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LETTER

Potential toxicity of dental nanomaterials to the central nervous system

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Dear editor

It was enlightening to read this comprehensive review of dental nanomaterials toxicity to the central nervous systems (CNSs) by Feng et al[1] published in the *International Journal of Nanomedicine*. There are many potential applications of nanomaterials in dentistry.[2] Composite resins have been widely used in restorations of dental caries;[3] however, it is estimated that approximately 50% of prepared restorations need to be remade, the secondary caries is one of the most frequent causes of failure,[4] and the use of nanomaterials could decrease the incidence of these complications. Thus, the application of nanomaterials can bring numerous benefits in dentistry, especially in caries prevention; however, there is an important question about the safety of these materials for the nervous system. In the study by Feng et al[1] a vast array of nanomaterials types and their major applications were outlined.

A strong point of this study[1] is the detailed description of the role of blood–brain barrier (BBB) to prevent potentially harmful substances from entering into the CNS.[5] This BBB is formed by tight junctions, basement membrane, and glial cells that protect the neurons and glial cells, preventing the passive transport of molecules >500 Da between CNS and blood capillaries.[6,7] However, as discussed by Feng et al[1] some nanomaterials that have been utilized as drug carriers can cross the BBB. This possibility to cross the BBB has important concerns about the use of nanomaterials and possible neurotoxicity, especially in children. Another important point in the paper is the discussion about a complex topic as nanomaterials is comprehensive, but in simple language, which makes it accessible for general dentists and neurologists.

First and foremost, it becomes clear to the reader how faster and more efficient it has been the development and spread of nanoparticles (NPs) than its biosecurity research counterpart. As an example, the authors could not find any study on NPs elimination from the CNS. Moreover, on the exploration of this final via in the metabolism of NPs, the new recent findings regarding a CNS lymphatic system should be considered.[8] On the other hand, although not entirely understood, the pathways for systemic absorption and CNS distribution of NPs could be reviewed extensively by the authors and this is a major virtue of this study.

Given all the current and potential future impacts to human health, there is a need for the regulatory and governmental agencies to lean over this matter. This could have been better explored in this study. There are some ongoing initiatives from the Food and Drug Administration: its National Center for Toxicological Research is conducting toxicity studies on nanomaterials and the Center for Drug Evaluation

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and Research has ongoing research projects to identify the limitations of current test methods to assess the quality and safety of NP-based therapeutics.[9]

The main research challenges, as discussed in Figure 5 regarding the existing problems in assessing the neurotoxicity of NPs, could be summarized in three main front lines. Methodological standardization is a must to enable interpretation of results of multiple studies and to allow replicability, an undervalued step for science progress. As the authors demonstrated, standard procedures are still lacking to evaluate NPs toxicity. Second, the process of translating the current knowledge from pre-clinical experiments to human Phase I/II studies is still in its beginning. In this regard, we may have even more incognito after effects in different age groups and/or comorbid conditions. Ultimately, considering that many toxicity effects present on the long-term, to achieve early results with clinical significance, identification of reliable surrogate endpoints will be demanded.

Disclosure

The authors have no conflicts of interest to disclose.

References

1. Feng X, Chen A, Zhang Y, Wang J, Shao L, Wei L. Application of dental nanomaterials: potential toxicity to the central nervous system. *Int J Nanomedicine*. 2015;10:3547–3565.
2. Alenazy MS, Mosadomi HA. Clinical implications of calcifying nanoparticles in dental diseases: a critical review. *Int J Nanomedicine*. 2014;9:27–31.
3. Cheng L, Zhang K, Weir MD, Melo MA, Zhou X, Xu HH. Nanotechnology strategies for antibacterial and remineralizing composites and adhesives to tackle dental caries. *Nanomedicine (Lond)*. 2015;10(4):627–641.
4. Kuper NK, Opdam NJ, Bronkhorst EM, Huysmans MC. The influence of approximal restoration extension on the development of secondary caries. *J Dent*. 2012;40(3):241–247.
5. Beduneau A, Saulnier P, Benoit JP. Active targeting of brain tumors using nanocarriers. *Biomaterials*. 2007;28(33):4947–4967.
6. Blyth BJ, Farhavar A, Gee C, et al. Validation of serum markers for blood–brain barrier disruption in traumatic brain injury. *J Neurotrauma*. 2009;26(9):1497–1507.
7. Paiva WS, Correia AD, Marie SK. Neuroinflammatory responses to traumatic brain injury. *Neuropsychiatr Dis Treat*. 2015;11:773–776.
8. Louveau A, Smirnov I, Keyes TJ, et al. Structural and functional features of central nervous system lymphatic vessels. *Nature*. 2015;523(7560):337–341.
9. U.S. Food and Drug Administration. 2015. Available from: www.fda.gov

Authors' reply

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Dear editor

We thank Dr Solla and his colleagues for their thoughtful comments on our review. We are glad to see this paper might be enlightening for general dentists and neurologists to understand the potential toxicity of nanomaterials to the central nervous system (CNS). In the meantime, we would like to put forward some viewpoints to their major comments.

