Estrogen Sulfotransferase: Intracrinology Meets Metabolic Diseases

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Over the past two decades, the female hormone 17β-estradiol (estrogen) has emerged as an important contributor to energy homeostasis in both males and females. Early clinical evidence involved the observation that men lacking estrogen synthesis secondary to mutations in aromatase—the enzyme that converts androgen to estrogen—or men harboring estrogen resistance secondary to mutation of the estrogen receptor (ER)α, develop visceral obesity, insulin resistance, and/or glucose intolerance (1,2). As an experimental confirmation, it was observed that elimination of the aromatase or ERα genes in male and female mice produced the same metabolic syndrome as in humans (3,4). Thus, it is reasonable to assume that although men have lower circulating estrogen concentrations than premenopausal women, aromatization of circulating androgen to estrogen in target metabolic tissues equilibrates cellular estrogen concentrations, and ER activation is critical in both sexes in promoting fuel homeostasis (5). This is consistent with the paradigm that estrogen functions as a circulating hormone in premenopausal women. Conversely, in men and in postmenopausal women—in whom estrogen concentrations are low—estradiol does not function as a hormone; instead, it is synthesized in extragonadal sites such as breast, brain, bone, and fat where it acts locally as a paracrine or intracrine factor (6). Thus, in men and in postmenopausal women, the driver of estrogen action is not circulating estrogens; rather, it depends on estrogen biosynthesis from a circulating source of androgenic precursors such as testosterone. A logical consequence of these observations is that estrogen metabolism or inactivation that shortens the duration of estrogen activity is an essential parameter of cellular estrogenic output.

Estrogen sulfotransferase (EST) is a cytosolic enzyme that provides a molecular switch in target cells to inhibit estrogen activity by conjugating a sulfonate group to estrogens, thereby preventing binding to the ER and enhancing estrogen urinary excretion (7). Thus, EST protects male reproductive tissues from estrogen-induced feminization. With regard to metabolism, EST is not detectable in white adipose tissue (WAT) of normal-cycling female mice but is highly expressed in male WAT and is induced by testosterone in both sexes (8). Transgenic female mice overexpressing EST in adipose tissue at the level of males—which inactivates estrogen in this tissue—show impaired adipocyte differentiation and smaller WAT depots in subcutaneous and parametrial areas associated with WAT insulin resistance, a phenotype reminiscent of partial lipoatrophy (9). EST is also expressed in human subcutaneous adipose tissue.

In patients with obesity and metabolic syndrome, EST correlates with the expression of proinflammatory factors, suggesting that excess estrogen inactivation in WAT may predispose these individuals to the metabolic syndrome (10). In addition, early work from Leiter et al. (11) first reported that EST is markedly induced in the liver of insulin-resistant and diabetic *db*/*db* mice, again suggesting that estrogen inactivation in the liver may participate in insulin resistance. In a study featured in this issue of *Diabetes*, Gao et al. (12) reveal that eliminating EST in female mouse models of type 2 diabetes induced by genetic leptin deficiency (*ob*/*ob*), glucocorticoid exposure, or high fat feeding improves glucose homeostasis. The major effect seems to rely on the loss of liver EST expression that restores hepatic estrogen action, ameliorating insulin resistance and insulin's ability to suppress hepatic glucose production (12). Interestingly, the antidiabetic effect of EST elimination was not observed in *ob*/*ob* males. In fact, EST elimination in *ob*/*ob* males produced adipose tissue inflammation, which aggravated the diabetic phenotype by provoking pancreatic islet inflammation and β-cell failure (12). EST elimination did not produce β-cell failure via a direct islet effect since EST is not expressed in islets (12), and estrogen action in islets would be expected to improve β-cell function and survival (13–17). Rather, β-cell failure was associated with WAT estrogen excess that provoked local WAT macrophage infiltration and WAT inflammation followed by β-cell macrophage infiltration and apoptosis. An obvious explanation is that EST expression is high in male WAT (8) to protect from excessive estrogen actions. Thus, EST suppression has produced WAT estrogen excess leading to inflammation. Consistent with this possibility is the observation that estrogen treatment leading to high blood concentrations produces WAT inflammation even in females (18).

