Frontiers in Neuroendocrinology 35 (2014) 550–557

Contents lists available at ScienceDirect

Frontiers in Neuroendocrinology

journal homepage: www.elsevier.com/locate/yfrne

Review

The role of hypothalamic estrogen receptors in metabolic regulation

Aaron Frank [b], Lynda M. Brown [a], Deborah J. Clegg [b,*]

[a] Food and Nutrition Sciences Program, North Carolina Agricultural and Technical State University, Greensboro, NC 27411-0002, USA
[b] Department of Internal Medicine, Touchstone Diabetes Center, University of Texas Southwestern Medical Center, Dallas, TX 75390-8854, USA

ARTICLE INFO

Article history:
Available online 29 May 2014

Keywords:
Body weight
Energy balance
Hypothalamus
17β-Estradiol
Estrogen receptor alpha (ERS1)
Estrogen receptor beta (ERS2)
G protein-coupled estrogen receptor (GPER)
Neuropeptides

ABSTRACT

Estrogens regulate key features of metabolism, including food intake, body weight, energy expenditure, insulin sensitivity, leptin sensitivity, and body fat distribution. There are two 'classical' estrogen receptors (ERs): estrogen receptor alpha (ERS1) and estrogen receptor beta (ERS2). Human and murine data indicate ERS1 contributes to metabolic regulation more so than ESR2. For example, there are human inactivating mutations of ERS1 which recapitulate aspects of the metabolic syndrome in both men and women. Much of our understanding of the metabolic roles of ERS1 was initially uncovered in estrogen receptor α-null mice ($ERS1^{-/-}$); these mice display aspects of the metabolic syndrome, including increased body weight, increased visceral fat deposition and dysregulated glucose intolerance. Recent data further implicate ERS1 in specific tissues and neuronal populations as being critical for regulating food intake, energy expenditure, body fat distribution and adipose tissue function. This review will focus predominantly on the role of hypothalamic ERs and their critical role in regulating all aspects of energy homeostasis and metabolism.

1. Introduction

The brain is the central integration site for body weight regulation. Within the brain, the hypothalamus is a complex structure of nuclei, pathways and neurotransmitter systems that controls food intake and energy expenditure (Zhang et al., 2008; Grill and Kaplan, 2002; Williams et al., 2001; Xu et al., 2011). Early interest in the hypothalamus stemmed from findings that lesioning specific hypothalamic nuclei produced dramatic changes in food intake and energy homeostasis. In 1954, Dr. Stellar suggested the hypothalamus was the central neural structure involved in the control of food intake (Stellar, 1954). The so-called "Dual-Center Hypothesis" was based on earlier experiments by Hetherington and Ranson where electrolytic lesions were placed in two brain regions of rats. Lesions of the ventral medial hypothalamus (VMH) increased food intake and induced obesity (Hetherington and Ranson, 1942, 1940). It was hypothesized the lesions affected satiety, leading the VMH to be dubbed the 'satiety center' (Weingarten et al., 1985; Vilberg and Keesey, 1984). In contrast, lesions of the lateral hypothalamic area (LHA) decreased food intake and provoked weight loss (Anand and Brobeck, 1951); this region became known as the 'hunger center' (Ungan and Karakas, 1989). Electrical stimulation of the two hypothalamic centers supported the hypothesis: stimulation of the VMH caused rats to stop eating (Saito et al., 1988), while stimulation of the LHA caused sated rats to eat (Bernardis and Bellinger, 1996). Thus, the Dual-Center Hypothesis became the dominant theory of how the central nervous system (CNS) controls food intake (Stellar, 1954; Elmquist et al., 1999; Jeanrenaud and Rohner-Jeanrenaud, 2000). Recently, elegant studies using viral vector technology and generation of transgenic mice with selective deletions or targets of specific brain regions have substantiated these original findings and clearly demonstrated that