First, we agree with the important role of blood–brain barrier (BBB) to prevent potentially harmful substances from entering the CNS. The physiology of the vasculature in the CNS including the BBB adds much difficulty to the delivery of most drugs to the brain.[1] However, nanotechnology-based carriers have been exploited as an effective approach for drug delivery in the CNS.[2] In our second review published in the *International Journal of Nanomedicine*, applications of nanotechnology targeting the CNS have been thoroughly discussed.[3] The mechanism of this nanoparticle-mediated drug transport through the BBB appears to be receptor-mediated endocytosis which was followed by transcytosis into the brain or by drug release within the endothelial cells.[4]

In the review, the main pathways through which nanomaterials enter the CNS, including transport across the BBB and translocation via sensory nerve, are stated in detail. On the other hand, the knowledge and understanding of nanoparticle elimination pathways in the CNS lag far behind. In a recent study performed by Geraet, the author found some decrease in Ti levels of the investigated tissues (including the brain) after oral and intravenous administration of titanium dioxide nanoparticles in rats, but the elimination of nanoparticles may rather be related to dissolution.[5] Limited solubility in combination with persistent exposure will eventually result in accumulation in tissues. So how do these residual nanoparticles leave the brain? As pointed out in our review, little is at present known about the elimination of nanomaterials in the CNS. Accumulation of nondegradable nanoparticles in the body over time could lead to unwanted toxicity and cell death. Thus, related investigations are urgently needed.

We also thank Dr Solla and his colleagues for their valuable suggestion on the recent finding regarding a CNS lymphatic system.[6] The discovery of meningeal lymphatic system may call for a reassessment of the long-held concept of the absence of lymphatic vasculature in the CNS. Nevertheless, this paper was an exploratory experiment and mainly focused on the structural and functional features of the CNS lymphatic vessels. Whether these structures do act as an elimination route for waste products including nanoparticles into the blood circulation associated with the explicit elimination mechanism requires further investigations. Their data may at present not permit evidence or answers to these theoretical considerations.

Another point of their comments referred to the safety assessment of nanomaterials conducted by regulatory and governmental agencies such as the Food and Drug Administration. In fact, we totally agree with the recent Food and Drug Administration's guidance documents on the potential safety issues of nanomaterials.[7] As noted in our review, nanomaterials possess typical nanostructure-dependent properties, which may differ greatly from the properties of their bulk counterparts. For this reason, the traditional toxicity testing methods may not be fully applicable due to nanomaterial's distinctive properties and behavior. The main limitations of the current toxicological testing have been deeply discussed and further summarized in Figure 5. Here we have to admit that the toxicology considerations of Food and Drug Administration's guidance documents may be more comprehensive (including nanomaterial characterization and exposure routes) for the current framework of safety assessment and are considered to be appropriate for a variety of materials. In comparison, our review paid particular attention to the application of dental nanomaterials and their exposure pathways may be much more limited. We hope more appropriate analytical methods suitable for the specific nanomaterial could be developed in the future.

Finally, we are happy that they agree with our suggestions on the future research prospects on nanomaterial neurotoxicology. They additionally mentioned two important points: first, more efforts are needed in the process of translating the

current knowledge from preclinical experiments to human Phase 1/2 studies; second, they suggest that identification of reliable surrogate endpoints on the long-term toxicity will be demanded. We thank them for their valuable recommendations. In recent years, nanomaterials continue to bring promising advances to science and technology due to their unique physicochemical properties. However, compared with their wide applications, the nano-related safety assessment is still in its beginning. Because investigations into the possible harmful effects of nanoparticles have been performed only for a few years, it is not surprising that many studies suffer from shortcomings. Until now, definitions for nanomaterials proposed by various government, industry, and standards organizations are often inconsistent in their elements and scope, which may lead to confusion in determining whether a material is considered to be a "nanomaterial".[8] With regard to surrogate endpoints on the long-term toxicity of nanomaterials, we believe an animal model of extended longevity (compared with rats and mice), such as primates, might be more predictive of human exposures. But regretfully, no data were found to date. We believe there is still much work to do.

Disclosure

The authors have no conflicts of interest to disclose.

References

1. Aryal M, Arvanitis CD, Alexander PM, McDannold N. Ultrasound-mediated blood-brain barrier disruption for targeted drug delivery in the central nervous system. *Adv Drug Deliv Rev*. 2014;72:94–109.
2. Jain KK. Nanobiotechnology-based strategies for crossing the blood-brain barrier. *Nanomedicine (Lond)*. 2012;7(8):1225–1233.
3. Feng X, Chen A, Zhang Y, Wang J, Shao L, Wei L. Central nervous system toxicity of metallic nanoparticles. *Int J Nanomedicine*. 2015;10:4321–4340.
4. Kreuter J. Drug delivery to the central nervous system by polymeric nanoparticles: what do we know? *Adv Drug Deliv Rev*. 2014;71:2–14.
5. Geraets L, Oomen AG, Krystek P, et al. Tissue distribution and elimination after oral and intravenous administration of different titanium dioxide nanoparticles in rats. *Part Fibre Toxicol*. 2014;11:30.
6. Louveau A, Smirnov I, Keyes TJ, et al. Structural and functional features of central nervous system lymphatic vessels. *Nature*. 2015 Jun 1.
7. U.S. Food and Drug Administration. 2015. www.fda.gov
8. Boverhof DR, Bramante CM, Butala JH, et al. Comparative assessment of nanomaterial definitions and safety evaluation considerations. *Regul Toxicol Pharmacol*. 2015 Jun 23.