MOLECULAR METABOLISM

Commentary

Estradiol and appetite: To eat or not to eat

In addition to their extensive role in reproduction and on the hypothalamic-pituitary-gonadal (HPG) axis, estrogens are highly involved in the regulation of energy homeostasis by modulating both food intake and energy expenditure [1,2]. Reduced levels of estradiol (E2, the main ovarian estrogen) after menopause in women and ovariectomy (OVX) in rodents lead to hyperphagia and reduced energy expenditure (EE) inducing overall weight gain. On the other hand, E2-replacement therapy prevents or reverses those effects [1—3]. To generate aforesaid beneficial metabolic effects, E2 acts at peripheral and central levels, especially in hypothalamic nuclei, such as the arcuate (ARC), where it inhibits feeding [4,5] and the ventromedial (VMH), in which it stimulates brown adipose tissue (BAT) thermogenesis, promoting EE [3,4].

E2 and other estrogens, such as estrone (E1) and estriol (E3) are lipophilic molecules that quickly diffuse through biological membranes and interact with intracellular receptors. Two types of nuclear estrogen receptors (ER) were described: ERα and ERβ. Both ERs behave as ligand-dependent transcription factors: the binding of specific ligands induces ER dimerization, allowing their interaction with estrogen response elements (ERE) in the promoter region of target genes [1,2]. The anti-obesity effects of estrogen have also been demonstrated by global and conditional null mice of ERα, which totally and partially, respectively, recapitulate most of the effects of OVX-associated estrogen deficiency [4]. In addition to its transcriptional role, ERα has been described to act extracellularly to promote short-term quick actions, for example negative feedback modulation of pituitary gonadotropin secretion [1,2].

This "classical view" of estrogen action has been largely considered as a canonical dogma as it nicely integrates not only the actions of E2 on energy balance, but also its effects on the HPG axis. Moreover, the adaptive metabolic responses to estrogen deficiency in puberty, estrous cycle and pregnancy, all of them states characterized by major changes in the estrogen milieu, are also part of this canonical E2-mediated regulation [1,2]. In this issue of *Molecular Metabolism,Yu et al.* add new knowledge that challenges that dogma by showing a bidirectional role of estrogen on feeding depending upon the energy state [6]. In fact, they show that endogenous E2 is required to sustain refeeding in fasted female mice and that this effect is directly mediated by the membrane-bound ERα, and not by its transcriptional activity. Moreover, they demonstrate that membrane-bound ERα activity is essential for hypothalamic responses to hypoglycemia.

Initially, by using OVX mice (totally depleted of endogenous estrogens) fed *ad libitum* treated with E2, they observed, as expected, that OVX-induced hyperphagia was corrected by hormonal replacement. Notably, OVX mice fasted overnight, displayed a dichotomic response: treated with vehicle, the refeeding was lower than Sham (control) mice; however, when treated with E2, their refeeding pattern concurred with that of Sham mice. This indicated that endogenous E2 was required to maintain starvation-induced refeeding. Next, they aimed to investigate whether the refeeding orexigenic action was mediated by membrane-bound or transcriptional actions. In this sense, they took advantage of two mutant mouse models: ERα-C451A, deficient in membrane-bound activity, and ERα-AF2^0, exhibiting impaired transcriptional actions. Their data showed that overnight fasting induced a decreased refeeding in ERα-C451A mice, an effect that was absent in ERα-AF2^0, highlighting the central role of membrane bound activity in maintaining refeeding responses. Although those experiments provide interesting preliminary evidence, they have a major limitation: it remains unclear whether the opposite refeeding responses could be artifactual and actually related to body weight modulation, as both OVX and ERα-AF2^0 mice were heavier than their respective controls. To overcome that limitation, authors induced central glucopenia through intracerebroventricular (ICV) injections of 2-Deoxy-D-glucose (2-DG), a glucose analog in which the 2-hydroxil group is replaced by hydrogen, preventing its glycolysis degradation and use. Thus, 2-DG ICV induced a transient state of central glucopenia, mirroring fasting without inducing weight loss. Remarkably, although 2-DG-induced feeding in ERα-AF2^0 was comparable to littermates, it was significantly diminished in ERα-C451A, supporting the idea that E2 actions on refeeding were dependent on membrane-bound ERα activity. Next, to gain anatomical and functional insight of their findings, they investigated the effect of neuronal firing of ERα neurons in the ARC and VMH of wild-type, ERα-C451A and ERα-AF2^0 mice. Their data showed that propyl pyrazole triol (PPT; a specific ERα agonist)-induced firing was decreased in ERα, specifically in ARC and VMH neurons of ERα-C451A, but not in wild-type and ERα-AF2^0 mice. In keeping with this, glucose-inhibited (GI)-ERα neurons in the ARC and GI and glucose-excited (GE)-ERα neurons in the VMH of ERα-C451A mutant mice also had attenuated firing responses. Overall, this evidence demonstrates that the membrane-bound, but not the transcriptional, role of ERα was required to sustain the glucose-sensing functions in the ARC and the VMH and, therefore, the refeeding adaptation to starvation (Fig. 1).

