Discovery suggests way to block fetal brain damage produced by oxygen deprivation

September 1 2011

Examining brain damage that occurs when fetuses in the womb are deprived of oxygen, researchers at The Scripps Research Institute have discovered that damage does not occur randomly but is linked to the specific action of a naturally occurring fatty molecule called LPA, acting through a receptor that transfers information into young brain cells.

This observation made in mice suggests that LPA may also be linked to the damage caused by oxygen deprivation in human fetuses. If that proves to be the case, the research may help scientists and physicians better understand and find new ways to address the numerous developmental disorders that can arise when fetuses are deprived of oxygen in the womb—including mental retardation, epilepsy, schizophrenia, autism, cerebral palsy and a range of other physical and mental problems.

"Fetal brain damage from oxygen deprivation involves specific changes that are, surprisingly, mediated by this lipid signal called LPA," said Scripps Research Professor Jerold Chun, MD, PhD, a member of the Dorris Neuroscience Center who led the research, which appeared in an advance, online issue of the journal *Proceedings of the National Academy of Sciences* (*PNAS*) this week.

"Because this pathway can be targeted with drugs," he added, "the discovery suggests that creating new medicines that target LPA receptors may be a way of limiting or preventing serious developmental brain diseases."

Currently, there is no way to treat the neurological damage produced by oxygen deprivation.

How Lack of Oxygen Affects the Fetal Brain

A developing fetus might be temporarily deprived of oxygen—a condition known as "hypoxia"—for any number of reasons, including disruption of blood flow, exposure to smoke, carbon monoxide, or physical trauma.

Physicians have long known that hypoxia can lead to brain damage and increased risk of developmental disorders, and existing public health efforts are aimed at mitigating these risks. Awareness that carbon monoxide from cigarettes can cause hypoxia, for instance, is the major reason why women are warned not to smoke when they are pregnant.

Still, there is a need to find other ways to address the problem, since not every situation in which fetuses might be subjected to oxygen deprivation is preventable. The discovery by Chun, graduate student Keira Herr, and colleagues suggests that there may be a way to mitigate the damage caused by hypoxia directly, by drugs targeting the molecules in the brain that mediates this damage—specifically, the receptor for the phospholipid molecule lysophosphatidic acid (LPA).

Phospholipids, molecules of fat with a charged head on one end, are universally found in biological organisms because they are an essential building block of cellular membranes, defining the boundaries of cells and keeping things inside a cell separated from that which is outside.

But lipids do more than just form barriers. LPA acts as a signal to affect the development of mammalian brains—something that Chun and his colleagues first demonstrated several years ago. His laboratory identified the first cellular receptor to which LPA binds, and they discovered that

LPA acts as a signal that influences neurogenesis, the formation of new neurons when fetal brains are developing in the womb, along with the architecture of the brain.

As the brain grows in developing fetuses, it forms specialized regions very quickly. Many of these regions must be up and running by the time a baby is born. Newborns need to be able to breathe, drink, digest, respond to stimuli, and function in countless other basic ways in order to survive.

Problems that arise as the early brain develops may lead to developmental disorders.

Findings that Provide a New Strategy to Block Damage

The prominent role LPA plays in fetal brain development is what led Chun and his colleagues to investigate whether it also played a role in developmental disorders, many of which are believed to be linked to brain disorganization that arises during early development as has been documented in the clinical literature following hypoxic insults.

The team studied the effect of hypoxia in the brains of developing mice and also on brains temporarily grown in Petri dishes. In particular, the researchers studied the changes that occur in young neurons of the cerebral cortex, the part of the brain believed to be involved in higher functions, like memory, cognition, reasoning, and the interpretation of sensory input.

Chun and his colleagues discovered that when hypoxia damages developing cerebral cortical neurons, it does so in very specific ways that require LPA signaling. Scientists had long assumed that the association

between hypoxia and brain damage was a non-specific one in which individual neurons all over the brain were randomly killed as a result of being deprived of oxygen.

What Chun and his colleagues found, however, is that hypoxia causes the neurons to become overstimulated, mimicking effects produced by excessive LPA exposure. Genetically removing the receptors for LPA or blocking them through drugs stopped these effects.

Knowing that hypoxia causes brain damage through this LPA signaling pathway provides a strategy to target and block that damage. Blocking LPA signaling may be a new way to prevent damaging changes to the brain and attenuate or prevent diseases linked to hypoxia, a concept that awaits further testing in humans.

More information: The article, "Stereotyped fetal brain disorganization is induced by hypoxia and requires lysophosphatidic acid receptor 1 (LPA) signaling," (doi: 10.1073/pnas.1106129108) by Keira Joann Herr, Deron R. Herr, Chang-Wook Lee, Kyoko Noguchi, and Jerold Chun appears in the journal *PNAS*.

Provided by The Scripps Research Institute