It is now recognized that estrogen activation of its main receptor, ERα, is important in selective cellular populations to prevent diabetes and obesity. Thus, elimination of ERα in hypothalamic neurons impairs energy homeostasis (19), knockout of ERα in macrophages produces a metabolic syndrome and accelerates atherosclerosis (20), and null deletion of ERα in pancreatic islets impairs insulin biosynthesis and β-cell survival and predisposes to glucolipotoxicity (13–17). The study by Gao et al. adds a novel dimension of estrogen intracrinology to our knowledge of metabolic diseases. It is now emerging that estrogen output depends not only on ER signaling and sensitivity itself. Indeed, upstream of the ER, more focus should be given to the availability of androgenic precursors, the activity of

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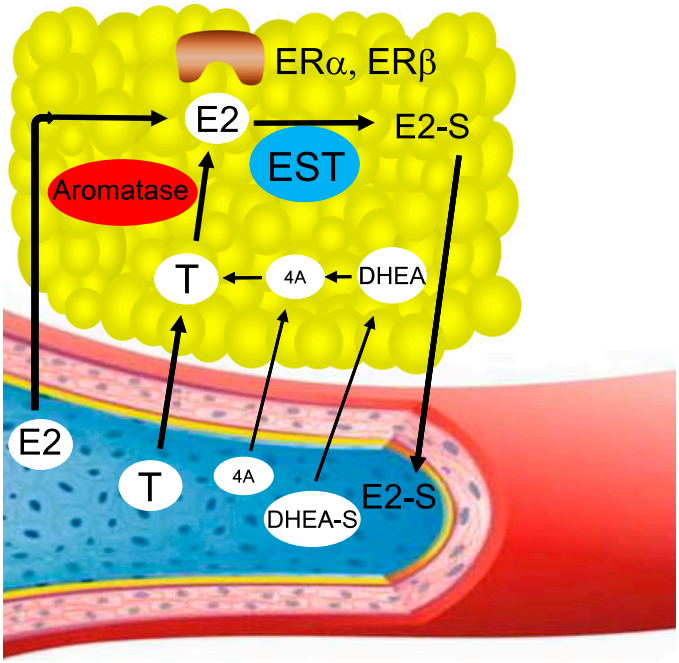

FIG. 1. Intracrinology of estrogen in adipose tissue. In premenopausal women, estrogen (E2) functions as a circulating hormone. Conversely, in men and in postmenopausal women, E2 is locally synthesized from androgenic precursors such as testosterone (T), androstendione (4A), or dehydroepiandrosterone (DHEA) in extragonadal sites such as breast, brain, bone, and fat. Cellular estrogenic output depends on *1*) the ER signaling and sensitivity, *2*) the activity of enzymes such as aromatase involved in the biosynthesis of E2 from androgenic precursors, and *3*) the inactivation of E2 in E2 sulfate (E2-S) by the EST.

enzymes involved in the tissue-selective biosynthesis of estrogen, and importantly, the metabolism and inactivation of estrogen by EST that seems to be dysregulated in diabetic models (Fig. 1).

Several questions remain unanswered. What is the mechanism of WAT and islet inflammation in EST-deficient diabetic male mice? Is inflammation secondary to excessive estrogen action in adipocytes or is it the consequence of high estrogenic activity in macrophages from WAT and islets? Also of importance is the relevance to humans. Is EST overexpressed in liver from type 2 diabetic patients, and is EST expressed to higher levels in WAT of men? A major difference between mice and humans is the absence of aromatization in WAT of mice. Thus, WAT from male mice does not benefit from testosterone aromatization into estrogen; rather, male mice WAT relies on low circulating estrogen (unlike humans). Therefore, the function of EST in humans may not be as sexually dimorphic as in mice. Finally, endocrine disrupting chemicals such as polychlorinated biphenyls are powerful inhibitors of EST (21). Studies are needed to determine whether polychlorinated biphenyls can have the same sex-specific effect on type 2 diabetes as observed in the study by Gao et al. (12).

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