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Comparison of distribution and toxicity following repeated oral dosing of different vanadium oxide nanoparticles in mice

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ABSTRACT

Vanadium is an important ultra-trace element derived from fuel product combustion. With the development of nanotechnology, vanadium oxide nanoparticles (VO NPs) have been considered for application in various fields, thus the possibility of release into the environment and human exposure is also increasing. Considering that verification of bioaccumulation and relevant biological responses are essential for safe application of products, in this study, we aimed to identify the physicochemical properties that determine their health effects by comparing the biological effects and tissue distribution of different types of VO NPs in mice. For this, we prepared five types of VO NPs, commercial (C)-VO_2 and -V_2O_5 NPs and synthetic (S)-VO_2, -V_2O_3, and -V_2O_5 NPs. While the hydrodynamic diameter of the two types of C-VO NPs was irregular and impossible to measure, those of the three types of S-VO NPs was in the range of 125–170 nm. The S- and C-V_2O_5 NPs showed higher dissolution rates compared to other VO NPs. We orally dosed the five types of VO NPs (70 and 210 μg/mouse, approximately 2 and 6 mg/kg) to mice for 28 days and compared their biodistribution and toxic effects. We found that S-V_2O_5 and S-V_2O_3 NPs more accumulated in tissues compared to other three types of VO NPs, and the accumulated level was in order of heart > liver > kidney > spleen. Additionally, tissue levels of redox reaction-related elements and electrolytes (Na^+, K^+, and Ca^{2+}) were most clearly altered in the heart of treated mice. Notably, all S- and C-VO NPs decreased the number of WBCs at the higher dose, while total protein and albumin levels were reduced at the higher dose of S-V_2O_5 and S-V_2O_3 NPs. Taken together, we conclude that the biodistribution and toxic effects of VO NPs depend on their dissolution rates and size (surface area). Additionally, we suggest that further studies are needed to clarify effects of VO NPs on functions of the heart and the immune system.

1. Introduction

Nanotechnology is defined as the manipulation of matter that has at least one size dimension as small as 1–100 nm. Unusual physical, chemical, and biological properties can emerge in materials at this nanoscale, and these can differ in important ways from the corresponding properties of bulk materials and single atoms or molecules (National Nanoechnology Initiative, 2014). Given the rapid development of nanotechnology, governments have invested billions of dollars to create new materials and devices with applications in diverse fields, such as in medicine, electronics, biomaterials, energy production, and consumer products (Allianz AG and the Organisation for Economic Co-operation and Development, 2005). On the other hand, toxicologists have continuously raised concerns about the potential for adverse health effects that could be associated with increased human and environmental exposure to nanomaterials.

Vanadium is an important ultra-trace element derived from fuel product combustion, so it is widely distributed in nature (Bell et al., 2014; Imtiaz et al., 2015). Additionally, it has received special and long-standing attention in the pharmacological area including the regulation of intracellular signaling, as a cofactor of enzymes essential in energy metabolism, as an alternative therapeutic agent for the treatment of diabetes mellitus, and as a potential cancer chemo-preventative agent owing to its unique biological function (Basu et al., 2014; Bishayee and Chatterjee, 1993; Thompson, 1999). Vanadium pentoxide (V_2O_5) has been also widely used as a catalyst for ferrovanadium and sulfuric acid production in industry owing to its high oxidation state (Reference). Moreover, engineers

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have recently been studying vanadium oxide (VO) nanoparticles (NPs) as a material for potential use in electrochemistry, catalysis, and energy storage (Langeroodi, 2012; Ng et al., 2009; Zhu et al., 2015). On the other hand, many researchers have suggested that VOs are not suitable for application in the pharmaceutical area due to the possibility of strong biological side effects (Domingo, 1996; Reul et al., 1999) and that their release into the environment should be rigorously regulated (Basu et al., 2014; Beyersmann and Hartwig., 2008; Keil et al., 2016; Kim et al., 2003; Magari et al., 2002). For example, although symptoms such as hyperglycemia, hyperphagia, and polydipsia were significantly ameliorated by vanadium treatment in diabetic rats, side effects such as tissue accumulation, decreased weight gain, and death were observed in all vanadium treated-rats. (Domingo et al., 1991). Furthermore, inhalation of V_2O_5 has been shown to impair immune cell function and increase the risk of cancer (Cohen et al., 2007; Ehrlich et al., 2008; Pinon-Zarate et al., 2008).

