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Estrogen, astrocytes and the neuroendocrine control of metabolism

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Abstract Obesity, and its associated comorbidities such as type 2 diabetes, cardiovascular diseases, and certain cancers, represent major health challenges. Importantly, there is a sexual dimorphism with respect to the prevalence of obesity and its associated metabolic diseases, implicating a role for gonadal hormones. Specifically, estrogens have been demonstrated to regulate metabolism perhaps by acting as a leptin mimetic in the central nervous system (CNS). CNS estrogen receptors (ERs) include ER alpha (ERα) and ER beta (ERβ), which are found in nuclear, cytoplasmic and membrane sites throughout the brain. Additionally, estrogens can bind to and activate a G protein-coupled estrogen receptor (GPER), which is a membrane-associated ER. ERs are expressed on neurons as well as glia, which are known to play a major role in providing nutrient supply for neurons and have recently received increasing attention for their potentially important involvement in the CNS regulation of systemic metabolism and energy balance. This brief overview summarizes data focusing on the potential role of astrocytic estrogen action as a key component of estrogenic modulation responsible for mediating the sexual dimorphism in body weight regulation and obesity.

Keywords Obesity · Sexual dimorphism · Estrogens · Leptin · Astrocytes

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1 Introduction

Obesity has become a global health challenge of staggering proportions, and its prevalence continues to increase. Obesity is associated with comorbidities including type 2 diabetes, the metabolic syndrome, cardiovascular disease, cancer, sleep apnea and osteoarthritis [1]. Obesity is believed to be associated with a pattern of moderate but chronic inflammatory processes in both peripheral organs and the central nervous system (CNS), which contributes to leptin and insulin resistance [2].

Obesity affects males and females differently. The metabolic response to dietary regimes and pharmacological treatments for obesity differ between the sexes [3–9]. Differences in the levels of circulating gonadal steroids are critical for many of the sexually dimorphic characteristics. Estrogens are sex steroid hormones with known essential roles in reproduction, but additionally, estrogens mediate protective actions against body weight gain and metabolic diseases [10–15]. Estrogens exert their influence on diverse target tissues, including the CNS where they bind and activate receptors in

neurons and astrocytes [16–18]. These sex steroids also have neuroprotective and anti-inflammatory actions in the CNS, with some of these actions being mediated by effects on glial cells [19, 20], which express both estrogen receptors (ER) isoforms, ERα and ERβ [21]. Astrocytes participate in diverse neuroendocrine functions [22, 23], including CNS regulation of systemic metabolism as well as in the pathogenesis of metabolic diseases [24–26]. Although the role of estrogens in the control of energy balance has been studied extensively, the exact neuroendocrine circuits and intracellular signaling pathways implicated in estrogenic neuroendocrine regulation of systemic metabolism remain to be completely characterized. This review provides a brief overview of the potential role of neuroendocrine estrogen signaling as a mediator of the sexual dimorphism in body weight regulation and obesity with a specific focus on the emerging role of estrogen action in astrocytes.

2 Sexual dimorphism and metabolic control

Males and females differ in where body fat is stored, endocrine secretory patterns, and how the brain responds to hormonal signals that regulate food intake and body weight [13, 14, 27, 28]. Sex differences in body fat distribution are evident after puberty [29, 30]. Females predominantly accumulate subcutaneous body fat, resulting in a "pear" shape, while males deposit more body fat viscerally, resulting in an "apple" shape [31]. However, these sex differences in body fat distribution diminish after estrogen deficiency caused by menopause. Post-menopausal females tend to accumulate more visceral fat and become more susceptible to metabolic disorders than pre-menopausal women [32, 33].

The sexual dimorphism in fat content and distribution has functional implications in regulating body weight [7]. Body adiposity and body fat distribution are factors that contribute to determining baseline levels of circulating cytokines and adipokines, such as leptin [34], and regulate hormone sensitivity, inflammatory responses, and even circulating levels of steroids [7]. However, the sexual dimorphism in body weight cannot be explained only by differences in body fat composition. For instance, circulating leptin levels are higher in females than males, regardless of body fat content [35–37], and sex steroids are involved in the modulation of leptin levels [38]. Taken together, these findings suggest that sex hormones, potentially estrogens, may be involved in body weight homeostasis.

3 Role of estrogens in metabolic control

Estrogens act as modulators of metabolism by regulating body weight, fat storage, energy expenditure, feeding behavior and glucose and lipid metabolism in both sexes [10–13, 15, 27, 39–42]. Estrogens exert their actions predominantly through two ERs, ERα and ERβ, which are classically thought to act as nuclear receptors [43]. Acting as transcription factors, ERs regulate numerous downstream genes, including those involved in cell cycle regulation, proliferation and apoptosis [44]. In addition to their actions as nuclear transcription factors, a portion of estrogen-induced signaling can be attributed to an extranuclear, non-genomic pathway and the activation of rapid phosphorylation cascades, which, in addition to membrane-associated ERα and ERβ (mERs), may be mediated via the G protein-coupled ER (GPER).

