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Review or mini-review

Consideration of interaction between nanoparticles and food components for the safety assessment of nanoparticles following oral exposure: A review

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ABSTRACT

Nanoparticles (NPs) are increasingly used in food, and the toxicity of NPs following oral exposure should be carefully assessed to ensure the safety. Indeed, a number of studies have shown that oral exposure to NPs, especially solid NPs, may induce toxicological responses both in vivo and in vitro. However, most of the toxicological studies only used NPs for oral exposure, and the potential interaction between NPs and food components in real life was ignored. In this review, we summarized the relevant studies and suggested that the interaction between NPs and food components may exist by that 1) NPs directly affect nutrients absorption through disruption of microvilli or alteration in expression of nutrient transporter genes; 2) food components directly affect NP absorption through physico-chemical modification; 3) the presence of food components affect oxidative stress induced by NPs. All of these interactions may eventually enhance or reduce the toxicological responses induced by NPs following oral exposure. Studies only using NPs for oral exposure may therefore lead to misinterpretation and underestimation/overestimation of toxicity of NPs, and it is necessary to assess the synergistic effects of NPs in a complex system when considering the safety of NPs used in food.

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1. Introduction

With the rapid development of nanotechnology, engineered nanoparticles (NPs) are increasingly produced and applied not only in health and medicine, but also food science. According to Nanotechnology Consumer Product Inventory (CPI) created by the Woodrow Wilson International Center for Scholars and the Project on Emerging Nanotechnology, a number of commercial food or food-related products contain NPs, with Ag, TiO_2, ZnO and SiO_2 NPs being the most popular (Vance et al., 2015). These NPs could be directly added into food as additives or used for food packaging for a variety of applications (Bumbudsanpharoke and Ko, 2015; Wang et al., 2013). Specifically, TiO_2 NPs (referred as E171 in the food industry in EU) could be used as food additives for color quality due to their natural white color, and food grade TiO_2 NPs have been identified in commercially available food products (Periasamy et al., 2015). Ag NPs (referred as E174 in the food industry in EU) could be used in food packaging for antimicrobial and sterilization purposes due to their antimicrobial activity toward a broad range of microbes

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(Antony et al., 2015). Similarly, ZnO NPs could also be used as food additives or in packaging due to their strong antibacterial ability especially to gram-positive bacteria (Bumbudsanpharoke and Ko, 2015; Shi et al., 2014). Another important application of ZnO NPs in food science is that they could be added as food additives for Zn supplement, since Zn is one of the most important essential trace element for human beings (Wang et al., 2013). SiO_2 NPs (referred as E551 in the food industry in EU) are used in clearing beers and wines, and as anti-caking and anti-clumping agents (Wang et al., 2013). The use of engineered NPs in food products inevitably increases the oral exposure of human beings to NPs. According to the CPI report, a total of 72 food and beverage products contained engineered NPs, and ingestion could be the third major exposure route for NPs from the use of consumer products (count for 16% products evaluated), next to the primary exposure pathway skin (58%) and inhalation (25%) (Vance et al., 2015). To ensure the safe use of NPs in food, it is therefore necessary to assess the potential adverse health effects of NPs following oral exposure.

Indeed, extensive studies have shown that oral exposure to NPs, especially solid NPs, was associated with damage to gastrointestinal tract (GIT) as well as the secondary organs (Antony et al., 2015; Gaillet and Rouanet, 2015; Lappas, 2015; Wang et al., 2013; Warheit and Donner, 2015). However, most of the studies only used NPs for in vivo or in vitro exposure to assess the safety, whereas the interaction between NPs and food components, which is likely to happen in real life, is ignored. In this review, we summarized the relevant studies and suggested that the interaction between NPs and food components may exist by that 1) NPs directly affect nutrients absorption through disruption of microvilli or alteration in expression of nutrient transporter genes; 2) food components directly affect NP absorption through physico-chemical modification; 3) the presence of food components affect oxidative stress induced by NPs. All of these interactions may change the toxicological responses induced by NPs following oral exposure.

