METABOLISM

Breastfeeding protects offspring from obesity

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Over the past years, the prevalence of obesity has reached an alarming rate and it is now critically affecting public health. Although evidence suggests that early-life determinants such as maternal nutrition affect the metabolic status of the fetus, the effects of breastfeeding by the infant on the reprogramming of energy balance in early and adult life are still unclear. In a new study published in *Nature Metabolism*, Pena-Leon, Folgueira, Barja-Fernández et al. show that prolonged breastfeeding in rodents protects them against obesity in adulthood via long-lasting effects on the hypothalamus mediated by liver-secreted factors.

Previous studies have shown that neonatal maternal high-fat diet (HFD) intake during lactation can affect the offspring's metabolism. In this new study, the authors examined whether prolonged breastfeeding (delayed weaning- DW) can act on energy reprogramming in Sprague-Dawley rats that consumed either a chow diet or HFD until adulthood.

First, the researchers identified that DW reduced body and fat mass induced by HFD in rats. Second, by exposing rats to a thermoneutral or to a cold environment, they demonstrated that DW protection occurs via an activation of brown adipose tissue thermogenesis and browning of the white adipose tissue, which stimulates energy expenditure. These DW-induced changes were accompanied by an improved glucose tolerance and leptin sensitivity, without alteration of food intake.

Hepatic steatosis, a condition of fat accumulation in the liver associated with HFD, was also ameliorated in DW-HFD rats. FGF21, a hepatokine with a role in thermogenesis, was increased in the plasma and liver of DW rats. To investigate the role of FGF21 in their model, the researchers used hormone and gene manipulation techniques in rats, which showed that downregulation of hepatic *Fgf21* attenuated DW-induced body mass loss. Using multiple in vivo viral vector experiments in rats and elegant transgenic mouse models along with in-depth metabolic phenotyping techniques, they revealed that hepatic FGF21 decreases the body mass via an augmentation of BAT thermogenesis by increasing dopamine 2 receptor (D2R) expression in the lateral hypothalamic area and the zona incerta of the hypothalamus, thereby suggesting hypothalamic D2Rs mediate the beneficial effects of prolonged breastfeeding. Finally, the investigators identified that FGF21 acts directly on these D2R-expressing GABAergic neurons via its receptor FGFR1.

This new study highlights the mechanisms behind liver-to-hypothalamus communication and the long-term metabolic benefits of breastfeeding, opening new avenues for hypothalamic metabolic regulation research at a clinical level.

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