Circulating levels of 17β-estradiol (E_2), the major physiological form of estrogen, correlate inversely with visceral fat mass [45], protecting against adipose accumulation and diminishing pro-inflammatory signaling [11, 39, 40, 42]. The loss of E_2, either from menopause [41, 42], ovariectomy (OVX) [11], or the inactivation of aromatase, an enzyme essential for E_2 synthesis [46], leads to increased food intake and adiposity, both of which can be reversed by physiological E_2 replacement [47]. These restorative effects of E_2, however, are blocked in ERα knockout (ERαKO) mice regardless of sex [15]. Moreover, intracranial injection of E_2 in rats leads to anorexia. These observations indicate that E_2, similar to leptin, has direct anorexigenic functions in the CNS, specifically in the ventral medial (VMN) and arcuate nuclei (ARC) of the hypothalamus [48, 49].

The hypothalamus plays a key role in controlling energy and weight homeostasis. This brain area receives afferent and sends efferent messages to the periphery in order to regulate body weight by precisely balancing the intake of food, energy expenditure and nutrient deposition in adipose tissue. Early studies showed how lesions in specific hypothalamic nuclei, such as the VMH [50, 51] or the lateral hypothalamic area (LH) [52–54] produced drastic changes in food intake and body weight. More recently, studies have identified other hypothalamic sites, like the ARC, as key targets for hormonal and neuropeptide signals involved in sensing and controlling energy homeostasis [55].

E_2 acts on the hypothalamus through its specific receptor subsets, which are expressed in several hypothalamic nuclei, including the ARC and the VMH. ERα is more abundantly expressed throughout the whole brain compared to ERβ, which coincides with ERα being considered the more relevant ER for regulating energy homeostasis. Mice with mutations in ERα are obese [56] and resistant to the restorative effects of E_2 replacement [15], whereas mice with ERβ deletions maintain a normal body weight [57]. However, ERβ appears to act as a modulator of E_2 actions in the brain since the hypophagic effect of central E_2 is blunted by ERβ gene manipulation [58]. ERα is more abundant in the ARC compared to other relevant nuclei and is predominantly expressed in pro-opimelanocortin (POMC) neurons [48, 59]. Increased circulating estrogens are

directly correlated with ERα mRNA levels in ARC POMC neurons [60] and synaptic input to these neurons [47]. ERα signaling in these ARC POMC neurons appears to mediate a degree of the anorectic actions of estrogens as the selective deletion of ERα in these neurons results in hyperphagia without altering energy expenditure [48]. Conversely, silencing of ERα in the VMH using RNA interference [61] or selective deletion in steroidogenic factor-1 (SF-1) neurons [48] leads to obesity and glucose intolerance as the consequence of reduced energy expenditure with no effect on food intake, which suggests a neuroanatomical segregation of the homeostatic effects of ERα [48].

In addition to its central actions, estrogen signaling also regulates certain peripheral hormones, such as leptin, that influence feeding, meal size and thermogenesis through their actions in the CNS. Leptin is a metabolic hormone, which is generally believed to cross the blood-brain barrier (BBB) to interact with leptin receptors in the hypothalamus and brainstem [62–68], resulting in the inhibition of food intake and increased energy expenditure [63, 65, 67–73]. Although there are at least six alternatively spliced isoforms of the leptin receptor, the long form of the leptin receptor (OB-Rb) is the one primarily involved in metabolic control [74]. Ob-Rb co-localizes with ERα in the ARC [75], suggesting a coordinated interaction, and ARC Ob-Rb mRNA is, in fact, modulated by estrogens [76]. Females have higher circulating levels of leptin compared to males, and these levels are independent of differences in body composition [35–37]. Leptin sensitivity in females varies throughout life depending on basal levels of estrogens, with a direct relationship between estrogen levels and hypothalamic leptin sensitivity [77, 78]. E_2 treatment of both males and OVX females increases central leptin sensitivity [78], indicating a relevant interaction between leptin and E_2, with both hormones exerting similar patterns of metabolic actions in the hypothalamus [47, 79].

4 Role of hypothalamic astrocytes in the control of metabolism

Astrocytes are the most abundant glial cells in the mammalian brain. After the first descriptions of glia as passive supporters of neurons [80], data in subsequent years have revealed considerable evidence suggesting that glia are actively involved and required for effective function of the CNS. Glia are critical to synaptic transmission, regulation of neural immune responses, antioxidant defense, structural and nutritive support of neurons, and neuronal survival [81–87].