1.1. *NPs affect nutrients absorption*

The small and large intestines are the major sites for the uptake of nutrients as well as particles. Some studies already showed that absorption of particles into intestinal cells can modulate the function of intestines, which is expected to consequently affect the absorption of nutrients and induce adverse health effects after long time exposure. For example, repeated oral exposure of mice to different sizes (3–20 nm) and concentrations of Ag NPs was associated with significant and dose-dependent loss of body weight, which was supported by the observation that Ag NPs induced damage to intestinal microvilli and glands (Shahare and Yashpal, 2013). In another study, oral exposure of Drosophila melanogaster to SiO_2 NPs (<30 nm) resulted in uptake of particles via endocytic vesicles and by direct membrane penetration into mid-gut cells (this model was utilized because the mid-gut of Drosophila melanogaster is similar to human intestines, thus may mimic the response of human intestines to orally exposed NPs), which was associated with membrane destabilization, mitochondrial membrane potential loss, oxidative stress as well as expression of heat shock genes (Pandey et al., 2013). Although this study did not further investigate the effect of SiO_2 NPs on nutrients absorption, it could be expected that the observed effects on mid-gut cells will impair nutrients uptake.

Under in vitro conditions, studies also showed loss of microvilli of intestinal cells after incubation with even low concentrations of NPs. It has been shown that exposure of food grade TiO_2 as well as TiO_2 isolated from the candy coating of chewing gum (both of the samples contain a portion of nano-sized TiO_2) elicited a bona fide biological response and resulted in disruption of the brush border to Caco-2BBe1 human derived cell system, which was independent of particle sedimentation. At the lowest concentration (i.e., 350 ng/ml), approximately 42% of microvilli were lost after exposure (Faust et al., 2014). The same group also reported that food-grade SiO_2 particles disrupted microvilli at 1 μg/ml by using the same cellular model, and increased production of reactive oxygen species (ROS) was also observed (Yang et al., 2016). Although the mucosal layers could be recovered within few days, it still remains unknown if the observed effects will affect nutrient uptake, especially during long time and continuous uptake of food containing NPs.

The oral exposure to NPs may affect iron absorption, as shown by a pilot study. Under in vitro conditions, exposure of polystyrene NPs to co-cultures (Caco-2 and HT29-MTX, with or without the presence of Raji B cells) increased iron uptake, which could be explained by the disruption of membrane of intestinal cells. Under in vivo conditions, acute exposure of chickens to NPs significantly decreased iron absorption, whereas chronic exposure resulted in remodeling of the intestinal microvilli to increase the surfaces for iron uptake (Mahler et al., 2012). This study provided direct evidence that oral exposure of NPs can affect nutrients uptake by the modulation of intestinal function.

NP exposure may also affect nutrient absorption by the modulation of expression of nutrients transporters. A recent study showed that TiO_2 NPs (12 nm and 20 nm) up-regulated the expression of number of genes encoding nutrient transporters as well as efflux pumps from the ATP-binding cassette transporter family in Caco-2 cells. In addition, oxidative stress was induced, showing an elevated production of ROS and impaired antioxidant systems, but no cytotoxicity or genotoxicity was observed. The authors suggested that the up-regulation of nutrients transporters may reflect a response of intestinal cells to NP-induced starvation, whereas the up-regulation of efflux pumps may reflect a protective response against NPs (Dorier et al., 2015).

To summarize from this part, some studies showed that NP exposure may affect the function of intestinal cells by the damage of membranes or expression of nutrients transporters. All of these effects may finally affect nutrients uptake, although more work is needed in the future to directly assess the impact of NP exposure on nutrients uptake, especially in the context of long time exposure (Table 1).

1.2. *Food components affect NP absorption*

The physico-chemical properties play a crucial role in defining the uptake and toxicological responses of NPs to intestinal cells. Indeed, a number of studies showed that changing physico-chemical properties of NPs by surface coating altered the uptake and biological responses of NPs to intestinal cells (Bohmert et al., 2015; Bohmert et al., 2012; Mu et al., 2014; Teubl et al., 2015). In addition, digestion has also been shown to affect uptake of NPs into intestinal cells or translocation of NPs across intestinal barriers (Bohmert et al., 2014; Song et al., 2015; Walczak et al., 2015). Therefore, it is not surprising that digestion with the presence of food components, e.g., proteins and other biomolecules, which can rapidly bind to NPs, affect the physico-chemical properties of NPs and change the nano-bio interaction by the formation of protein/biomolecule corona, can alter the biological responses of NPs following oral exposure (Docter et al., 2015). However, only very few studies have addressed this issue until present. For example, a recent study showed that the protein corona was formed on magnetite NPs when they were digested with the presence of bread. Moreover, the formation of protein corona apparently enhanced uptake and affected cellular localization of NPs, although this was not quantitatively measured (Di Silvio et al., 2016). In another study, the presence of main food components, namely carbohydrates, proteins and fatty acids, significantly increased the uptake