Scientists identify mechanism that may explain why males are more at risk than females for neurodevelopmental disorders

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Researchers have recently begun to realize that biological sex plays a key role in disease risk. Sex plays a role in hypertension, diabetes, arthritis—and in many neurological and psychiatric disorders.

Depression and anxiety affect females more, while neurodevelopmental disorders, including autism spectrum disorders, early onset schizophrenia, and attention deficit hyperactivity, affect more males. Males are also more sensitive to prenatal insults, such as gestational stress, maternal infection and drug exposure.

To better understand the molecular underpinnings of this disparity, Tracy Bale of the University of Maryland School of Medicine, along with several colleagues, focused on a molecule that plays a key role in placental health. In a study of mice, they found that the molecule, O-linked N-acetylglucosamine transferase (OGT) works by establishing sex-specific patterns of gene expression.

The study was published this week in the journal *Nature Communications*.

OGT seems to work via an epigenetic modification that broadly controls transcription, H3K27me3. Epigenetics is the study of changes in how genes are expressed. Dr. Bale showed that high levels of H3K27me3 in the female placenta produce resilience to stress experienced by the mother. This indicates at least one molecular pathway that allows females to be more resilient to maternal stress than males.

"This pathway could help explain why we see this profound neurodevelopmental difference in humans," said Dr. Bale. "OGT and H3K27me3 in the placenta are crucial to a lot of protein encoding that occurs during pregnancy, and so this process has a lot of downstream effects. The OGT gene is on the X chromosome, and seems to provide a level of protection for the female fetus to perturbations in the maternal environment."

Dr. Bale has focused much of her research on the links between stress and subsequent risk for neurodevelopmental disorders, including autism

and schizophrenia in offspring. Her previous work on the placenta has found novel sex differences that may predict increased prenatal risk for disease in males.

She has previously found that, in mice, a father's stress can affect the brain development of offspring. This stress can alter the father's sperm, which can alter the brain development of the child. Dr. Bale has also found that male mice experiencing chronic mild stress have offspring with a reduced hormonal response to stress; this response has been linked to some neuropsychiatric disorders, including PTSD. This suggests that even mild environmental challenges can have a significant effect on the health of offspring.

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