These findings are highly consistent as they demonstrate for the first time a dichotomic effect of E2 on both feeding responses and glucose sensing. This is relevant for several reasons. Firstly, they clearly indicate that the effect of estrogen depends on energy status and that in a food-deprived scenario, which actually mimics natural evolutive conditions in a better way than animal housing or human lifestyle, E2 is needed to elicit and efficiently adapt to refeeding. However, when animals are satiated, E2 inhibits feeding, allowing a balanced metabolic/energetic situation. This is of interest in the clinical context. For example, it is known that women suffering from anorexia nervosa (AN) display decreased appetite and impaired responses to fasting, associated with an estrogen-deprived state and amenorrhea [7]. Thus, it is possible that the lack of circulating E2 could impair refeeding responses in these subjects. In line with this, recent data have reported that blunted hypothalamic glucose reactivity might be related to the pathophysiology of AN [8]. Whether that effect may be related to depleted E2 levels would require further investigation. Secondly, this study establishes a new basis for the molecular mechanisms mediating E2 actions on energy balance. While transcriptional actions of ERα mediate E2's anorectic effect in *ad libitum* fed conditions [9], the current evidence shows that refeeding responses (induced either by starvation or glucopenia) depend on membrane-bound actions. Moreover, this study clearly reinforces the idea that the central action of E2 on ARC and VMH neurons [3—5] plays a major role in the modulation of energy balance. In this sense, a limitation of the current