Abbreviations: AgRP, agouti-related peptide; Akt/PKB, protein kinase B; ARC, arcuate nucleus; CCK, cholecystokinin; CNS, central nervous system; E2, 17β-estradiol; ER, estrogen receptor; ERE, estrogen response element; ERS1, ER alpha; $ERS1^{-/-}$, ER alpha null mouse; ERKO, ER knock-out mouse; ERαKO, ER alpha knockout mouse; ERS2, ER beta; HPG, hypothalamic pituitary gonadal axis; $Ghsr^{-/-}$, GHSR null mice; GHSRs, growth hormone secretagogue receptors; GPCR, G protein-coupled receptor; GPER, G protein-coupled ER; i3vt, intra-third ventricular; leprb, long form of the leptin receptor; LHA, lateral hypothalamic area; αMSH, alpha melanocyte stimulating hormone; MAP, mitogen-activated protein; MC3/MC4, melanocortin-3, -4 receptors; MCH, melanin-concentrating hormone; MNAR, modulator of nongenomic activity of ER; MPOA, medial preoptic area; NERKI, nuclear ERα knock-in mouse; NPY, neuropeptide Y; NTS, nucleus of the solitary tract; OVX, ovariectomy; PI3K, phosphatidylinositol 3-kinase; POMC, pro-opiomelanocortin; PVN, paraventricular nucleus; SF1, steroidogenic factor-1; sh, short hairpin; VMH, ventromedial hypothalamus; ZI, zona incerta.

* Corresponding author. Address: Department of Internal Medicine, Touchstone Diabetes Center, UT Southwestern Medical Center, 5323 Harry Hines Blvd., K5.252, Dallas, TX 75390-8854, USA. Fax: +1 214 648 8720.
E-mail address: deborah.clegg@utsouthwestern.edu (D.J. Clegg).

http://dx.doi.org/10.1016/j.yfrne.2014.05.002
0091-3022/

the hypothalamus is one of the major brain centers for the regulation of energy homeostasis and food intake.

The hypothalamus exerts its influence on energy homeostasis through regulation of both anabolic and catabolic pathways (Schwartz et al., 2000; Benoit et al., 2004; Woods et al., 1998). Anabolic pathways increase food intake, decrease energy expenditure and consequently increase body weight/adiposity. These pathways are activated when energy stores are low (negative energy balance). Catabolic pathways are activated by positive energy balance. These pathways decrease food intake, increase energy expenditure and decrease body weight/adiposity. The interplay of various hypothalamic nuclei with peripheral hormones, neuropeptides and nuclear receptors represents a critical aspect of hypothalamic regulation of energy metabolism (Schwartz et al., 2000; Benoit et al., 2004; Woods et al., 1998).

Surprisingly, despite thousands of reports published since the 1930s investigating the role of various hypothalamic nuclei in the regulation of food intake and body weight (Bray, 1984; Bray et al., 1982; York and Bray, 1972), studies on the effect of sex in regulating hormonal and neuronal pathways of energy regulation have been sparse. However, recent data demonstrate that males and females do differ in terms of CNS regulation of body weight and homeostasis (Clegg et al., 2003, 2006). Both testosterone and estrogens influence metabolism, energy homeostasis, food intake, and body fat distribution, partially through hormonal receptors which are co-localized with hunger (orexic) and satiety (anorexic)-inducing neuropeptides within the hypothalamus. This review will explore the relationship of estrogens, estrogen receptors (ERs) and peripheral hormones in hypothalamic regulation of energy homeostasis.

1.1. The role of ERs and genomic vs. non-genomic signaling

The 'classical' nuclear ER was cloned in 1985 (Green et al., 1986) and renamed estrogen receptor alpha (ERα/ESR1) when a second nuclear estrogen receptor (estrogen receptor beta (ERβ/ESR2)), was discovered 10 years later (Kuiper et al., 1996). The ER subtypes are expressed differentially throughout the brain (Kuiper et al., 1996; Osterlund et al., 1998; Merchenthaler et al., 2004; Simonian and Herbison, 1997; Voisin et al., 1997; Simerly et al., 1990; Shughrue et al., 1997a,b; Mitra et al., 2003), and in many cases their distribution differs by sex.

