Why low oxygen levels soon after birth may raise risk for learning and behavioral disorders

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New research published in the *Journal of Leukocyte Biology*, shows that the development of white matter in the mouse brains is delayed when they are exposed to chronic low oxygen levels shortly after birth. If true in humans, this may help explain why infants born with cyanotic heart disease, prematurity and/or severe lung disease often exhibit developmental disabilities that effect learning during childhood, years after the low-oxygen exposure. This knowledge may inform future studies focused on the development of effective treatment strategies.

"We found that chronic hypoxia is a state of neuroinflammation in the developing brain," said Lakshmi Raman, MD, a researcher involved in the work from the Department of Pediatrics at the University of Texas Southwestern Medical Center in Dallas, Texas. "Therefore, developing therapies to mitigate potentially detrimental inflammation may help reduce brain injury in infants exposed to chronic hypoxia and at-risk for developmental delay."

Scientists exposed experimental groups of mice to low oxygen from days three through 28 after birth. Control mice were exposed to normal oxygen levels (21% oxygen, i.e., room air). Researches studied brain development when exposed to low oxygen through multiple methods, including quantifying myelin protein, the number of myelin-producing cells, called oligodendrocytes, total brain inflammation and the activation of brain-targeting white blood cells. The aim was to determine

if perinatal chronic hypoxia produces permanent injury to the brain, including a four-week recovery period. They found that mice exposed to perinatal chronic hypoxia lost myelin in the developing brain, which resulted in motor learning deficits that persisted for weeks after the end of hypoxic exposure. The long-term myelin loss was associated with increased inflammation in the brain, as well as an increased presence of CD4 T cells in the blood that were reactive to myelin. Therefore, perinatal chronic hypoxia induced an inflammatory response in the brain with concomitant demyelination, ultimately leading to long-term behavioral deficits.

"These findings are important since the neurological effects of low neonatal oxygen levels, if extended to humans, could have clinically actionable treatment options like oxygen supplementation," said John Wherry, Ph.D., Deputy Editor of the *Journal of Leukocyte Biology*. "The link between low oxygen or hypoxia and inflammation is becoming clear in a number of settings and the connection to inflammatory pathways may reveal additional anti-inflammatory treatment options for nervous system hypoxia."

More information: S. B. Ortega et al. Perinatal chronic hypoxia induces cortical inflammation, hypomyelination, and peripheral myelin-specific T cell autoreactivity, *Journal of Leukocyte Biology* (2015). DOI: 10.1189/jlb.5HI0914-447R

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