

Title: Periventricular White Matter Injury Prevention.

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Research Project Description:

Periventricular white matter injury in premature infants (PWMI; also referred to as diffuse white matter injury, or leukoencephalopathy of prematurity) is a neurological disorder characterized by reduction of white matter in periventricular and other brain regions. Up to 30% of low birth weight preterm infants manifest some form of PWMI, making it the most common form of brain injury affecting premature infants. Risk factors for PWMI include perinatal infection resulting in brain inflammation and hypoxia. In animals, PWMI-like features can be induced by exposing neonates to hypoxia, hypoxia-ischemia, or by reduction in cerebral blood flow. Despite the wide prevalence of PWMI and the considerable morbidity associated with it, no direct treatments are available to either treat or prevent the white matter injury that these infants.

Reduced white matter is a major feature of PWMI, raising the possibility that there is abnormal development of oligodendrocytes. OL maturation involves a complex series of events during which progenitor cells undergo dramatic morphological and biochemical changes that lead to the formation of OLs that myelinate axons.

To begin to develop drugs to treat hypomyelination, our lab used high-throughput screening to identify compounds that would stimulate PreOL proliferation. These studies identified diazoxide as a stimulator of PreOL proliferation. Although diazoxide showed efficacy in promoting myelination and reducing ventriculomegaly in a murine model of PWMI, it was not completely effective in preventing PWMI, leading the lab to look for other compounds that are potentially even more effective than diazoxide. These efforts lead to the discovery of four, novel lead compounds that are in the process of being analyzed.

The potential roles of medical students will be to assess the effectiveness of these compounds to prevent PWMI through the use of brain slice cultures and in vivo mouse experiments.

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