Hypothalamic EZH2: A Key Regulator of Leptin Sensitivity in Obesity

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Obesity is a severe health problem predicted to affect one in two U.S. adults by 2030. Leptin, an adipocyte-derived satiety-inducing peptide hormone, plays a critical role in mediating food intake and energy metabolism, with the levels of leptin production directly correlated to an individual's body fat mass. However, in obesity, leptin becomes ineffective in suppressing appetite and countering body weight gain, even though leptin and leptin receptor gene mutations are rare. Revealing the underlying epigenetic mechanisms in leptin resistance is essential for developing effective anti-obesity treatments. Since dietary and lifestyle factors can influence gene expression, obesity and leptin resistance were investigated through an epigenetics approach. I found that high-fat diet-induced obesity in mice is associated with significantly suppressed hypothalamic gene expression levels of enhancer of zeste homolog 2 (EZH2), a histone methyltransferase, through qPCR. After administration of EZH2-inhibitor into the brain of lean mice, a less pronounced decrease in food intake and body weight was observed. It was further observed that intermittent fasting improved leptin sensitivity in obese mice, accompanied by increased hypothalamic EZH2 gene expression to normal levels. After brain administration of EZH2-inhibitor, the leptin sensitizing-effect of intermittent fasting was significantly abolished. These results reveal, for the first time, the critical role of EZH2 in maintaining hypothalamic leptin sensitivity in the context of obesity and the benefits of intermittent fasting in recovering EZH2 expression in the brain. The study advances our knowledge of the epigenetic implications of leptin sensitivity and identifies a lifestyle intervention strategy to combat obesity.

Awards Won:

Second Award of $2,000

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