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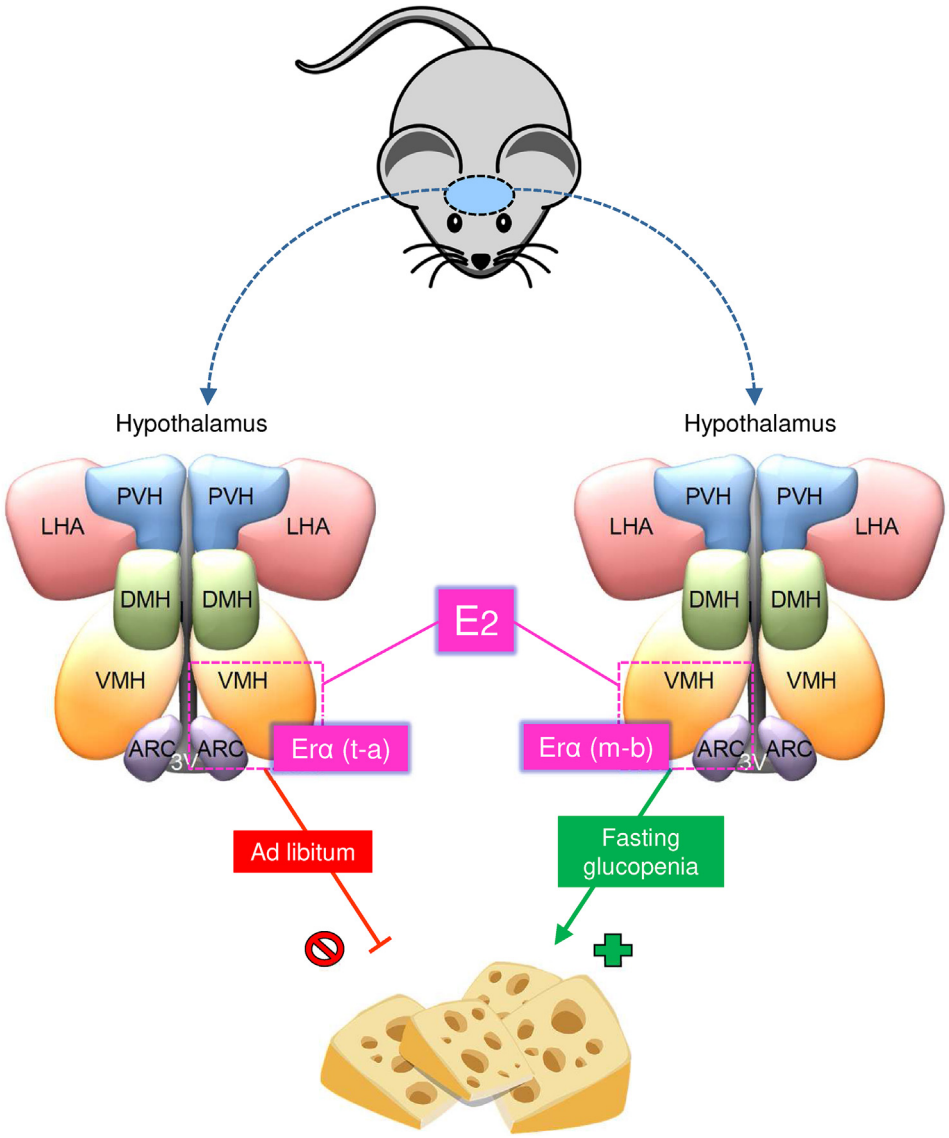

Figure 1: Estradiol promotes bidirectional actions on feeding depending on nutritional status. The canonical view is that estradiol (E2) acts in the hypothalamus to inhibit food intake through estrogen receptor alpha (ERα) transcriptional activity (t-a). A recent study from *Yu et al.* demonstrates that the effect of E2 on feeding depends on the nutritional status. In an *ad libitum* food scenario, E2 inhibits feeding. However, after fasting or central glucopenia, E2 promotes refeeding, notably through ERα membrane-bound (m-b) activity. 3V: third ventricle; ARC: arcuate nucleus of the hypothalamus; DMH: dorsomedial nucleus of the hypothalamus; LHA: lateral hypothalamic area; PVH: paraventricular nucleus of the hypothalamus; VMH: ventromedial nucleus of the hypothalamus.

investigation, that will need to be addressed in further studies, is the molecular signature of ARC and VMH ERα neurons, as well as the molecular pathways regulating membrane-bound actions. In this sense, some candidates, such as AMP-activated protein kinase (AMPK) [3], mechanistic target of rapamycin (mTOR) [5], and endoplasmic reticulum stress [10], might be involved.

In summary, the study by *Yu et al* challenges the classical dogma and provides new insights into the dichotomic actions of E2 on the modulation of energy balance. Moreover, it demonstrates that membrane-bound capabilities of ERα play a major role on energy homeostasis. The understanding of the molecular details of this interaction and whether these effects are extensible to other E2 actions, such as the modulation of BAT thermogenesis, will be important for the development of new therapeutic strategies against obesity and conditions of estrogen deficiency.

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CONFLICTS OF INTEREST

Author declares no competing (financial, personal, or professional) interests.

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