Nanoprodrug Accumulates in Experimental Traumatic Brain Injury

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Introduction

Blast injuries are frequent in the current conflicts in Iraq and Afghanistan due to improvised explosive devices (IEDs) causing traumatic brain injuries.

Neuroprotective clinical trials for traumatic brain injury have shown no benefits; this has raised concerns regarding neuroprotection as a stand alone strategy.

There is therefore a compelling need to develop treatments that promote the repair and regeneration of injured brain tissue and functional recovery.

We have developed a nanoprodrug that is responsive to oxidative stress and induces release of active non-steroidal anti-inflammatory drugs in the presence of reactive oxogen species (ROS).

Methods

Twelve-week-old male C57/Bl6 mice (Jackson Laboratories) were anesthetized using isoflurane, followed by stereotaxic controlled cortical impact (Leica Microsystems Inc.) to the left parietal area at a velocity of 3 m/s, 0.5 ms impact time, 2 mm impact depth, with a 2 mm diameter piston. Mice were then recovered on a warming pad. Five minutes after injury, 18 mice were injected IP with 100 ul of nanoparticle (10 mg/ml) 6 mice were injected IV via the tail vein with 100 ul of nanoparticle, and 6 mice were injected IP with normal saline as a control. At 48 hours after injury, mice underwent behavioral testing (rotorod and open field test) and in vivo bioluminescence imaging (Xenogen) followed by euthanasia and collection of whole brain for confocal microscopy.

Results

The ibuprofen-containing nanoprodrug is released at high concentrations specifically in the presence of oxidative stress. This "proof-of-concept" of specific delivery of nanoprodrugs to TBI establishes this novel paradigm as a platform to deliver multiple modalities of brain protection and neural regeneration in TBI.

Functional analyses of behavioral testing (rotorod and open field testing) one day after injury confirmed that there was no neurobehavioral sequelae after nanoprodrug infusion.

Conclusions

Nanoprodrugs accumulate at high concentrations in areas of TBI allowing imaging and highly specific therapy.

Learning Objectives

Discuss nanomedicine therapy for TBI.

Discuss theories of nanomedicine accumulation in TBI.

References

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