TiO_2 NPs are used as an additive in toothpaste, cachou, capsule, drug carriers, etc. Wang et al. (2007a) showed that 2 weeks after oral administration to TiO_2 NPs titanium content was significantly elevated in the brain, as compared to controls. Nonetheless titanium mainly accumulated in the liver, kidneys, spleen and lung of mice. However, more recent research showed that TiO_2 NPs were not significantly accumulated after oral administration, likely due to the minimal absorption from the gut (Cho et al., 2013).

As TiO_2 NPs are commonly used in cosmetics another important gate of entry seems to be dermal absorption. In a study by Kertész et al. (2005) human skin xenografts taken from different patients were exposed to Anthelios XL F60, a cosmetic containing micronised TiO_2 NPs. The result showed that TiO_2 NPs penetrated to the disjunctum part of the *stratum corneum*. In two cases TiO_2 NPs penetrated also to the *stratum granulosum*. Gamer et al. (2006) have investigated *in vitro* penetration of TiO_2 NPs in cosmetic formulations through porcine skin. TiO_2 NPs were detected on the outermost surface of the *stratum corneum*, but did not penetrate through porcine skin. Penetration of four types of rutile TiO_2 NPs into intact and damaged Yucatan micropig skin *in vitro* was also studied by Senzui et al. (2010). TiO_2 NPs did not penetrate through skin irrespective of the NPs size and coating, even if the *stratum corneum* was damaged. It should be noted that after hair removal some NPs penetrated into vacant hair follicles, although they were not detected in dermis or viable epidermis. In yet another study, a homemade static diffusion cell was used for *in vitro* evaluation of the cutaneous penetration of TiO_2 NPs through the porcine skin. It was shown that the titanium was deposited mainly at the surface and *stratum corneum*, but no titanium was detected in permeate fluid. The result was the same, even if skin was damaged, irradiated or damaged and irradiated (Miquel-Jeanjean et al., 2012). The study aimed on determination of the influence of subchronic exposure of TiO_2 NPs on the hairless rat skin showed that nanoparticles were not located in the viable skin areas. TiO_2 NPs were observed only in the *stratum disjunctum* and keratinized layer of the *follicular infundibulum*. Moreover, no penetration to major organs was observed, despite the significant increase in titanium content in lung after 8 weeks exposure. That was, however, rather due to the inhalation of TiO_2 NPs than to the direct absorption from the skin (Adachi et al., 2013). On the contrary, Wu et al. (2009) demonstrated that after exposure of porcine ear skin to formulation containing 5% TiO_2 NPs for 30 consecutive days, TiO_2 NPs were observed in the *stratum corneum*, *stratum granulosum*, prickle and basal cell layer. The effect was size dependent and the penetration capacity increased with the decreased TiO_2 NPs size. Furthermore, the authors showed that TiO_2 NPs penetrated through the skin and entered into various organs and caused pathological changes, mainly in the skin and liver. However, the presence of titanium in the brain was almost negligible.

Inhalation is an another portal of TiO_2 NPs entry into the body. Inhaled nanoparticles are deposited in three different regions of the respiratory tract: nasopharyngeal, tracheobronchial and alveolar region, and can be translocated to the central nervous system, mainly through sensory nerves (Simkó and Mattsson, 2010). Wang et al. (2007b) investigated distribution of TiO_2 NPs in the olfactory bulb of mice after nasal inhalation. After one month exposure the microbeam SRXRF mapping analysis showed that TiO_2 NPs were taken up by the olfactory bulb via the primary olfactory neurons and accumulated in the olfactory nerve layer, olfactory ventricle and granular cell layer. The concentration and distribution area of titanium in the olfactory bulb increased with increasing particles size. In the consecutive studies, Wang et al. (2008a,b) showed that intranasally installed TiO_2 NPs translocated to the central nervous system and accumulated mainly in the hippocampus.

Geiser et al. (2005) analyzed the intrapulmonary distribution of inhaled TiO_2 NPs in rats. They found that nanoparticles were localized in the lung tissue compartment (air-filled spaces, epithelium/endothelium, connective tissue and capillary lumen), especially in the airspace. Further investigations detected that distribution of TiO_2 NPs within the four compartments of rat lung was not random and depended on time after exposure. Nanoparticles were transported from the airspaces to the connective tissue and subsequently released into the systemic circulation. However, the majority of TiO_2 NPs were still observed within the airspace (Mühlfeld et al., 2007). In concordance, Li et al. (2010) indicated that after intratracheally installation of TiO_2 NPs once per-week for 4 consecutive weeks, NPs might translocated to the blood circulation and then to extrapulmonary tissues, and they were able to pass through the blood–brain barrier and induced to brain damage. In the latest study by Baisch et al. (2014), rats were exposed to

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