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Study finds a new mechanism for how methamphetamine affects the developing fetal brain

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(PhysOrg.com) -- University of Toronto researchers have discovered a new mechanism in mice that shows how the exposure to the illicit drug methamphetamine (METH) during pregnancy can adversely affect the developing fetal brain.

METH is converted in the fetal brain to unstable free radical metabolites that react with oxygen within cells to produce highly active oxygen intermediates, termed reactive oxygen species (ROS). ROS can cause oxidative damage to structures within the cell. One of these targets is DNA, which normally directs the manufacture of proteins essential for brain development. If the repair of oxidative DNA damage is insufficient, the fetus is born looking normal, but exhibiting long-term impairments in brain function.

"Although oxidative DNA damage has long been associated with mutations and cancer, our study provides the most direct evidence to date that this mechanism can adversely affect critical events in the developing fetus," said Professor Peter Wells of the Leslie Dan Faculty of Pharmacy, senior author of the study that appears in the September issue of the Journal of Neuroscience.

Using genetically altered pregnant mice lacking an important protein for repairing oxidative DNA damage, oxoguanine glycosylase 1 (OGG1), Wells, doctoral students Andrea Wong and Winnie Jeng, and

postdoctoral fellow Gordon McCallum showed that METH-exposed fetuses lacking OGG1 had higher levels of oxidative DNA damage in the brain compared to littermates with normal OGG1 activity. They also had a correspondingly greater deficiency in motor coordination for at least 3 months after birth.

METH-exposed fetuses with normal OGG1 activity were normal and comparable to control fetuses exposed only to the saline vehicle, indicating that normal DNA repair was completely protective at this level of METH exposure.

These results show not only that oxidative DNA damage can adversely affect the developing fetus, but also that fetal deficiencies in the pathways that repair this damage can constitute a risk factor for neurodevelopmental deficits, in this case manifested by long-term motor coordination deficits.

Although the team's findings cannot be extrapolated to humans without further study, Wells believes they do suggest a novel mechanism through which METH may contribute to neurodevelopmental deficits, as well as potential risk factors for individual susceptibility.

Provided by University of Toronto