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Drug therapy for premature infants destroys brain cells in mice

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A class of drugs that are used in premature infants to treat chronic lung damage can cause damage in the brain. New research at Washington University School of Medicine in St. Louis suggests the drugs may cause cognitive and motor-control problems even when they are given before birth.

The researchers have identified the cells damaged by the drugs, called glucocorticoids, as well as the time window during which brain injury can occur. They say it may be possible to avoid damage to brain cells and still aid the development of premature lungs if synthetic forms of the drugs can be replaced with hormones made naturally in the body.

The researchers reported their findings today at Neuroscience 2008, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Studying the effects of the drugs in mice, the investigators found that the synthetic glucocorticoids dexamethasone and betamethasone, commonly prescribed to spur the development of premature lungs, cause damage in the brain's cerebellum, the structure that controls movement, as well as other functions.

Brain cells in the mice died following glucocorticoid treatment when the drugs were given between four and 10 days after birth. The corresponding window in human infants would be approximately 20 weeks of gestation to six weeks following birth. That's also the time span

in which these drugs are given to pregnant women at risk for preterm birth or to prematurely born infants who are having problems breathing.

"The cells that are damaged are called neural progenitor cells, which are responsible for producing new neurons," says first author Kevin K. Noguchi, Ph.D., a scientist in the Department of Psychiatry. "So you can imagine that if you kill the cells responsible for producing new neurons, you can cause severe neurodevelopmental deficits."

That's exactly what the researchers found when they studied adolescent mice that had been treated with glucocorticoids during infancy. A single exposure to glucocorticoid drugs permanently decreased the number of neurons in the cerebellum of the mouse brain.

In the past, the steroid drugs were given to low-birthweight infants after they were born, but studies determined that exposure to the drugs following birth could lead to cognitive problems and neuromotor deficits, particularly difficulty with balance and coordination. In 2002, the American Academy of Pediatrics recommended post-natal glucocorticoid use be stopped unless used in clinical trials, but the drugs still are given frequently to mothers at risk for preterm birth.

"The cerebellum connects to other brain structures, so when granule cells in the cerebellum are lost, you also have detrimental effects on cognitive function in non-motor regions of the brain," says senior investigator Nuri B. Farber, M.D., associate professor of psychiatry. "Other researchers have found I.Q. declines in children who have received these drugs early in life, and our findings may help explain why."

But both Farber and Noguchi say therapy with these drugs may be essential for some children with immature lungs as a lifesaving measure. They believe, however, that it may be possible in the future to use different drugs to help the lungs mature without damaging brain cells.

"We're looking at differences between glucocorticoids that are made naturally in the body and hormones that are manufactured," says Noguchi. "The brain has some natural defenses against exposure to endogenous glucocorticoids but not the synthetic ones. So it may be possible to administer some of those natural hormones, which can help the lungs mature without putting the brain at risk."

It also may be possible to develop other drugs that would assist with lung development without killing cells in the cerebellum. But as they study those possibilities, the investigators say they want parents to know that the observed toxic effects of steroid drugs are not a problem for adults and older children. They estimate that by about three months of age, human infants no longer are at high risk for this damage.

"The toxic effects decline when the cerebellum finally finishes its development," Farber says. "These drugs are used for many different purposes, so there are other reasons why a baby might get prednisone or dexamethasone or another glucocorticoid, but our research in mice suggests once a human infant is a few months old, these drugs have fairly innocuous effects in the brain."

Source: Washington University School of Medicine