Maternal inflammation boosts serotonin and impairs fetal brain development in mice

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Fighting the flu during pregnancy sickens a pregnant woman, but it may also put the fetus at a slightly increased risk for neurodevelopmental disorders like autism later in life. A new study in pregnant mice, published June 1 in *The Journal of Neuroscience*, offers a potential mechanism explaining why: Inflammation alters neurotransmitters and impairs growth of nerve cells in the developing fetal brain.

Prenatal infections are associated with a slight risk for disorders like autism and schizophrenia in children, and evidence suggests the mother's inflammatory response may be a cause. Studies in rats indicate high levels of inflammatory molecules in the maternal blood supply are linked to lifelong behavioral abnormalities in offspring. Just how inflammation affects the developing brain has remained a mystery.

The fetal brain requires the neurotransmitter serotonin to develop healthy neural circuits. The placenta supplies serotonin by converting the amino acid tryptophan circulating in the mother's blood into the neurotransmitter. Researchers at the University of Southern California wanted to know how maternal inflammation affects this conversion and whether this affects the developing fetal brain.

To answer these questions, they injected pregnant mice with either an immune-stimulating compound or a placebo 12 days into the pregnancy. The compound produces a mild inflammatory response in mice as well as causes brain and behavioral deficits in their offspring. After either 24 or 48 hours, the team analyzed the maternal blood, placenta, and fetal brains.

In addition to having more inflammatory molecules in their blood streams, the treated mice had more than double the amount of tryptophan in their placentas 24 hours after the injection. After 48 hours, tryptophan levels had returned to normal, but the enzyme converting tryptophan into serotonin, tryptophan hydroxylase, was more active in treated mice. A separate experiment demonstrated that treated placenta produced four times as much serotonin. Finally, while the researchers found the offspring of treated mice had higher levels of serotonin in their brains, they also had fewer serotonin-containing nerve cells.

The results suggest maternal inflammation increases the amount of serotonin in the placenta and the fetal brain, impairing the growth of serotonin nerve cells, the researchers say.

The results "represent a paradigm shift for the effect of inflammation on the fetal brain development," said Irina Burd, an associate professor of gynecology and obstetrics at Johns Hopkins University who studies fetal brain development and was not involved in the study. "It may be possible that there are several ways that maternal inflammation may impact the fetal brain, and one of the mechanisms is through aberrant neurotransmitter levels."

Dysfunction of serotonin-producing cells is implicated in mood disorders such as depression and anxiety, and prenatal inflammation increases the risk of mood disorders in offspring. However, the researchers caution that understanding whether early disruptions in brain development caused by maternal inflammation contribute to later mood disorders requires additional study.

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