CERIUM OXIDE NANOPARTICLES REDUCE PORTAL HYPERTENSION AND SHOW ANTIINFLAMMATORY PROPERTIES IN CCl_4-TREATED RATS

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Background and Aims. During the last few years nanoparticles (NPs) have emerged as a new technology allowing enhanced levels of precision in treating disease. Cerium oxide (CeO_2) NPs have proven to behave as free radical scavenger and/or antiinflammatory agents. However, whether CeO_2NPs are of therapeutic value in liver disease is not known. We assessed the organ distribution, subcellular localization, metabolic fate and systemic and hepatic effects of the iv administration of CeO_2NPs to CCl_4-treated rats. The aim of the study was to determine whether CeO_2NPs display hepatoprotective properties in experimental liver disease. **Methods.** Organ and subcellular distribution of NPs was assessed using magnetic resonance imaging (MRI) and transmission electron microscopy (TEM), respectively. The metabolic fate of CeO_2NPs was investigated by measuring daily urinary and fecal excretion of Ce (ICP-MS). The systemic and hepatic effects of NPs were assessed in CCl_4-treated rats receiving CeO_2NPs (0.1 mg/kg, n=10) or vehicle (n=15) twice weekly for two weeks and CCl_4 treatment was continued for 8 additional weeks. Thereafter, mean arterial pressure (MAP) and portal pressure (PP) were assessed and serum samples obtained to measure standard hepatic and renal function tests. Liver samples were also obtained to evaluate mRNA expression of genes related to inflammatory or vasoactive activity, macrophage infiltration, α-smooth muscle actin (α-SMA) expression and hepatic apoptosis. **Results.** More than 90% of the NPs were located in the liver and spleen 30 min after administration. The remaining targeted lungs and kidneys. No NPs were located in the brain. CeO_2NPs were internalized by parenchymal cells and found in either, peroxisomes or free in the cytoplasm. Most NPs were excreted by the urine. CeO_2NPs ameliorated systemic inflammatory biomarkers (LDH: 879±229 vs 392±67, ALT: 1287±419 vs 304±40 U/L; $p<0.05$) and improved PP (9.9±0.4 vs 8.2±0.4 mm Hg, $p<0.05$) without affecting MAP. A marked reduction in mRNA abundance of inflammatory cytokines (TNFα: 53±11.1 vs 18.3±4.7, IL1β: 61.6±10 vs 31.2±5.4; $p<0.05$), iNOS: (537±158 vs 94±35, $p<0.05$) and ET-1 (14.2±2.7 vs 6.3±1.9, $p<0.05$), infiltration of macrophages (29.5±0.8 vs 25.7±0.7 cells/field) and protein expression of caspase-3 (21±2.9 vs 7.1±2.7 DAU, $p<0.05$) and α-SMA (7.1±0.3 vs 5.8±0.3 %, $p<0.01$) was observed in the liver of rats receiving CeO_2NPs. **Conclusions.** CeO_2NPs administration to CCl_4-treated rats protects against chronic liver injury by markedly attenuating the intensity of the inflammatory response and reducing portal hypertension, thereby suggesting that CeO_2NPs may be of therapeutic value in chronic liver disease.