Review

MOLECULAR METABOLISM

Central regulation of energy metabolism by estrogens

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ABSTRACT

Background: Estrogenic actions in the brain prevent obesity. Better understanding of the underlying mechanisms may facilitate development of new obesity therapies.

Scope of review: This review focuses on the critical brain regions that mediate effects of estrogens on food intake and/or energy expenditure, the molecular signals that are involved, and the functional interactions between brain estrogens and other signals modulating metabolism. Body weight regulation by estrogens in male brains will also be discussed.

Major conclusions: 17β-estradiol acts in the brain to regulate energy homeostasis in both sexes. It can inhibit feeding and stimulate brown adipose tissue thermogenesis. A better understanding of the central actions of 17β-estradiol on energy balance would provide new insight for the development of therapies against obesity in both sexes.

1. INTRODUCTION

Besides the regulation of the reproductive function, estrogens have a key role in the central regulation of the energy homeostasis including both modulation of feeding behavior and energy expenditure [1–3]. Increased life expectancy implies that many women will live an increasing number of years in a state of ovarian insufficiency. This leads to a steady surge in obesity incidence reaching a staggering figure of more than 70% in women older than 60 years [4]. Although, the interrelationship between estrogen deficiency and obesity was the subject of some discussion, pooled data derived from 107 trials showed that hormone-replacement therapy in menopausal patients led to reduced abdominal obesity, insulin resistance and new-onset diabetes [4], providing a cause–effect relationship between estrogen deficiency, obesity, and metabolic complications. However, this application has been hampered mainly due to side effects of 17β-estradiol, including venous thrombosis and endometrial and breast cancers [5,6]. One solution is to better understand the mechanisms of estrogenic actions, which may facilitate development of novel therapies that provide anti-obesity benefits with fewer side effects.

Central action of 17β-estradiol in metabolic control has been a focus of many research groups and has been summarized by a number of recent review articles [7–9]. In this review, we will recap current literature regarding distinct brain regions that mediate 17β-estradiol's effects on feeding and energy expenditure. Importantly, we will discuss advances in our understanding about the molecular signals initiated by 17β-estradiol in neurons that are involved in body weight control. Further, the functional interactions between 17β-estradiol and other appetite-regulatory signals will also be discussed. 17β-estradiol also acts in the peripheral tissues to regulate energy homeostasis, and the audience is directed to read the other excellent reviews in this special issue of *Molecular Metabolism*.

2. BRAIN ESTROGENS SUPPRESS FEEDING BEHAVIOR

The anti-obesity actions of estrogens have been well documented. For instance, surgical depletion of endogenous estrogens by ovariectomy (OVX) causes increases in food intake, body weight, and body fat in female animals; 17β-estradiol administration in OVX animals can reduce feeding and prevent obesity [10–15]. Bazedoxifene (a selective estrogen receptor modulator), combined with conjugated equine estrogens, has been used to provide estrogen-mediated benefits while reducing endometrial and breast cancer risk in post-menopausal women [16]. Interestingly, this regimen has been shown to reduce body weight but does not alter feeding in OVX mice [17]. The lack of effect on feeding by the conjugated equine estrogens is likely due to minimal penetration of estrogens to the brain [18], further highlighting the essential actions of brain estrogens in the regulation of feeding.

Anti-obesity effects of 17β-estradiol appear to be primarily mediated by estrogen receptor-α (ERα), one of the *"classical"* estrogen receptors. Mutations in the ERα (Esr1) gene cause obesity in mice and humans [19,20]. Mice lacking ERα are not responsive to anti-obesity effects of 17β-estradiol [12]. In particular, injections of 17β-estradiol into various brain regions decrease food intake in animals [21,22].

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Review

These early observations were further supported by findings from genetic mouse models. For instance, Clegg and colleagues generated mice lacking ERα only in the brain, which developed obesity [23]. Increased food intake, low energy expenditure, and low locomotion were observed in these mutant mice [23]. Interestingly, deletion of ERα in the brain also impairs negative feedback regulation by estrogens, resulting in higher 17β-estradiol in blood [23]; yet, the elevated 17β-estradiol level in the circulation fails to prevent obesity, suggesting that brain ERα plays a predominant role in the regulation of energy balance. Many brain regions express high levels of ERα, including the arcuate nucleus of hypothalamus (ARC), the nucleus of solitary tract (NTS), the dorsal raphe nuclei (DRN), and the medial preoptic area (MPOA) [24]. As discussed below, recent efforts using genetic mouse models have dissected out the physiological functions of ERα in some of these brain regions in the regulation of energy homeostasis.

2.1. ERα in POMC neurons

Pro-opiomelanocortin (POMC) neurons in the ARC are the first order neurons in the hypothalamus that sense and integrate nutritional and hormonal cues to regulate energy balance [25]. A portion (20—30%) of ARC POMC neurons co-express ERα [23,26,27]. 17β-estradiol was reported to enhance glutamatergic synapses onto POMC neurons, which results in stronger miniature excitatory postsynaptic currents [28]. Further, 17β-estradiol acutely activates firing of POMC neurons, which can be blocked by an inhibitor of the inwardly rectifying K^+ channels [29]. Propylpyrazole triol (PPT, an agonist of ERα) depolarizes POMC neurons that express ERα, but not those without ERα [7]. Importantly, female mice with ERα selectively deleted in POMC neurons are hyperphagic and develop modest obesity [23]. 17β-estradiol-induced suppression in food intake is attenuated in these mutant mice [30]. Thus, 17β-estradiol's anorexigenic effects are at least partly mediated by POMC neurons that express ERα [23].

