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Research paper

The protective study about alleviation of simvastatin on the damages of PEG-BNs in mice

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ABSTRACT

Boron nitride nanoparticles have been proved to cause various toxicities, damages or inflammations after entering into *in vivo* in previous reports. However, up to now, there are rare investigations about the alleviation of damages caused by nanoparticles *in vivo* through natural small molecule drugs. Therefore, in this work, PEG-BNs with high solubility was successfully synthesized, and then their biodistribution in mice were studied using radiolabeling technique. And the heart, lung, liver, spleen, kidney tissues and blood samples were done for histology and biochemical analysis. The results showed that PEG-BNs were mainly distributed in lung, liver, kidney and spleen with an obviouse decreasing distribution as the experimental time was increasing. Besides, significantly serum biochemical and tissue pathological changes induced by PEG-BNs were confirmed. Moreover, after simvastatin (SST) exposure to the PEG-BNs model mice, the damages and biochemical indexes were recovered significantly as compared to the single exposure group mice in serum, which indicates a good treatment effect on the toxicity of PEG-BNs *in vivo* in mice. This study provides some basic data and useful information for the treatment of damages caused by the nanoparticles in mice in the future.

1. Introduction

Boron nitride (BN), known as white graphene, are structurally analogues with graphene in which C atoms are replaced by the alternating B and N atoms (Chhowalla et al., 2013; Elkady et al., 2012; Joshi et al., 2014; Raccichini et al., 2015; Wang et al., 2012; Xu et al., 2013). Based on the structural characteristics, BN demonstrate improved lubricating properties, resistance to chemical attack and oxidation, high thermal conductivity, excellent temperature stability, low thermal expansion, better heat conductivity and excellent electrical insulation (Lin et al., 2009; Mosleh et al., 2009; Wu et al., 2001). Therefore, for special chemical and physical characteristics of BN nanoparticles, many researchers have used these nanoparticles in biomedical domain, such as the drug carriers, nano-imaging and nanotransducers (Danti et al., 2014; Weng et al., 2014; Zhang et al., 2013). However, before the clinical application of these nanoparticles, it is very important to investigate the biosafety both *in vivo* and *in vitro* (Ciofani et al., 2010; Liu et al., 2015; Weber et al., 1993). Many nanoparticles taken *via* oral or intravenous injection into the body are mainly distributed in liver, kidney and lung so as to lead to various inflammations in these organs. These nanoparticles include carbon nanoparticles, gold nanoparticles, silver nanoparticles and other metal and mental-oxide nanoparticles (Batista et al., 2017; Ciofani et al., 2014; Qi et al., 2014; Seiffert et al., 2015; Sendra et al., 2017). Compared to the carbon and other metal nanoparticles, BN nanoparticles have not been explored extensively in their damages or toxicity for body, up to now, only few works have been reported on investigating the toxicity and biosafety of BN nanoparticles *in vivo*.

It is well known that damage is the chief toxicity concern surrounding nanotechnology, and excessive exposure to nanoparticles with high concentration requires urgent elimination of the accumulated nanoparticles from biological organs as well as the treatment of inflammatory disorders. Therefore, some researchers have tried to study several anti-inflammatory drugs on the treatment of toxicity of nanoparticles *in vivo*, and they found that those anti-inflammatory drugs could promote the excretion of nanoparticles that are accumulated in the body to certain extent in order to reduce or eliminate the tissue inflammatory (Carvalho et al., 2012; Shah et al., 2011; Tu et al., 2013). Clinically, statins were mainly used for anti-inflammatory, cardiovascular and cerebrovascular diseases (Carvalho et al., 2012; Endres, 2006; Rezende et al., 2015; Shah et al., 2011). Researchers have also praised stains for their ability to reduce cancer risks (Khurana

