Physiological cyclic stretch – impact of silica nanoparticle uptake into human endothelial cells

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In vitro static cell culture systems are often used to test cytotoxicity as well as efficacy of engineered nanoparticles for the application in humans. Indeed, those static in vitro models are not that sufficient for testing the effects of nanoparticles intended for intravenous administration. After injection, nanoparticles circulate within the bloodstream *in vivo* and interact immediately with proteins and cells. One of the first cell types that come in contact with nanoparticles are endothelial cells. They line the luminal side of blood vessels and built the first barrier nanoparticles have to overcome to reach their final destination. Since endothelial cells are known to be affected by physical forces such as shear stress and strain caused by pulsatile blood flow *in vivo* the phenotype of endothelial cells in living species are distinct to cells in static in vitro cell culture; even primary cells are used. Since shear stress has already been addressed by many groups we focused our examination of nanoparticles-cell interaction on another prominent force; cyclic stretch. In the present study, the impact of amorphous silica nanoparticles with different sizes and surface modifications on primary endothelial cells, which are cultured under physiological cyclic stretch conditions (1Hz, 5% stretch) was investigated and compared to cells maintained under standard static conditions. Cytotoxicity of silica nanoparticles to endothelial cells did not alter significantly under stretch compared to static culture conditions. Nevertheless, the uptake of nanoparticles decreased in cell cultures under stretch. Furthermore, it was shown, that the decreased uptake of the nanoparticles was neither due to inflammatory processes nor due to the induction of exocytosis. However, further results indicated that the reduced endocytosis of nanoparticle seemed to be a consequence of cyclic stretch itself (proven by the formation of stress fibres) and might finally be a result of membrane flattening [1] caused by cell stretching. This study demonstrates, that the impact of silica nanoparticles is not altered by the more physiological culture conditions but that in addition to shear stress stretch is a prominent factor, which should be considered to study cell-nanoparticle interactions *in vitro*. Furthermore, our improved *in vitro* cell culture model is valuable for the prediction of nanoparticle-cell interactions *in vivo* [2]. Hence, specified cell culture models that reflect the *in vivo* situation more precisely might play a pivotal role in reducing animal experiments and in consequence development costs of drug delivery systems and new pharmaceutics (e.g. bi-specific antibodies).

References

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