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Effect of divalent cations on the uptake of Mn_3O_4 nanoparticles by olfactory epithelial cells

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Motivation and Aim: Inorganic nanoparticles (NPs) are promising tools for the treatment of brain diseases. Given their high surface-to-volume ratio, NPs provide efficient loading of therapeutic molecules, while their material composition and structure properties offer alternative therapeutic possibilities. One of the most promising methods of drug delivery to the brain, bypassing the blood-brain barrier (BBB), is intranasal administration [1–3]. The success of the implementation of the therapeutic effect of NPs is largely determined by the intensity of their capture by target structures, which depends both on the physicochemical properties of the NPs themselves and on the functional state of the tissue. It is known that the transport system of divalent cations plays a key role in the transport of heavy metals from the nasal cavity to the brain. Whether this system is involved in the transport of insoluble NPs of the same metals is not known. The aim of this work was to evaluate the effect of various di-, tri-, and multivalent cations on the uptake of Mn_3O_4-NPs by nasal epithelial cells.

Methods and Algorithm: The work was performed on Balb/c of SPF-status mice at the age of 8 weeks. The accumulation of NPs in the olfactory bulbs was assessed using T1-weighted images obtained on a BioSpec 17/16USR ultrahigh-field magnetic resonance tomograph (Bruker, Germany) with a magnetic field strength of 11.7 T. Tomography was performed 1 hour after the introduction of NPs. Inhibitors were introduced 5 min before the introduction of Mn_3O_4-NPs. The Mn_3O_4-NPs used in the work had a particle size (20–80 nm), hydrodynamic diameter (118 ± 15 nm), surface charge (–18 ± 5.1 mV) and r1: 0.395 $mM^{-1}*s^{-1}$.

Results: Based on the data of T1-weighted MRI, the uptake of Mn_3O_4-NPs by nasal epithelium cells was affected by the preliminary administration of 1 mM solutions of $FeCl_2$, $CoCl_2$, $ZnCl_2$, but not $FeCl_3$, $GdCl_3$, $CaCl_2$, $MgCl_2$. The results obtained correspond to the data on the selectivity of the transport system of divalent cations (Cd^{2+} > Fe^{2+} > Co^{2+}, Mn^{2+} ≫ Ni^{2+}, but not Ca^{2+}, Mg^{2+}, Cu^{2+}, Fe^{3+}, Gd^{3+}) [4]. In addition, administration of a polyanion (0.1 mM heparin), a polycation (0.1 mM protamine), or inhibitors of L- and N-type voltage-gated calcium channels that regulate the excitability of the olfactory neuron also did not affect the nasal uptake of Mn_3O_4-NPs. At the same time, salinomycin, a known inhibitor of the divalent cation transporter (DMT 1) [5], significantly suppressed the uptake of Mn_3O_4-NPs.

Conclusion: For the first time, we were able to demonstrate the role of the non-transferin transport system of divalent cations in the uptake of insoluble metal oxide NPs by nasal epithelial cells. The results obtained will be useful both in the development of means for protecting the CNS from the penetration of xenobiotics and in solving the problems of

targeted delivery of NPs acting as independent therapeutic agents or "containers" for the drugs.

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