In vitro cardiotoxicity screening of silver and metal oxide nanoparticles using human induced pluripotent stem cell-derived cardiomyocytes

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Exposure risk to silver and metal oxide nanoparticles (NPs) continues to increase due to their widespread use in products and applications. *In vivo* studies have shown Ag, TiO_2 and CeO_2 NPs translocate to the heart following various routes of exposure. Thus, it is critical to assess NP systemic toxicity including their effects on the heart and properties regulating NP cardiotoxicity. This study examined the cardiotoxicity of 4 Ag (10 or 110 nm,) citrate (cit) or polyvinylpyrrolidone (PVP) coated, 3 CeO_2 (7 - 105 nm), 3 TiO_2 (10 - 40 nm) NPs using human induced pluripotent stem cell-derived cardiomyocytes (CM). Metal oxide NPs were sonicated in medium containing 20% fetal bovine serum while Ag NPs were resuspended without sonication. Cytotoxicity was determined using Cell Titer Blue, MitoTracker Deep Red, and nuclear staining assays at 48 h post-exposure to 3 – 50 µg/ml of NP or $AgNO_3$. CM function was monitored using microelectrode array technology measuring field potential duration, beat period, sodium spike amplitude, beat rate prior to exposure and at 1, 24, and 48 h post-exposure to each NP at 3 or 25 µg/ml, or $AgNO_3$ at 3 µg/ml. CM isoproterenol (ISO) (25 and 50 nM) responses were assessed at 48 h post-exposure. Ten nm Ag cit or PVP NPs were cytotoxic to CM at 50 µg/ml and $AgNO_3$ was cytotoxic at 6.3 µg/ml. At 3 µg/ml, only the 7nm CeO_2, 10 nm Ag cit or PVP coated NPs decreased all CM functional endpoints and ISO responses at 24 and 48 h post-exposure (toxicity ranking: 7 nm CeO_2 > 10 nm Ag PVP > 10 nm Ag cit). Our results demonstrate: i) altered electrophysiology is a sensitive endpoint to assess human NP CM toxicity; ii) size, composition and coating regulate human NP cardiotoxicity; and iii) establishment of an alternative model for human CM NP toxicity testing. (This abstract does not reflect Agency Policy)

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