Prenatal stress predisposes female mice to binge eating

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Stress changes our eating habits, but the mechanism may not be purely psychological, research in mice suggests. A study published May 30 in *Cell Metabolism* found that stressed mouse mothers were more likely to

give birth to pups that would go on to exhibit binge-eating-like behavior later in life. The female mouse pups from stressed mothers shared epigenetic tags on their DNA, but these epigenetic markers only made a difference when the researchers put the young offspring into a stressful situation. Furthermore, the researchers were able to prevent their binge eating by putting the young mice on a diet with "balanced" levels of nutrients such as Vitamin B12 and folate.

Previous studies have found an epidemiological link between binge eating and traumatic or stressful events during early life, but untangling the biology behind that correlation has proved difficult. "Here we established a model where we can actually show that early life stress increases the likelihood of binge eating in females," says senior co-author Alon Chen, a neurobiologist at the Weizmann Institute in Israel and the Max Planck Institute of Psychiatry in Munich, Germany. "The second thing that is really interesting is that prenatal stress is causing an epigenetic signature in the embryo's brain," says Mariana Schroeder, the postdoctoral fellow that led this study.

To test the impact of prenatal stress, the researchers genetically engineered a line of mice, where the brain circuit responsible for releasing cortisol and other stress hormones could be manipulated. Many different systems within the brain contribute to "stress," but the researchers wanted to be able to zero in on one specific neuroendocrine circuit—called the corticotropin-releasing factor (CRF) system—to see if it had an effect. In humans, high levels of CRF activity have been linked to increased anxiety, suppressed appetite, and inflammation, all of which can take a long-term toll.

When these mice became pregnant, the researchers activated the CRF system during their "third trimester" in order to kick the stress circuit into high gear. Their goal was to simulate chronic CRF stress in isolation, but because being handled by humans usually causes all of a

mouse's stress circuits to kick in, they developed a CRF-triggering technique with minimal intervention. "We didn't actually handle the mice at all; we just changed the water that included the genetic trigger in the third trimester," Chen says. Handling the mice is usually a source of stress.

They found that female pups from these stressed mice exhibited epigenetic markers in tissue from their hypothalami. However, the presence of epigenetic methyl tags alone was not enough to cause binge eating. The mouse pups' tendency to binge only surfaced when they were placed in a stressful situation where the researchers restricted their access to food. The mice on the "limited access" diet could eat as much this very rewarding food as they wanted, but they only had access to food for 2-hour windows three times per week, prompting some mice to eat excessively large amounts of food very quickly during the meal windows.

Interestingly, all 10 of the female mice that were subjected to the restricted feeding scenario exhibited a binge-eating phenotype. The researchers used an equal number of female offspring from the stressed out mothers that were not subjected to the restricted feeding schedule as a control. If the same pathways are involved in human eating disorders, it could partly explain why women diagnosed with eating disorders outnumber their male counterparts.

The chemicals that cells use to epigenetically annotate their genes come from food sources. In this case, the epigenetic marker was a methyl tag, and the cell grabs methyl groups from vitamins such as B12 and folate for epigenetic tagging, so the researchers decided to test what would happen if they adjusted the levels of methyl-donating vitamins in the mice's diet. The genetically predisposed mice on the methyl-balanced diet did not exhibit the binge-eating-like behavior, suggesting that non-invasive dietary interventions may be able to prevent binge eating.

However, the researchers emphasize that this is a pre-clinical study in mice. We don't know yet what a methyl-balanced diet for humans would look like or whether it would even have an effect on human eating disorders. "We found a balance, but it might not be the relevant balance for humans. This is something that needs to be tested," says Chen.

Chen hopes that this work will help researchers understand the neurobiology behind eating disorders. "The general public is less aware of the fact that we are dealing with a very biological mechanism that changes a person. People say, 'Oh, it's only in the brain.' And yes, it's in the brain. It involves changes in your genes, in your epigenome, and your brain circuits."

All of this underscores the importance of avoiding stressful situations as much as possible during pregnancy. "We all know this, but people ignore it for various social or economic reasons," says Chen. "But the price we pay later in life—whether it's psychiatric disorders, metabolic syndromes, or heart-related illnesses—is heavily impacted by the way your brain was programmed early in life."

More information: *Cell Metabolism*, Schroeder et al.: "A methyl balanced diet prevents CRF-induced prenatal stress triggered predisposition to binge eating-like phenotype" www.cell.com/cell-metabolism/f … 1550-4131(17)30287-5 , DOI: 10.1016/j.cmet.2017.05.001

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