Uptake and toxicity of metal containing nanoparticles in brain cells

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Metal-containing nanoparticles (NPs) have gained considerable interest during the last decade due to their exciting properties as antibacterial agents, for consumer products as well as for technical applications and diagnostics. Due to their frequent use, the likelihood that brain cells will encounter such NPs has strongly increased. To investigate potential adverse effects of NPs on brain cells, we have studied the biocompatibility, the uptake and the metabolism of metal-containing NPs such as iron oxide NPs (IONPs), copper oxide NPs (CuONPs) and silver NPs (AgNPs) on cultured primary brain cells. Cultured astrocytes, neurons and microglial cells accumulated IONPs efficiently in a time-, concentration- and temperature-dependent manner. However, despite of an accumulation of large amounts of iron in IONP-treated astrocytes and neurons, the viability of these brain cells was not compromised. In contrast, accumulated IONPs were toxic for microglial cells, most likely due to the rapid uptake and transfer of the IONPs into the lysosomal compartment which facilitates the liberation of iron ions from the accumulated particles. The presence of fetal calf serum in the incubation medium strongly decreased the rate of IONP uptake into brain cells. While some inhibitors of endocytotic pathways lowered IONP accumulation in serum-containing medium, these inhibitors did not affect the rapid IONP accumulation in serum-free conditions. Astrocytes that had been exposed to IONPs for only 4 h remained viable for up to 7 days, hardly releasing any iron during this incubation period and showed a transient appearance of reactive oxygen species and a strong upregulation of the iron storage protein ferritin. Similarly, AgNP-treated astrocytes were not compromised in their viability and increased their content of metal-storing metallothioneins. These data demonstrate that cultured brain astrocytes deal well even with large amounts of iron or silver that are accumulated as IONPs or AgNPs. In contrast, the treatment of cultured astrocytes with CuONPs caused severe oxidative stress-mediated toxicity that was prevented by copper chelators, suggesting that rapid liberation of copper from accumulated CuONPs is involved in the observed toxicity of these NPs to astrocytes. These data demonstrate that different brain cell types differ in their vulnerability to one type of metal-containing NPs and that NP toxicity on a given type of brain cells strongly depends on the content of applied NPs.