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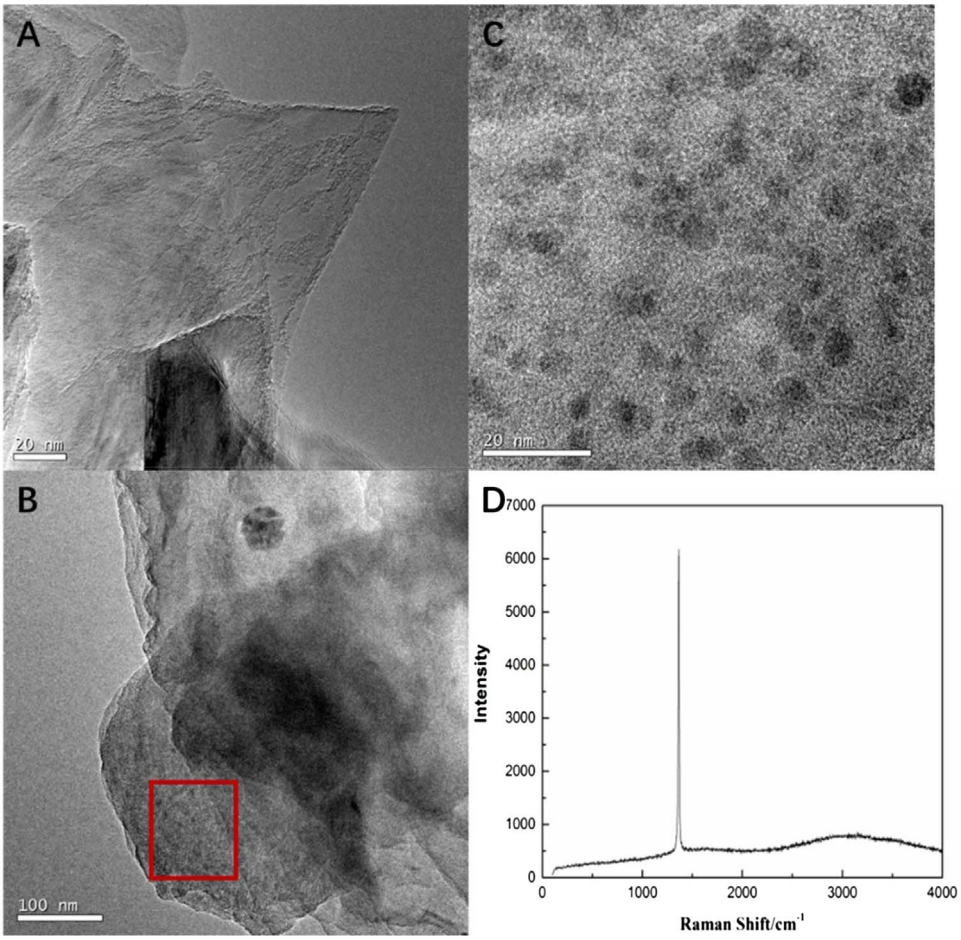

Fig. 1. TEM and Raman spectra of PEG-BNs.

et al., 2007; Simon et al., 2014; Wang et al., 2013; Yang et al., 2015). In addition, recent studies have shown that the stains can improve the bioavailability of the nanoparticles by promoting their excretion from the body (Ganesh et al., 2015; Raju, 2014). Simvastatin, one of nine known stains (atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin), is well known for its effects on cellular proliferation and inflammation and is widely used for preventing cardiovascular events and cancer (Kochuparambil et al., 2011). However, as far as we know, rare investigation has been performed to study the protective effect of simvastatin on mice model of tissue damage caused by the BN nanoparticles.

Considering that poor solubility and biocompatibility of BN materials make it too difficult to be used in biomedical applications, in this work, the PEG coated BN (PEG-BNs) were prepared successfully as reported in the previous literatures (Weng et al., 2014) to improve the water solubility and reduce the toxicity level of pristine BN, then we investigate the tissue distribution of PEG-BNs based on ^{131}I-labeled in mice *in vivo*. Additionally, the prevention and treatment capabilities of simvastatins (SST) on the toxicity of PEG-BNs in mice were explored. To the best of our knowledge, this is the first detail study of this kind to investigate the treatment of toxicity of BN nanoparticles *in vivo*.

2. Materials and methods

2.1. Synthesis and characterization of PEG-BNs

Solution of 6-arm-polyethyleneglycol-amine (Sunbio Inc.) (3 mg/mL) was mixed with BN sheets (0.5 mg/mL) (purchased from Baoding Zhong Pu Rui Tuo Technology. LTD), and the mixture was stirred at 200 °C for 4 d under the steady nitrogen flow environment. After cooling the reaction mixture to room temperature, about 60 mL H_2O was added for the extraction purpose (Shah et al., 2011). The solution was sonicated and centrifuged at 4000 rpm for 20 min, and the supernatants were collected and dialyzed for about 1 week by dialysis membrane (MD25) to remove the free PEG. Finally, the solution was dried at 50 °C in a vacuum oven, and the solid product in the form of PEG-BN was obtained. The prepared samples were then characterized by TEM (Tecnai G2 F30), XRD (XRD 600), Raman spectroscopy and thermogravimetric analysis and so on.

2.2. ^{131}I labeling PEG-BN and yield measurement

Na^{131}I (about 1.5 mCi) was provided by The First Hospital of Lanzhou University. According to the literature (Wang et al., 2004; Yang et al., 2011), chloramine-T method was used to label PEG-BNs with Na^{131}I. The labelled mixtures were centrifuged at 12,000 rpm for 10 min to purify ^{131}I PEG-BNs, and the supernatant was discarded to remove the free Na^{131}I. The yields of the labelled compounds were measured with paper chromatogram under the chromatographic solutions of normal saline and acetone. If the labelling yield was obtained over 60%, then the labelled compounds could effectively reflect their real distribution and metabolism *in vivo*.

2.3. Tissue distribution study

Kunming mice (female, about 15–18 g) were provided by the Laboratory Centre for Medical Science, Lanzhou University, Gansu, China. All animals were housed in individual cages with controlled environment at 21–22 °C and the lights were kept on from 08:00 to