The role of glial cells in metabolic control and obesity is an active area of investigation [2, 24–26, 88]. Hypothalamic astrocytes play a crucial role in brain homeostatic control of metabolism due in part to their strategic location close to the BBB. These cells transport and release many substances (e.g. ions, glucose, lactate, fatty acids, ketone bodies) from the peripheral circulation into the brain to provide nutrients for neurons and regulate the extracellular environment [84, 89, 90]. It is well known that hypothalamic neurons respond to hormones and possess the respective receptors, but astrocytes also express receptors for some of the same hormones involved in metabolic control, including leptin and estrogens [21, 91–96].

Astrogliosis, a reactive phenotype of astrocytes characterized by the up-regulation of structural glial proteins such as glial fibrillary acidic protein (GFAP) and vimentin [97], has been detected in the hypothalamus of high fat diet-induced obese rodents [24, 25], and precedes weight gain [25]. Astrogliosis is known to be associated with tissue injury and neurodegenerative diseases [98, 99]. However, the potential role of such reactive gliosis in the pathogenesis of metabolic diseases such as obesity has not yet been clarified. Hypothalamic astrogliosis in obese mice is accompanied by increased cytokine expression [25], weakened leptin signaling in hypothalamic neurons and increased astrocytic ObR expression [91, 100], suggesting that astrocytes are involved in the regulation of leptin signaling.

4.1 Astrocytic estrogen action and metabolic control

Astrocytes are targets for estrogen action [20, 101–105] as reflected by the fact that astrocytes express both ERα and ERβ receptors either on their plasma membranes or intracellularly [21, 92–96]. Activation of the mER initiates a rapid, free cytoplasmic calcium concentration ($[Ca^{2+}]$) flux via the phospholipase C (PLC)/inositol trisphosphate (IP_3) pathway [96]. Recently, the transmembrane ER, G protein-coupled estrogen receptor (GPR) 30, was reported to mediate non-genomic and rapid estrogen signaling in astrocytes [106–108], contributing to the neuroprotective effects of E_2. Despite these reports, ERα appears to be primarily responsible for the signaling in astrocytes [94, 101, 108, 109]. Kuo and colleagues observed that the E_2-induced $[Ca^{2+}]$ response was significantly attenuated in ERαKO mouse astrocytes, suggesting E_2 signaling through mERα. Furthermore, PPT, a selective ERα agonist, induced similar $[Ca^{2+}]$ responses to E_2 in astrocytes and glial progesterone synthesis is equally facilitated by PPT and E_2 [108].

Some effects of estrogens on astrocytes are sexually dimorphic. Specifically, the astrocyte-derived synthesis of steroids, which is necessary for positive estrogen feedback [103], is increased in females but not males in response to E_2 stimulation [110]. Likewise, astrocytes respond to E_2 stimulation by elevating the $[Ca^{2+}]$ levels in both sexes, but this stimulation is less powerful in males [109]. Moreover, E_2 increases the amount of ERα at the cell membrane of astrocytes, but only in adult females [110]. These results support the hypothesis

that astrocytes respond to hormones in a sexually dimorphic way [111, 112].

The majority of studies examining the central effect of estrogen on astrocytes have focused on anti-inflammatory actions [20, 113–115]. Specifically, estrogens are capable of reducing the expression of several inflammatory markers, such as interleukin 6 (IL-6), interferon γ-inducible protein 10 (IP-10) and NFκB, in cultured astrocytes [20, 114, 116–118]. Estrogens also regulate the expression of astrocytic molecules that are involved in the regulation of neuroendocrine events in the hypothalamus, such as growth factors [119] and glutamate transporters (GLT-1 and GLAST) [94], the expression of which increases in response to activation of GPR30 by E_2 [120]. However, little is known about the effects produced by estrogen on hypothalamic astrocytes in metabolic disorders such as obesity.

Estrogens are involved in metabolic control, not only controlling fat stores but also modulating central leptin sensitivity [28]. E_2 supplementation helps overcome central leptin resistance in diet-induced obesity [121]. Centrally-delivered estrogen, in the form of a GLP-1-estrogen conjugate, attenuates leptin resistance and reverses the metabolic syndrome in diet induced obese mice [122]. Moreover, the regulation of leptin signaling appears to be mediated by hypothalamic astrocytes [91], which, as mentioned above, are important estrogen targets in the CNS. These novel findings indicate that estrogens could act directly on astrocytes to ameliorate leptin resistance and control body weight through hypothalamic glial signals. In addition, since obesity produces a state of both peripheral and central inflammation, the estrogenic regulation of astrocytic proinflammatory cytokine secretion also may have an impact on the inflammatory response induced by obesity (Fig. 1). Therefore, in view of the existing body of data and given that the effects of E_2 on astrocytes are sexually dimorphic [111, 112], further experiments on the role of estrogens in astrocyte-mediated neuroendocrine actions are warranted in