2.2. ERα in the NTS

The NTS, a brainstem center for satiety signals, also expresses high levels of ERα [24,31,32]. Increased NTS neural activities have been reported to be associated with 17β-estradiol-induced anorexia in female mice [12,33]. Importantly, deletion of ERα blocks these responses [12,33]. In addition, microinjections of 17β-estradiol into the NTS enhance feeding-suppressing effects of cholecystokinin (CCK), a well-known satiety hormone secreted from the gut [34]. Therefore, NTS ERα signals appear to also mediate inhibitory effects of 17β-estradiol on feeding.

2.3. ERα in the DRN

The DRN expresses ERα [24], and the majority of these ERα-positive neurons are shown to be serotonin (5-HT) neurons [35]. 17β-estradiol treatment enhances neural activities within the DRN [36,37]; consistently, DRN 5-HT neurons are shown to be stimulated by PPT, an effect that can be blocked by genetic deletion of ERα [35]. Interestingly, female rats receiving 17β-estradiol injected into the DRN display anorexigenic responses [38]. Deletion of ERα selectively in 5-HT neurons blocks 17β-estradiol's effect of suppressing binge-like eating [35]. These observations indicate that 17β-estradiol can act upon DRN 5-HT neurons to inhibit food intake.

Roles of ERα in other brain regions remain elusive. For instance, 17β-estradiol injected directly into the MPOA suppresses feeding [38]. Similarly, suppression of food intake and body weight was observed when OVX female rats received 17β-estradiol implanted in the paraventricular nucleus of the hypothalamus (PVH) [21]. Supporting a role of the PVH, subcutaneous 17β-estradiol administration fails to reduce feeding in rats with the PVH being lesioned [39]. However, findings regarding the PVH were not duplicated by others [40]. Further, it is worth noting that only low levels of ERα are present in the PVH [24]. Importantly, 17β-estradiol is known to regulate food-associated reward [9], suggesting a role for ERs expressed by brain reward centers, including the nucleus accumbens (NAc) and the lateral hypothalamus (LH) [24]. Indeed, 17β-estradiol was shown to influence metabolism of several monoamines (e.g. dopamine, 5-HT, and norepinephrine) in the NAc [41], although effects of these estrogenic actions in the NAc on feeding behavior remain to be examined. Collectively, the current literature validated a few regions in the female brain (e.g. ARC, NTS and DRN) as important nodes that respond to 17β-estradiol and mediate its signals to suppress feeding; however, the roles of additional brain regions warrant further investigations.

3. BRAIN ESTROGENS STIMULATE ENERGY EXPENDITURE

3.1. BAT thermogenesis

In mammals, including humans, the main place for *adaptive thermogenesis* is the brown adipose tissue (BAT) [42—45]. In small mammals living in sub-thermoneutral environment, large quantities of active BAT are encountered [42,43]. In humans, BAT presence was shown to be inversely correlated with increasing age. However, recent evidences have demonstrated the presence of functional brown fat depots in healthy adults [44,46—49]. Histologically, brown adipocytes exhibit numerous small lipid droplets and a very high mitochondrial content. Through the movement of electron across the respiratory chain, the mitochondria produce energy temporarily stored as a proton gradient across the inner mitochondrial membrane. Later, the power derived from this proton gradient is used to generate ATP from ADP by the ATP synthase [50—52]. Alternative pathways, occurring in the internal membrane of BAT's mitochondria and involving the uncoupling protein 1 (UCP1), allow the retrograde transport of protons back into the mitochondrial matrix, sidestepping ATP synthase activity and releasing energy as heat [42,43,53].

BAT is regulated by both the central and peripheral nervous system. The sympathetic nervous system (SNS) has a critical role in BAT thermogenesis stimulation [42,43,45,54—56]. Increased firing rate of the sympathetic nerves subserving BAT induces the secretion of norepinephrine (NE) at the nerve terminal, inducing the subsequent activation of G-protein coupled receptors, named β-adrenergic receptors (β-ARs), expressed in the brown adipocytes; mainly the β_3 subtype (β_3-AR). The associated G protein coupled to β_3-AR activates adenylate cyclase (AC), inducing an increase of intracellular cAMP, which subsequently activates protein kinase A (PKA), inducing thermogenesis and downstream activation of p38 mitogen-activated protein kinase (MAPK) [42,45,54]. The acute response of PKA stimulates lipolysis leading to elevated cytosolic free fatty acid (FFA) levels. This FFA increase will occur following the sequential hydrolysis of triglycerides by the adipose triglyceride lipase (ATGL), the hormone-sensitive lipase (HSL; being pHSL the activated form), and the monoacylglycerol lipase (MGL). The FFAs-CoA - FFAs activated to acyl CoAs by acyl-CoA synthetase - are transferred into the mitochondria by the carnitine palmitoyltransferase 1a (CPT1a), where FA oxidation induces NADH and FADH production, which will be oxidized later in the electron transport chain [42,43,45,54].

3.2. Direct effects of 17β-estradiol on BAT

For the first time, in the 70s, it was shown that 17β-estradiol could bind to both interscapular brown and white adipocytes [57]. Physiological evidence demonstrated that 17β-estradiol could lead to

