Drug shown to aid injured adult brains may exacerbate cognitive problems in children

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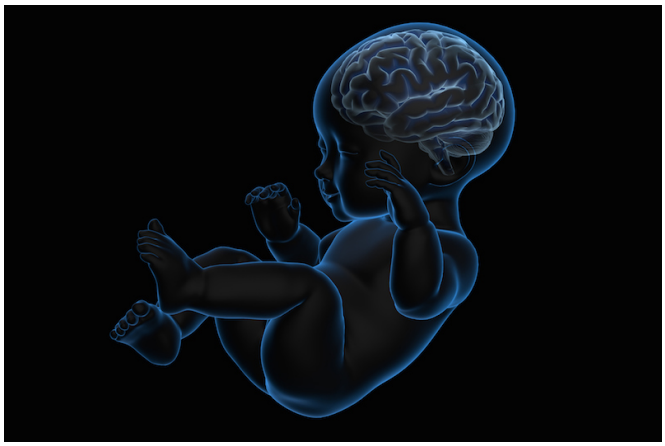

Credit: Drexel University

Traumatic brain injury (TBI) is one of the leading causes of disability and death in infants and children in the United States, with more than half a million affected annually, according to the Centers for Disease Control and Prevention. Those under age 4 who experience brain trauma can suffer lifelong problems with memory, attention and other executive functions.

While there are no drugs available to treat these injuries, scientists have shown that certain antibiotics—which inhibit the brain's inflammatory response—can improve outcomes for adult animal models that have suffered a blow to the head.

However, this treatment seems to negatively affect brains that have not yet developed, according to a new study from Drexel University College of Medicine. When administered to newborn rats immediately after head injury, the FDA-approved antibiotic minocycline exacerbated cognitive deficits, says the study, which was published in the journal *Experimental Neurology*.

"The developing brain is not the same as the fully mature brain," said Ramesh Raghupathi, PhD, a professor of neurobiology and anatomy in the College of Medicine. "This study suggests that acute interventions targeting the inflammatory cascade may not be a viable strategy for treating traumatic brain injury in infants and young children."

The drug minocycline works by decreasing the activation of microglia—the primary immune cells in the brain and spinal cord that protect against foreign pathogens. Inhibiting microglia appears to be an effective strategy to prevent long-term brain damage, since studies have shown an association between increased activity of these cells and neuron degeneration. And repurposing FDA-approved drugs to fit a new medical need is a desirable approach.

"In the pediatric animal model, we saw a microglia response that resembled what you would see in an adult brain. There was a lot of cell death, damage and inflammation," Raghupathi said. "You would hypothesize that if you block the microglia activity, you would see an improvement in function."

But when Raghupathi and his team treated the newborn rats with minocycline—one dose every day for three days—they saw that their brain activity did not improve. When the researchers increased the dosage to nine days instead of three, the animal models showed significant memory problems and other behavioral deficits.

Raghupathi believes the antibiotic had an adverse effect on the neonate rats, because microglia plays an important role during early brain development: These cells clear out dead neurons and debris to make a path for surviving neurons to function normally. By targeting the microglia in the pediatric animal model, the antibiotics seemed to prevent the brain from undergoing its natural maturation process.

"You can think of microglia in a developing brain

like a garden rake that clears debris out of the lawn to make sure the grass grows properly," Raghupathi said. "By removing the dead cells, it paves the way for the developing brain to rewire itself."

While treating acute inflammation in the pediatric brain may not be effective, the researchers hypothesize that extending the window of intervention could have more positive outcomes.

In upcoming studies, they plan to wait two or three weeks after injury to administer the minocycline, giving the pediatric brain more time to develop before receiving treatment.

"We think that long-term inflammation may be the target," Raghupathi said.

More information: L.A. Hanlon et al, Differential effects of minocycline on microglial activation and neurodegeneration following closed head injury in the neonate rat, *Experimental Neurology* (2017). DOI: 10.1016/j.expneurol.2016.12.010

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