Nanoparticles Exacerbate Both Ubiquitin and Heat Shock Protein Expressions in Spinal Cord Injury: Neuroprotective Effects of the Proteasome Inhibitor Carfilzomib and the Antioxidant Compound H-290/51

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Increased levels of ubiquitin and heat shock protein (HSP) 72 kD are often seen in spinal cord injury (SCI). However, their roles in cell injury or survival are not well known. Thus, we have investigated the possible relationship between ubiquitin and HSP expressions in relation to cell injury in healthy animals, or following nanoparticle (NP) intoxication in SCI animals. A focal SCI was inflicted on the T10?11 segments over the right dorsal horn; animals were allowed to survive from 5 to 8 h after trauma. Separate groups of rats were exposed to SiO2, Ag, or Cu NPs for 7 days and subjected to SCI on the eighth day. A marked increase in ubiquitin or HSP immunoreactive cells occurred in the T9 to T12 segments 5 h after the injury, which further extended to the T4 and L5 after 8 h of survival. At this time, a marked increase in blood?spinal cord barrier (BSCB) permeability to Evans blue and radioiodine, accompanied by an intense edema formation, was observed. Changes were further exacerbated in NP-treated traumatized rats. The most marked expressions of ubiquitin and HSP in SCI were seen in rats treated with SiO2, followed by Ag, and Cu NPs. Treatment with H-290/51 (50 mg/kg p.o., 30 to 60 min after injury) or carfilzomib (1 mg/kg, i.v., 30 to 60 min after trauma) significantly reduced the ubiquitin or HSP expressions, as well as the BSCB breakdown, the edema formation, and the cell injury in the cord both 5 and 8 h after the injury, in normal animals. However, a double dose of H-290/51 (100 mg/kg) or carfilzomib (2 mg/kg) is needed to reduce cord pathology or ubiquitin and HSP expressions in traumatized animals treated with NPs. H-290/51

showed superior beneficial effects in reducing cord pathology in SCI than carfilzomib. These observations are the first to demonstrate that (i) NP-treated traumatized animals induce a widespread BSCB leakage, edema formation, and cord pathology as well as an overexpression of ubiquitin and HSP, (ii) high doses of antioxidant compounds or proteasome inhibitors are required for neuroprotection in the NP-exposed traumatized group, and (iii) ubiquitin and HSP expressions play a key role in neuronal injury in SCI, not reported earlier.

Blood-spinal cord barrier

Carfilzomib

H-290/51

Heat shock protein

Nanoparticle

Spinal cord injury

Ubiquitin

antioxidant

carfilzomib

copper nanoparticle

h 290 51

heat shock protein

heat shock protein 72

nanoparticle

silica nanoparticle

silver nanoparticle

ubiquitin

unclassified drug

antioxidant

carfilzomib

copper

H290-51

heat shock protein 72

indole derivative

nanoparticle

nerve protein

neuroprotective agent

oligopeptide

proteasome inhibitor

silicon dioxide

silver

ubiquitin

animal experiment

animal model

animal tissue

Article

blood spinal cord barrier

controlled study

drug effect

edema

male

nerve cell lesion

neuroprotection

nonhuman

permeability barrier

protein expression

rat

spinal cord dorsal horn

spinal cord injury

thoracic spinal cord

animal

biosynthesis

complication

edema

genetics

metabolism

pathology

preclinical study

spinal cord

Spinal Cord Injuries

thoracic vertebra

upregulation

Wistar rat

Animals

Antioxidants

Copper

Drug Evaluation, Preclinical

Edema

HSP72 Heat-Shock Proteins

Indoles

Male

Nanoparticles

Nerve Tissue Proteins

Neuroprotective Agents

Oligopeptides

Proteasome Inhibitors

Rats

Rats, Wistar

Silicon Dioxide

Silver

Spinal Cord

Spinal Cord Injuries

Thoracic Vertebrae

Ubiquitin

Up-Regulation