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Obesity in mothers alters babies' weight through brain rewiring

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Obese mothers are more likely to have children with metabolic disorders such as diabetes compared with thin mothers, but the underlying molecular and cellular reasons for this effect have been unclear. A study published by Cell Press on January 23rd in the journal *Cell* reveals that the offspring of mouse mothers on a high-fat diet are predisposed to obesity and diabetes because of abnormal neuronal circuits in the hypothalamus—a key brain region that regulates metabolism. The findings suggest that mothers who consume a large amount of fat during the third trimester may be putting their children at risk for lifelong obesity and related metabolic disorders.

"Our study suggests that expecting mothers can have major impact on the long-term metabolic health of their children by properly controlling nutrition during this critical developmental period of the offspring," says study author Tamas Horvath of the Yale University School of Medicine.

More than one-third of children and adolescents are overweight or obese and thus are at risk for long-term health problems such as type 2 diabetes. Studies in humans have shown that mothers who are obese or have diabetes put their children at risk for metabolic problems, but researchers have not previously identified the exact brain circuits mediating this effect, known as metabolic programming. Moreover, past studies failed to pinpoint the most critical stage of pregnancy during which maternal nutrition has the greatest impact on offspring health.

To address these questions, Horvath teamed up with Jens Brüning of the

Max Planck Institute for Neurological Research and the University of Cologne to develop a mouse model of metabolic programming. They found that mouse mothers fed a high-fat diet during lactation had offspring with abnormal neuronal connections in the hypothalamus, as well as altered insulin signaling in this brain circuit. As a result, the offspring remained overweight and had abnormalities in glucose metabolism throughout their adult life.

Because of developmental differences between species—neural circuits in the hypothalamus continue to develop after birth in mice but are fully developed before birth in humans—the findings suggest that the third trimester of pregnancy in humans is the most critical time window for a mother's nutrition to have long-lasting effects on her offspring's health.

"Given that gestational diabetes frequently manifests during the third trimester, our results point toward the necessity of more intensified screening of mothers for altered glucose metabolism, as well as tightly controlled antidiabetic therapy if any alterations are detected during this critical period," Brüning says.

More information: *Cell*, Vogt et al.: "Neonatal insulin action impairs hypothalamic neurocircuit formation in response to maternal high fat feeding." dx.doi.org/10.1016/j.cell.2014.01.008

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