

## **Study shows why poor prenatal nutrition leads to obesity**

Poor nutrition in the womb may remodel the brain circuitry of newborn babies and predispose them to become obese in later life, research in mice suggests. The findings may help doctors to prevent the onset of obesity in susceptible infants who are born undernourished, say the researchers.

“Nutritional restriction during fetal life is not uncommon even in modern Western society,” says Norimasa Sagawa at Kyoto University Graduate School of Medicine, Japan, one of the researchers. “The important point is that after such nutritional stress during fetal life those (children) are exposed to high-calorie and high-fat diet during their later life.” A combination that may be a recipe for obesity.

Previous research has found that babies born to malnourished mothers are more likely to develop heart disease and diabetes in later life. These small babies have a phase of “catch-up” growth, where within their first months they grow more quickly than their bigger born counterparts, eventually reaching equal size. During catch-up, they also show elevated levels of the appetite-regulating hormone leptin. This is secreted by fat cells and acts to diminish appetite when reserves are high.

These children may have been pre-programmed with a “thrifty phenotype”, a term coined by David Barker at the University of Southampton, UK, and his colleagues. They reasoned that fetuses who sense food scarcity in the womb set their bodies to store more fat, more efficiently. But it was unknown exactly how this programming worked.

### **Feeding regimes**

To investigate the mechanism behind this, a team led by Shigeo Yura, also at Kyoto University Graduate School of Medicine, gave pregnant mice different feeding regimes – normal and underfed.

As in previous studies, they found that underfed mothers gave birth to lower-weight pups that grew quickly and caught up with normal pups after 10 days. When fed a diet with an average calorific content after weaning, pups from both normally fed and underfed mothers weighed the same and had similar fat reserves.

But when the pups that experienced fetal impoverishment were fed a high-fat diet, they grew much bigger than pups that had prenatal plenty. At 17 weeks, mice from the underfed group weighed about 15% more and stored 50% more fat than the prenatally well-nourished mice on the same high-fat diet.

The underfed pups also showed a premature spike in leptin levels at 8-10 days old, compared with a surge on day 16 in normally fed pups. To test whether this early spike was the cause of later obesity, the team injected leptin into normally fed mice at 10 days. These mice also tended to become obese under calorie-rich diets, even though they had experienced no fetal malnutrition.

### **Always hungry**

The authors conclude that the early leptin spike alters neural circuitry during a critical developmental window and interferes with the transport of leptin to the brain in adulthood. These changes effectively make the mice insensitive to “full” signals. Understanding this mechanism might help clinicians to reverse fetal programming, says Sagawa.

Susan Ozanne at Cambridge University, UK, who studies nutritional programming, cautions that it is difficult to translate these results from mice to humans, but she sees potential to treat obesity-prone children. “The evidence certainly suggests there are critical time periods in humans and there is some kind of postnatal plasticity where you have the potential to intervene.”

She adds that the results reinforce the importance of a balanced diet during pregnancy – not just the raw amount of calories. “You can have lots of food but still be starved in terms of a particular nutrient,” she says.

*Journal Reference: Cell Metabolism (vol 1, p 371)*

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