Bench to Bedside

How Targeting Fat Cells' Estrogen Receptors Could Fight Obesity

Tracy Hampton, PhD

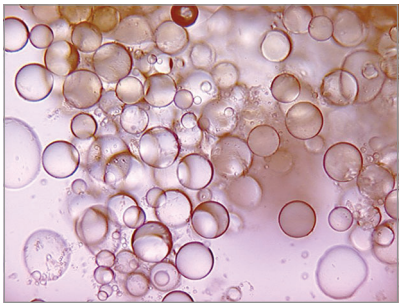
In adipocytes, fat cells, a particular estrogen receptor appears critical for energy-supplying mitochondria to function properly. The discovery points to a potential drug target for boosting fat tissue metabolism, which could help combat obesity and other metabolic conditions.

The research addresses a vexing problem that many middle-aged adults face as they get older—added fat tissue and weight gain due to a slowing metabolism. The problem is especially prominent for women, as estrogen deprivation after menopause leads to an increase in total body fat.

Previous studies have offered a potential explanation in a link between fat accumulation, mitochondria-related dysfunction, and lower expression of the gene *ESR1,* which encodes a form of the estrogen receptor called ERα. Indeed, healthy identical twins who differ by body mass index have different mitochondria-related RNA signatures in their fat cells, indicating a link between mitochondrial dysfunction and adiposity. In addition, *ESR1* expression is reduced in fat tissue from women with obesity and adipocyte ERα deletion disrupts metabolic balance in rodents.

With this knowledge in mind, investigators first examined the clinical relationships between *ESR1* expression and markers of metabolic health. "We hypothesized that low *ESR1* expression in adipose tissue—both variability in genetic inheritance as well as reduced expression as a consequence of environmental factors and aging—underlies susceptibility for obesity and metabolic dysfunction," Andrea Hevener, PhD, a professor in the division of endocrinology, diabetes, and hypertension at the University of California, Los Angeles (UCLA) David Geffen School of Medicine, said in an interview.

In a study published in *Science Translational Medicine*, Hevener and her colleagues discovered that *ESR1* fat tissue expression among more than 700 women and nearly 800 men was inversely associated with abdominal fat mass and positively correlated with insulin sensitivity. Therefore, people with lower levels of *ESR1* expression tended to have higher fat stores and insulin resistance, clinical features of metabolic dysfunction.



The findings in males were unexpected and suggest that men's estrogen levels could affect their body weight more than is currently appreciated. "Although it is known that estrogen action is important for metabolic health, because tissue *ESR1* expression and estradiol levels are much lower in men than women, many have assumed that estrogen action is less important for men compared with women," Hevener said. "Our findings do not support this notion."

The team next examined the mechanistic links between ERα absence, mitochondrial function, and obesity. In mice, selectively deleting the *Esr1* gene from energy-storing white adipocytes and energy-burning brown adipocytes impaired mitochondria. The deletion reduced the expression of Polg1, a subunit of the polymerase enzyme that replicates and transcribes mitochondrial DNA. This led to increased fat in white adipocytes and reduced energy burning in brown adipocytes.

The investigators have now pivoted to studying mice that overexpress *Esr1* in their white and brown adipose tissue. "We want to know if these mice will be protected against high-fat diet–induced weight gain and insulin resistance," Hevener explained. Her team is also studying the relationship between aerobic exercise training and adipose tissue *ESR1* expression. Their goal is to learn if people need ERα and healthy mitochondrial function in adipocytes to lose weight from exercising.

The researchers seek to translate their findings into clinical interventions to help counter obesity and metabolic dysfunction. Targeting ERα and its effects—along the lines of selective estrogen receptor modulators currently used to treat breast cancer and osteoporosis—may be especially promising among women during the menopausal transition. Although premenopausal women are less prone to metabolic disease than men, menopause reverses this protection.

Gail Greendale, MD, who was not involved with the study, is research director of the Iris Cantor–UCLA Women's Health Center and principal investigator for the Study of Women's Health Across the Nation, a multisite effort examining how women's midlife experiences affect their health and quality of life as they age. "Collectively, human and preclinical research suggests that the menopausal transition could be a period of time in which behavioral and potentially therapeutic interventions may be most helpful in restraining deleterious changes in body composition in women," she noted by email. Menopause lowers women's energy expenditure during rest, and this latest study "provides a fat cell–centric explanation for why these reductions occur, and in part, why adipose weight gain may accelerate in women during the menopausal transition," she said.

The study's potential implications for men are also intriguing, said Franck Mauvais-Jarvis, MD, PhD, director of the Diabetes Discovery Research and Sex-Based Medicine Laboratory at Tulane University School of Medicine. "We know that testosterone needs to be converted to estrogens to prevent abdominal fat accumulation in men and that men with mutations in ERα accumulate abdominal fat," he said in an email. More research is needed to explore the full range of metabolic effects of estrogens and their receptors in both women and men, he added. ■

Note: Source references are available through embedded hyperlinks in the article text online.

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