National Institute of Environmental Health Sciences

Superfund Research Program

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Commonly Manufactured Nanomaterial Induces Neurovascular Toxicity

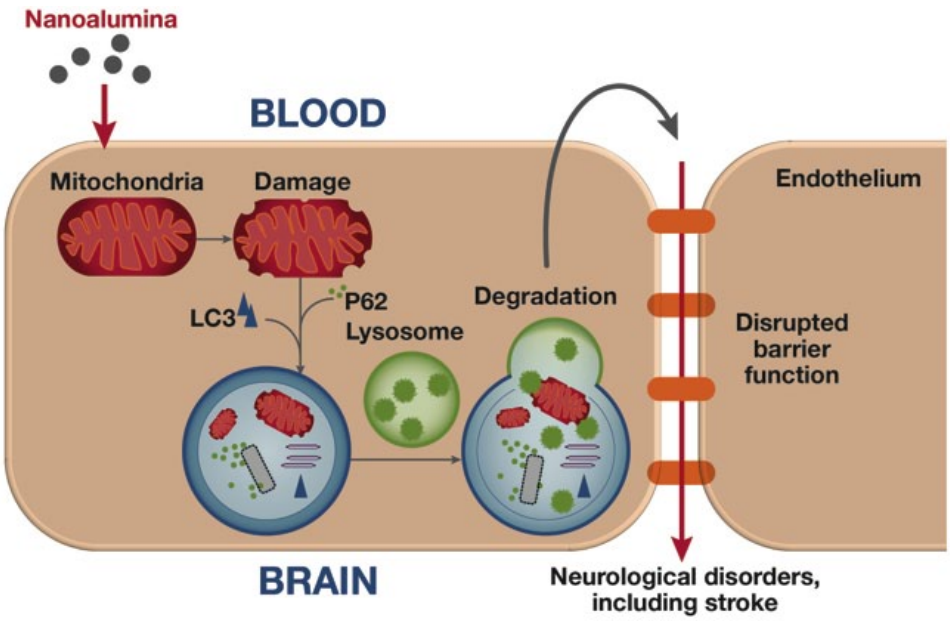
Nanoalumina, a widely manufactured nanomaterial, can accumulate in brain cells, inducing nerve and blood vessel damage and protein degradation in the brain, according to a 2012 NIEHS-funded study from the University of Kentucky Superfund Research Program (UK SRP). The study also suggests that exposure to nanoalumina disrupts the blood-brain barrier and may worsen the outcomes of neurological disorders such as stroke.

Many engineered nanomaterials (ENMs) have been developed in recent years for industrial applications, consumer products, and medical fields. Nanoalumina is one of the most abundantly manufactured ENMs. Nanoalumina is used as an additive in surface coatings and ceramics, in filtration membranes for water purification, and in devices for drug delivery, among other applications.

Lei Chen, M.D., Ph.D., with UK SRP investigator Michal Toborek, M.D., Ph.D., exposed both human and mouse brain cells to nanoalumina. They found that exposure to nanoalumina disrupted mitochondrial function and increased autophagy of brain endothelial cells. Autophagy, a highly conserved pathway of protein degradation involved in various cellular functions and cell death, is normally a cellular rescue mechanism to maintain balance within cells. However, over activated autophagy may lead to excessive protein degradation and cell death. Researchers observed increased autophagy of brain endothelial cells from nanoalumina in the central nervous system and revealed that autophagy is an important mechanism involved in neurovascular toxicity, or damage of nerves and blood vessels in the brain.

Researchers also observed a decrease in mitochondrial function in the brain cortex of exposed mice, with a dramatic decrease in levels of adenosine triphosphate (ATP). ATP transports chemical energy in the cells for metabolism and is produced in the mitochondria.

Exposure to nanoalumina also decreased the expression of the proteins occludin and claudin-5, which are involved in maintaining the integrity of the blood-brain barrier. Normal function of the blood-brain barrier, which is responsible for the exchange of nutrients and metabolites between the blood and the brain, is critical for central nervous system (CNS) stability. Persistent accumulation of nanoalumina in the CNS may increase the likelihood of the development of acute and/or chronic neurological disorders. In the study, researchers indicated that exposure to nanoalumina may worsen the outcome of stroke, a neurovascular disorder.



Nanoalumina induces mitochondrial damage and leads to the degradation of proteins, disrupted barrier function, and exacerbated neurological disorders, including stroke.

Although nanoalumina was highly toxic to cells and the brains of mice, nanocarbon, an ENM of similar size tested at the same concentrations, had a much less toxic effect. These results demonstrate that the chemical and physical properties as well as size of nanoparticles may influence biological activity and toxicity. The authors stress the need to investigate the toxicity of ENMs individually, not as a particle size group, to establish appropriate recommendations for risk assessment.

Chen is now at Mount Sinai School of Medicine in New York. Toborek is currently at the Miller School of Medicine, University of Miami.

Results in human cerebral microvascular endothelial cells	Results in mice
Nanoalumina entered and accumulated in brain cells when added to cell cultures	Significant expression of autophagy-related proteins in the brains of mice exposed to nanoalumina up to 30 days after exposure
Mitochondrial disruption seen in cells with treatment of nanoalumina	Nanoalumina induced expression of autophagy-related genes in the brains of exposed mice
Dose-dependent increase in autophagy-related proteins in cells with exposure to increasing concentrations of nanoalumina (0.01-10 µg/mL)	ATP levels in the mouse cerebral cortex significantly decreased with exposure
Elevated protein degradation in endothelial cells with increasing concentrations of nanoalumina	Levels of blood-brain barrier-related tight-junction proteins occludin and claudin-5 in mice decreased with exposure to nanoalumina

Study results show effects of nanoalumina on neurovascular toxicity in human brain cells and mice.

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To learn more about this research, please refer to the following source:

Chen L, Zhang B, Toborek M. 2013. Autophagy is involved in nanoalumina-induced cerebrovascular toxicity. Nanomedicine: Nanotechnology, Biology and Medicine 9: 212-221. doi: 10.1016/j.nano.2012.05.017