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Nano-titanium dioxide induced cardiac injury in rat under oxidative stress

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ABSTRACT

Heart diseases, which are related to oxidative stress (OS), negatively affect millions of people from kids to the elderly. Titanium dioxide (TiO_2) has widespread applications in our daily life, especially nanoscale TiO_2. Compared to the high risk of particulate matter ($\leqslant$2.5 μm) in air to heart disease patients, related research of TiO_2 on diseased body is still unknown, which suggest us to explore the potential effects of nanoscale and microscale TiO_2 to heart under OS conditions. Here, we used alloxan to induce OS conditions in rat, and investigated the response of heart tissue to TiO_2 in healthy and alloxan treated rats. Compared with NMs treatment only, the synergistic interaction between OS conditions and nano-TiO_2 significantly reduced the heart-related function indexes, inducing pathological changes of myocardium with significantly increased levels of cardiac troponin I and creatine kinase-MB. In contrast with the void response of micro-TiO_2 to heart functions in alloxan treated rats, aggravation of OS conditions might play an important role in cardiac injury after alloxan and nano-TiO_2 dual exposure. Our results demonstrated that OS conditions enhanced the adverse effects of nano-TiO_2 to heart, suggesting that the use of NMs in stressed conditions (e.g., drug delivery) needs to be carefully monitored.

1. Introduction

Nowadays, mainstream nanomaterials (NMs), e.g., nano-titanium dioxide (TiO_2), are produced with the rapid development of nanotechnology. TiO_2 NMs are in close contact with people, showing a trend to replace microscale TiO_2 in foods, cosmetic, etc. (Lanza et al., 2006; Vicent and Duncan, 2006; Wickline and Lanza, 2003). Further, due to their valuable physicochemical properties, recent studies suggested that nano-TiO_2 can work as drug delivery systems and additive in pharmaceuticals (Drobne et al., 2009; Lanza et al., 2006; Shin and Lee, 2008). However, adverse effects, such as cellular dysfunction, oxidative damage, inflammatory responses, induction of thrombosis, impaired the spatial recognition memory, and liver lesions were shown *in vitro* and *in vivo* after nano-TiO_2 exposure (Cai et al., 2011; Fabian et al., 2008; Hu et al., 2010; Iavicoli et al., 2012; Li et al., 2008; Sha et al., 2011; Valant et al., 2012). In the present situation, it will be the paramount thing to consider for the safe usage of nano-TiO_2 to human beings.

As the largest cause of deaths in the world, heart diseases are no longer geriatric diseases and attack young people as well (McGill et al., 2008). The imbalance between oxidants and antioxidants can lead to oxidative stress (OS), which affects the microenvironment of cells, tissues, and organs in the body (Singal et al., 1998). Accumulating evidences show the crucial and negative roles of OS conditions in different types of heart diseases, such as heart failure, cardiovascular disease (Griendling and Alexander, 1997; Heitzer et al., 2001), hypertensive heart disease (Kadiiska

Abbreviations: ANOVA, analysis of variance; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BW, body weight; DLS, dynamic light scattering; ELISA, enzyme linked immunosorbent assay; EDTA, ethylenedinitriletetraacetic acid; FBS, fetal calf serum; GSH, glutathione; H_2O_2, hydrogen peroxide; HRTEM, high resolution transmission electron microscopy; LDH, lactate dehydrogenase; MDA, malondialdehyde; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; NMs, nanomaterials; O_2^-, superoxide anion; OD, optical density; OS, oxidative stress; PI, propidium iodide; SAED, selected area electron diffraction; SEM, scanning electron microscope; SOD, superoxide dismutase; XRD, X-ray diffraction; TiO_2, titanium dioxide.

