Commentary

MOLECULAR METABOLISM

Mix 'n' match estrogens*

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Female sex hormones such as estrogen and progesterone are not only essential regulators of reproductive functions but play numerous physiological roles. Loss of endogenous hormone production after menopause can cause uncomfortable symptoms such as hot flashes and lead to the development of osteoporosis or cardiovascular disease. In order to maintain these beneficial anti-aging effects, various estrogen receptor ligands have been clinically tested for their use as postmenopausal hormone replacement therapy. To avoid potentially harmful stimulation of breast or endometrial cell proliferation, so-called selective estrogen receptor modulators or SERMs, have been developed. These compounds do not display the same profile as pure agonists or antagonists but can have differential effects in different tissues [1]. In this issue of Molecular Metabolism, Kim et al. investigate the use of the SERM bazedoxifene (BZA) in combination with estrogens to counter the weight gain and glucose intolerance associated with menopause [2]. The authors use ovariectomized mice fed a high fat diet and treated with various combinations of estrogen receptor (ER) ligands to study their effects on energy homeostasis. They demonstrate that a tissue-selective estrogen complex (TSEC) consisting of BZA plus conjugated equine estrogen, improves glucose homeostasis and insulin sensitivity without affecting the reproductive system. This therapy (BZA + CE) has been successful in the prevention of postmenopausal symptoms in phase III clinical trials, but its metabolic effects have not yet been studied [3,4]. Estrogen therapy for metabolic dysfunction is not a new concept [5,6], but, interestingly, the data presented by Kim et al. suggest that estrogens and BZA act via different pathways to increase hepatic lipid oxidation. As shown by ELISA and qRT-PCR assays on liver homogenates, only treatment with classical estrogens increases FGF21 expression levels, whereas BZA-containing complexes induce Sirtuin-1, PPARα and AMPK. FGF21 is known for its insulin-sensitizing potential and significant beneficial effects on several metabolic parameters [7]. Sirtuin-1 is the founder of the famous sirtuin deacetylase family, whose members play important roles in the regulation of lifespan and insulin sensitivity [8]. Likewise, the energy-sensing kinase adenosine monophosphate (AMP)-activated protein kinase (AMPK) has emerged as a central mediator of metabolism. AMPK responds to changes in the AMP:ATP ratio by promoting glucose and fatty acid catabolism or by inhibiting anabolic pathways. Linked to these pathways is the peroxisome proliferator-activated receptor PPARα, another nuclear receptor family member known to regulate fatty acid oxidation [9]. Activation of all of these pathways serves to enhance hepatic lipid oxidation and to elevate overall metabolic rate, and could explain the prevention of weight gain and insulin resistance observed during the experiments.

How FGF21 activation in response to estrogens can achieve these effects to a similar extent as BZA-mediated SIRT1/PPARα/AMPK induction remains an open question. In the future, it will be revealing to determine the molecular mechanism for these observations. One might speculate how these ligands induce distinct target genes in the liver, for example by differential binding of ERα to target sites in the enhancer regions of *Fgf21* versus *Sirt1/PPARα*. That would require BZA-bound ERα to bind to a different set of cis-regulatory elements than estrogen-ligand receptor. Another possibility would involve the activation of signaling pathways that indirectly influence hormone responses. It would also be interesting to test whether different receptor conformations lead to differential recruitment of coregulators. Finally, it is still unknown if these differential effects are only achieved via liver-specific pathways, or if systemic TSEC administration affects other systems such as adipose tissue, skeletal muscle or neuronal networks.

Taken together, these findings provide mechanistic insight into ER-regulated metabolic gene programs and will hopefully provide a useful weapon in the battle against metabolic syndrome.

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