This is your brain on estrogen

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It's no secret that women often gain weight as they get older. The sex hormone estrogen has an important, if underappreciated, role to play in those burgeoning waistlines.

Now, researchers reporting in the October Cell Metabolism, a Cell Press publication, have traced those hormonal effects on metabolism to different parts of the brain. The findings may lead to the development of highly selective hormone replacement therapies that could be used to combat obesity or infertility in women without the risks for heart disease and breast cancer, the researchers say.

"When women approach menopause, they gain weight in fat and their energy expenditure goes down," says Deborah Clegg of the University of Texas Southwestern Medical Center. Estrogen levels decline and women grow increasingly susceptible to obesity and metabolic syndrome.

Estrogen acts on receptors found throughout the body, in fat, on ovaries and in muscle. But when it comes to the hormone's influence on metabolism, Clegg suspected receptors in the brain.

Others had traced the effects of estrogen on energy balance specifically to estrogen receptor-α (ERα). When her team deleted those receptors from the entire brains of mice, "we got very, very fat mice," Clegg said. The animals consumed more calories and burned less.

The researchers showed female mice lacking ERα in one part of the brain (the hypothalamic steroidogenic factor-1 or SF1 neurons) gained

weight without eating any more. Loss of ERα from another brain area (the hypothalamic pro-opiomelanocortin or POMC neurons) had the opposite effect: animals ate more without gaining weight. Loss of ERα receptors in those same neurons also led to various problems in ovulation and fertility.

The findings suggest that drugs developed to specifically target estrogen receptors in the brain might offer a useful alternative to hormone replacement therapies that hit receptors throughout the body. The researchers say they would like to continue to isolate other estrogen-related effects and symptoms, for instance, on hot flashes and cognition.

"The more we know about estrogen's sites of action, the more likely it is we could develop designer hormone replacement therapies targeting tissue X, Y or Z," Clegg said.

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