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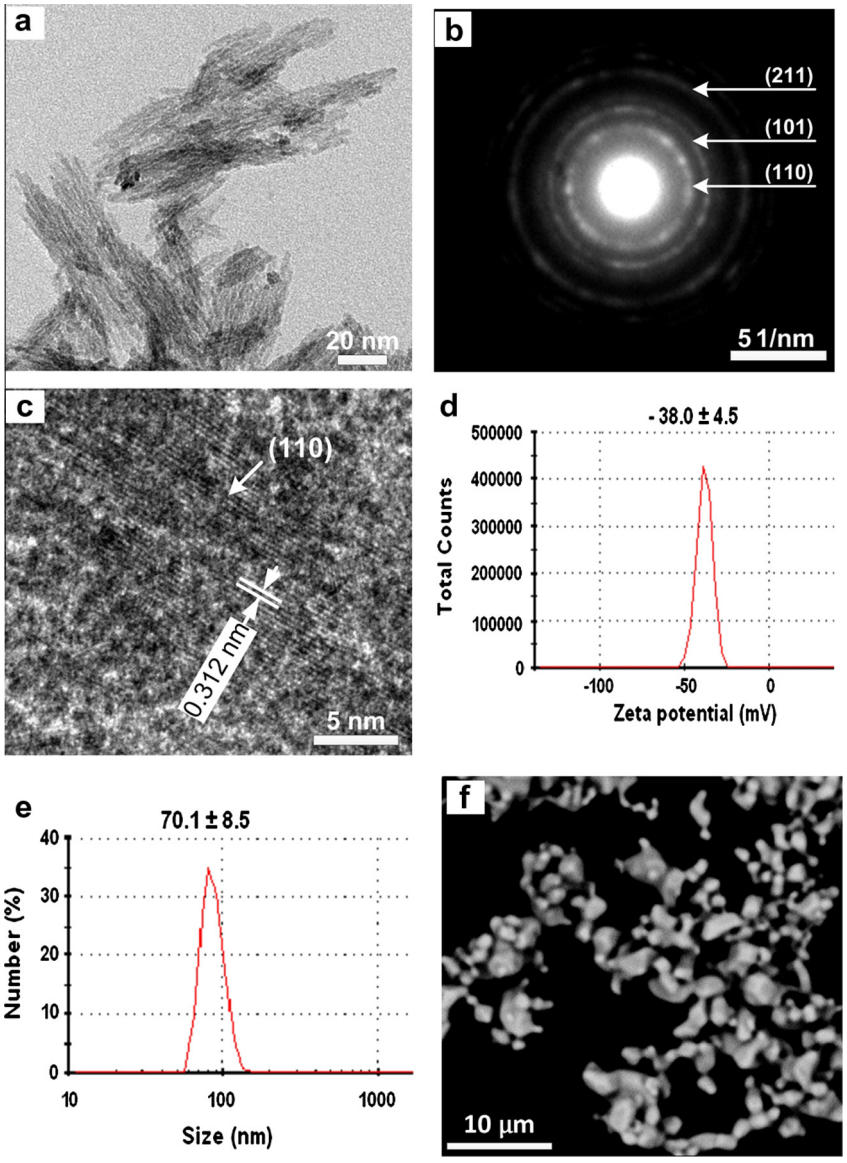

Fig. 1. Characterization of TiO_2 particles. (a) TEM micrograph of nano-TiO_2 dispersed in ethanol; (b) SAED pattern of nano-TiO_2; (c) crystal lattice plane of nano-TiO_2; (d) zeta potential of nano-TiO_2 (5 mg/mL) was the average after 12 runs of 15 measurements; (e) size distribution of nano-TiO_2 (5 mg/mL) was shown after 15 runs of 30 measurements; and (f) SEM image of micro-TiO_2.

et al., 2012), ischemic heart disease (Borillo et al., 2010), and cardiomyopathy (Cesselli et al., 2001). Compared to the high risk of particulate matter (PM, diameter $\leqslant$2.5 μm) to heart disease patients (Peters et al., 2001; Pope et al., 2006), the adverse effects of TiO_2 to heart tissue under OS conditions remain unknown, although several studies have shown that nano-TiO_2 can accumulate in healthy heart tissues *in vivo* (Chen et al., 2006; Wang et al., 2009b).

Based on the low toxicological potential and biological response of nano-TiO_2, in this study, we used alloxan to induce the artificial OS conditions, and investigated the potential synergistic effect of TiO_2 and OS conditions during cardiac injury in Sprague–Dawley (SD) rats. Compared to NMs exposed healthy rats, rats in conditions of OS showed the significantly reduction of heart rate (HR), stroke volume index (SVI), and cardiac index (CI) after nano-TiO_2 exposure, following the pathological changes of myocardium and the significantly increased levels of cardiac troponin I (cTnI) and creatine kinase-MB (CK-MB). In addition, a type of micro-TiO_2 was used as a control to study the different responses of rat hearts exposed to nanoscale and microscale TiO_2 particles, and to explore the potential synergy between nano-TiO_2 and OS conditions during cardiac injury.

2. Methods and materials

2.1. Reagent preparation

Alloxan monohydrate, nano-TiO_2 and micro-TiO_2 were purchased from Sigma–Aldrich Trading Co., Ltd., (Shanghai, China). Glutathione (GSH), brain natriuretic peptide (BNP), cardiac troponin I (cTnI), creatine kinase-MB (CK-MB), and myoglobin (MYO) enzyme linked immunosorbent assay (ELISA) kits were obtained from Roche Ltd., (Shanghai, China), R&D Systems and Jiancheng Bioengineering Company (Nanjing, China).

2.2. Characterization of TiO_2

To avoid contamination during rat experiments, TiO_2 was firstly sterilized through 140 °C dry heat for 5 h. Dry heat sterilized TiO_2 was suspended in 0.9% saline solution and 30 min ultrasonic treatment in advance before rat experiments. Morphology, selected area electron diffraction (SAED) pattern and crystal lattice plane of sterilized nano-TiO_2 were checked using high resolution transmis-