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Mammalian placenta reflects exposure to stress, impacts offsprings' brains, research finds

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The mammalian placenta is more than just a filter through which nutrition and oxygen are passed from a mother to her unborn child. According to a new study by a research group from the University of Pennsylvania School of Veterinary Medicine, if a mother is exposed to stress during pregnancy, her placenta translates that experience to her fetus by altering levels of a protein that affects the developing brains of male and female offspring differently.

These findings suggest one way in which maternal-stress exposure may be linked to neurodevelopmental diseases such as autism and schizophrenia, which affect males more frequently or more severely than females.

"Most everything experienced by a woman during a pregnancy has to interact with the placenta in order to transmit to the fetus," said Tracy L. Bale, senior author on the paper and an associate professor in the Department of Animal Biology at Penn Vet. "Now we have a marker that appears to signal to the fetus that its mother has experienced stress."

Bale also holds an appointment in the Department of Psychiatry in Penn's Perelman School of Medicine. Her coauthors include lead author and postdoctoral researcher Christopher L. Howerton, graduate student Christopher Morgan and former technician David B. Fischer, all of Penn Vet.

Published in the Proceedings of the National Academy of Sciences, the study builds on previous work by Bale and her colleagues which found that female mice exposed to stress during pregnancy gave birth to males who had heightened reactions to stress. Further research showed that the effect extended to the second generation: The sons of those male mice also had abnormal stress reactions.

Meanwhile, human studies conducted by other researchers have shown that males born to women who experience stress in the first trimester of pregnancy are at an increased risk of developing schizophrenia.

The Penn team hoped to find a biomarker that could account for these changes and risk factors. To be an effective signal of maternal stress, the researchers reasoned, a biomarker would need to show differences in expression between male and female offspring and would need to be different between stressed and unstressed mothers. They also wanted to find a marker that behaved similarly in humans.

They went about their search by first exposing a group of female mice to mild stresses, such as fox odor or unfamiliar noises, during the first week of their pregnancies, a time period equivalent to the first trimester of a human pregnancy. Another group of pregnant mice was unexposed.

In a genome-wide screen of the female's placentas, one gene stood out as meeting the researchers' criteria: Ogt, an X-linked gene that codes for the enzyme O-linked-N-acetylglucosamine transferase (OGT). Placentas from male offspring had lower levels of OGT than those from female offspring, and all placentas from stressed mothers had lower levels than placentas from their unstressed counterparts.

To determine how placental exposure to reduced levels of OGT might differentially affect the brains of male and female offspring, Bale's team developed a mouse in which they could genetically control OGT's

expression. Comparing females with normal levels of placental OGT to females that had been manipulated to have half as much, the researchers observed changes in more than 370 genes in the offspring's developing hypothalamus. Many of these genes are known to be involved in energy use, protein regulation and synapse formation, functions that are critical to neurological development.

In addition, Bale and colleagues found promising signs that these results translate to humans. They analyzed human placentas that had been discarded after the birth of male babies. No identifying information was associated with the tissue, but the researchers discovered that the male (XY) side of the placenta had reduced OGT expression compared to the maternal (XX) side, similar to this genes regulation in mouse placenta.

Together, the results suggest that the OGT enzyme may be acting to protect the brain during gestation but that males have less of this protective enzyme to begin with, placing them at an increased risk of abnormal neurodevelopment if their mother is stressed during pregnancy.

If OGT's status as a biomarker for exposure to prenatal stress and heightened risk for neurodevelopmental problems is confirmed in humans, Bale said it could help detect vulnerable individuals earlier in life than is currently possible.

"We want to get to the point where we can predict the occurrence of neurodevelopmental disease," Bale said. "If we have a marker for exposure, we can meld that with what we know about the genetic profiles that predispose individuals to these conditions and keep a close eye on children who have increased risks."

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