The physicochemical properties of NPs, especially shape and size, play a central role in determining their toxicity, therefore should be extensively evaluated in defining regulatory guidelines. Accumulating evidence also shows that the toxicity of VO NPs can be influenced by oxidation state (Rhoads et al., 2010; Wörle-Knirsch et al., 2007). When V_2O_5 (rod-type, 50 ± 20 nm) and VO_2 (spherical type, 30 ± 10 nm) NPs were inhaled via a nose-only system for 2 weeks (0.1, 0.25, and 0.5 mg/m^3, 6 h/day, 5 days/week), VO_2 NP-exposed rats showed higher levels of lactate dehydrogenase (LDH), gamma glutamyl transferase (gamma-GT), and alkaline phosphatase (ALP) compared to V_2O_5 NP-exposed rats (Kulkarni et al., 2014). Evaluation on the levels of oxidative stress markers (malondialdehyde and reduced glutathione) also demonstrated a higher toxic potential of VO_2 NPs in this model. These changes became close to normal levels only in the V_2O_5-exposed rats after a 7-day recovery period. Additionally, histopathological damage and inflammatory responses were greater in the lung of VO_2 NP-exposed rats, and these changes persisted even after a 7-day recovery period. Meanwhile, increasing reports show that VO NPs have different dissolution rates in water based on their oxidation state (Bock et al., 2013; Bruyère et al., 1999; Larsson et al., 2015), and that dissolution rates can be an important factor determining the toxicity of NPs through disturbance of ion homeostasis in the body (Holmes et al., 2016; Ivask et al., 2014; Wang et al., 2016; Zhang et al., 2016). In this study, we aimed to identify the physicochemical properties that determine the toxicity of VO NPs by comparing the biological effects and tissue distribution of different types of VO NPs administered to mice, thus prepared five types of VO NPs, commercial (C)-VO_2 and -V_2O_5 NPs and synthetic (S)-VO_2, -V_2O_3, and -V_2O_5 NPs. According to previous studies, LD_{50} values for V_2O_5 and other pentavalent vanadium compounds ranged from 10 to 160 mg/kg bw, and those for tetravalent vanadium compounds were in the range 448–467 mg/kg bw when orally dosed in mice (WHO, 2001). In addition, acute clinical symptoms were observed in animals exposed to 1 mg/m^3 concentration of V_2O_5 (ATSDR, 2012). Moreover, the upper limit dose volume of 10 mL/kg is recommended for oral dosing in terms of animal welfare. Considering that dissolution rate can be influenced by pH condition, and that health effects by oral dosing can be more affected by pH compared to other exposure routes such as inhalation, skin and blood stream, we administered five types of VO NPs (1 mg/mL) with different properties by gavage (70 and 210 μg/mouse, approximately, 2 and 6 mg/kg, 6 days/week, 1 time/day) for 28 days, and then compared their tissue distributions and biological effects.

2. Materials and methods

2.1. Preparation of VO NPs

VO_2 NPs were synthesized via a one-step sol gel-assisted hydrothermal process (Shidong et al., 2011). V_2O_5 (0.9 g, 99%, Sigma-Aldrich, St. Louis, MO, USA) powder was dissolved in a solution of 25 mL of deionized water (DW) and 5 mL of hydrogen peroxide (H_2O_2, 30 wt%, OCI Company, Seoul, Korea) with continuous stirring. After standing for 24 h, the V_2O_5 solution turned into an amorphous gelatinous form. Then, a hydrazine monohydrate solution ($N_2H_4 \cdot H_2O$; 98%, Sigma-Aldrich) was added to this gel under vigorous mixing. Within a few minutes, the gel turned to a black-colored stiffer gel. This resulting gel was transferred to a Teflon-lined stainless-steel autoclave and hydrothermally reacted at 220 °C for 24 h. After the hydrothermal reaction was completed, the obtained product was collected by centrifugation, thoroughly washed with DW and ethanol, and dried in a vacuum oven at 70 °C. To prepare the same size of V_2O_3 and V_2O_5 NPs, respectively, as-synthesized VO_2 NPs were heat-treated at 400 °C for 4 h in reduced atmosphere flowing H_2(5%)/Ar mixed gas and 300 °C for 2 h in air atmosphere. We also purchased the commercial (C)-VO_2 (99%) and -V_2O_5 (99.999%) powders purchased from Kojundo Co. and Alfa Aesar, respectively.

2.2. Characterization of vanadium oxides

All of S- and C-VO NPs were loaded in drinking water at a concentration of 1 mg/mL and sonicated using a bath-type sonicator (150 W, 40 kHz) for 5 min to disperse the VO NPs in a stable fashion. The temperature of the sonicator was kept below 30 °C to prevent agglomeration of particles. The phases and shapes of the S- and C-VO NPs were investigated using X-ray powder diffraction (XRD; D8-Advance, Bruker, Germany), transmission electron microscopy (TEM), and field emission scanning electron microscopy (FESEM; S-4800, Hitachi, Japan). The surface areas were estimated using a Brunauer–Emmett–Teller surface area analyzer (BET, ASAP2020, Furnace & Ceramics, Micrometrities Co., USA). In addition, the surface charge and hydrodynamic diameter (HDD) of the dispersed VO NPs were characterized using a Zeta Potential and Particle Size Analyzer (ELSZ-1000, Otsuka Electronics co. ltd, Japan). Herein, we hypothesize that the particle size and interface effect related to solubility can be described by the Noyes–Whitney equation.

$$\frac{dC}{dt} = \frac{DA}{Vh}(C_s - C_x) \quad (1)$$

where dC/dt is dissolution rate, D is diffusion coefficient, A is surface area of the interface between the dissolving substance and the solvent, V is the volume of the dissolution medium, C_s is saturation solubility, andC_x is the mass concentration of the substance in the bulk of the solvent, and h=hydrodynamic boundary layer thickness.

2.3. Housing and VO NPs treatment

6-weeks old male ICR mice (specific pathogen free, 26–28 g, OrientBio, Seongnam, Korea) were housed at our specific pathogen free facility (23 ± 3 °C, relative humidity of 50 ± 10%, 12-h light/dark cycle [150–300 lx], and ventilation of 10–20 times/h) for 1 week before the initiation of experiment, a point water and food were supplied *ad libitum*. Five types of VO NPs were dosed by gavage (70 and 210 μg/mouse, approximately, 2 and 6 mg/kg and 6.5 mL/kg, 6 days/week, 1 time/day, 6 mice/group) for 28 days, and the control group was treated with sterilized drinking water. Body weight was checked one time per week. The experiments (IACUC