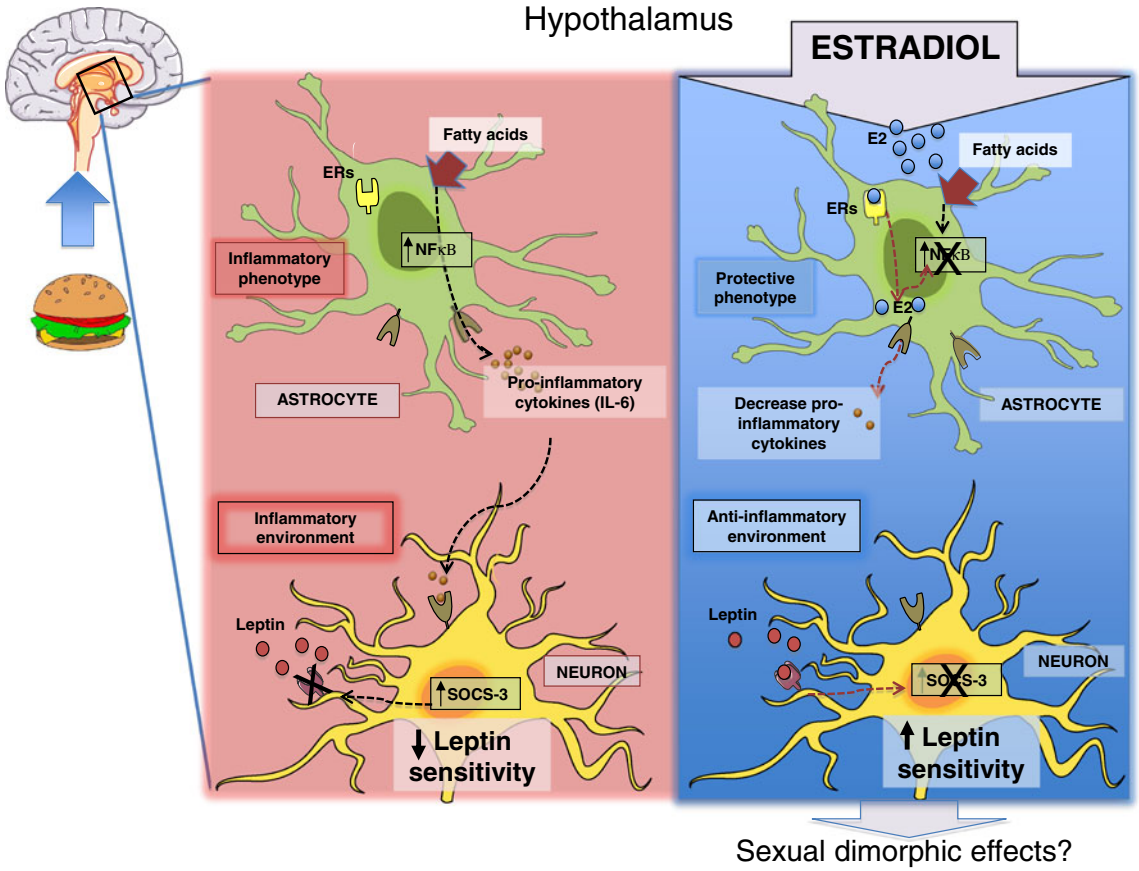

Fig. 1 Potential anti-inflammatory effects of estrogens on hypothalamic inflammatory processes induced by overnutrition. HFD feeding induces astrogliosis through activating NFκB pathway and releasing pro-inflammatory cytokines (IL-6). These astrocyte actions develop an inflammatory enviroment which could have detrimental effects on neurons such as the lack of leptin sensitivity as result of an increase in SOCS3 levels induced by inflammatory pathway activation in these cells and leading a positive energy balance. Estrogens are well-known for their protective effects in several cell types and thus, we hypothesize that estrogens could reduce astrocyte inflammatory phenotype through reducing fatty acids-activated NFkB activity and consequently decreasing inflammatory mediators synthesis. These astrocyte effects mediated by estrogens could be behind of the restoration of leptin signaling and sensitivity in neurons. *ERs* estrogen receptors; *E2* estradiol; *IL-6* Interleukin; *NFκβ* nuclear factor-κB; *SOCS-3* suppressor of cytokine signaling 3

order to explore the development of sex-specific therapeutics for a more personalized treatment of obesity and related metabolic disorders.

Conflict of interest The authors declared no conflict of interest.

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