The stress of dieting: what a rat model may tell us about weight loss in women

In the United States, obesity and concomitant diseases such as hypertension and diabetes have soared in older adults—and obesity is especially pronounced in women after menopause. Numerous strategies are used to combat excess weight, with the most common being dieting. When eating is reduced, stores of ‘fuels’ are mobilized, allowing the needs of the body to be met and contributing to initial weight loss. However, physiological processes change with time on a diet, reducing the utilization of fuels and mitigating the weight loss benefits of dieting. As a result, the long-term success of dieting remains questionable. Numerous studies of humans and laboratory animals have shown that the ovarian hormone, estrogen, reduces eating and body weight; nevertheless, it is unclear whether the lack of estrogen impacts post-menopausal women’s weight loss success while dieting. Therefore, to determine whether replacing estrogen would facilitate weight loss on a diet, we conducted studies in female rats that had undergone ovariectomy and were restricted to feeding for two hours each day to mimic dieting.

Fig. 1.

Restricted feeding caused weight loss, but rats that had estrogen replacement lost more weight than rats that did not receive estrogen. Interestingly, the enhanced weight loss in estrogen-treated rats occurred despite consumption of excessively large meals each day, as typically occurs during dieting. Neuronal activity in areas of the brain that receive input about gastric fill and metabolic hormones increased after eating, regardless of whether rats had estrogen replacement. These findings suggest that the greater weight loss in rats with estrogen did not depend on differences in the amount of food consumed, or on how the brain detects signals related to eating, raising the

question of whether estrogen enhances weight loss during dieting by differentially influencing metabolism of carbohydrates or fats.

Hepatic stores of glycogen were unaffected by estrogen replacement, but circulating levels of glucose were reduced, in accord with previous reports of elevated metabolism in rats with estrogen replacement. Nonetheless, these lower circulating glucose levels were maintained regardless of dieting, and did not depend on insulin levels, which were comparably decreased in dieted rats regardless of estrogen replacement. Neither hepatic nor adipose levels of triglycerides were affected by estrogen replacement or by dieting, but circulating levels of both triglycerides and free fatty acids were impacted by dieting, as expected. However, both were greater in rats that had estrogen replacement, which may indicate a preferential utilization of fats by rats with estrogen replacement during a diet. Nonetheless, elevated triglycerides and free fatty acids did not depend on circulating leptin levels, which were comparable regardless of estrogen replacement.

What, then, accounts for differences in carbohydrate and fat metabolism in rats with estrogen replacement despite the lack of effects on insulin and leptin? Though commonly thought of as a ‘stress hormone’, corticosterone also affects metabolism. Limited metabolic fuels during a diet likely serves as a physiological stressor; accordingly, we measured circulating levels of corticosterone. Corticosterone was elevated in rats with estrogen replacement that were dieted, consistent with the idea that dieting is a physiological stressor. Additionally, corticosterone was further increased after these rats were allowed to eat, implying that consumption of excessively large meals also serves as a stressor. Together, these findings show that the physiological stress of reduced metabolic fuels **and** of eating large meals stimulates corticosterone release in estrogen-treated rats which, in turn, enhances fat metabolism. Thus, estrogen not only may promote weight loss by increasing metabolism in the un-dieted condition, but also may promote greater weight loss during the physiological stress of dieting via the metabolic effects of corticosterone.

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