Once thought to function solely as genomic transcription factors (Pappas et al., 1995; Razandi et al., 1999); ERs have also been shown to participate in non-genomic signaling pathways. "Classical" genomic activity of ERs occurs over the course of hours following ligand binding which induces conformational changes of the receptor, allowing it to dissociate from chaperone heat-shock proteins and dimerize with other ERs (McDonnell and Wardell, 2010). The ligand–dimer complex binds either directly to estrogen response elements (ERE) in target gene promoters or indirectly to AP-1 or SP-1 response elements via protein tethering to DNA (Safe and Kim, 2008). The physiologic responses mediated by ERs vary across cells and depend upon the presence and concentration of ER subtypes, ligands, and co-activator and co-repressor proteins (McDonnell and Wardell, 2010; Powell and Xu, 2008). Interestingly, while highly active estrogens such as 17 beta-estradiol (E2) function as ER ligands, many pharmacological, as well as environmental and food compounds, are capable of binding and promoting ER activity (McDonnell and Wardell, 2010). Once ligand has bound and activated the ER, transcription proceeds in a cyclic fashion, cycling on and off target promoters as long as ligand is present.

Non-genomic steroid/steroid receptor activation of ERs occurs more quickly than the classical pathway, typically over the course of minutes or seconds. Extra nuclear and membrane-associated isoforms of ESR1 and ESR2 localize to plasma membrane caveolae and congregate with signaling molecules, including G proteins, growth factor receptors, tyrosine kinases (Src), linker proteins (MNAR), and orphan GPCRs, facilitating interaction and rapid intracellular signaling in the presence of ligand (Kelly and Levin, 2001). For example, the E2/ER complex induces activation of the mitogen-activated protein (MAP) kinase cascade and phosphatidylinositol 3-kinase (PI3K) pathways, causing a rise in intracellular calcium (Balthazart et al., 2001; Sutter-Dub, 2002). ERs also activate protein kinase B (PKB/Akt) in neurons (Wilson et al., 2002; Singh, 2001; Ivanova et al., 2002), and activation of the PI3K/Akt cascade mediates a variety of E2's central actions, including neuronal excitability, neuro-protection, reductions in inflammation, and neurite outgrowth (Vasudevan and Pfaff, 2008), as well as body weight regulation. While E2 activates G protein-coupled estrogen receptor (GPER; also called GPR30), the role of GPER in body weight regulation still requires validation. In one study of female mice lacking GPER, the obesity phenotype emerged in only one of four GPER mutant mouse lines (Davis et al., 2014; Langer et al., 2010). Multiple groups have described collaboration between membrane-localized ESR1 and GPER, presumably at the membrane of several E2-sensitive cell lines. GPER also induces the expression of ERS136, a transcriptionally inactive and truncated version of the classical long isoform of ERS1, ERS166 (Kang et al., 2010); however, its function with respect to metabolism remains unclear.

In an attempt to better describe the various mechanisms of estrogenic action, Park et al. examined whether E2 regulates body weight homeostasis through the classical or non-classical ER signaling pathways by generating a novel mouse model with a knock-in mutation blocking the DNA binding domain of ESR1 (Park et al., 2011). These mice, termed NERKI (nuclear ESR1 knock-in mice), were leaner and had normal glucose homeostasis, insulin sensitivity, energy homeostasis, and physical activity when compared with ERS1 knock-out (ERKO) or wild-type mice. NERKI mice had lower leptin levels than ERKO and enhanced hypothalamus-specific leptin sensitivity as measured by phospho-STAT3 activation. The authors also found an increase in phosphorylated Akt after E2 injections in the ventral medial nucleus. Together this data indicates that non-classical ER signaling plays a critical role in mediating the metabolic effects of estrogens.

1.2. Hypothalamic ERs and metabolic regulation

ESR1 mediates the anti-obesity effects of estrogens; deletion of the receptor increases adiposity and causes the metabolic syndrome in both male and female mice (Heine et al., 2000). ESR2 is less effective in this regard; its deletion does not promote obesity or any of the metabolic consequences associated with obesity (Ohlsson et al., 2000). ESR1 is expressed in several different brain regions implicated in regulating energy homeostasis, including the ventrolateral portion of the VMH (VL VMH), the arcuate nucleus (ARC), the medial preoptic area (MPOA), and the paraventricular nuclei (PVN) (Osterlund et al., 1998; Merchenthaler et al., 2004; Simonian and Herbison, 1997; Voisin et al., 1997; Simerly et al., 1990; Shima et al., 2003; Wilkinson et al., 2002).

Early attempts to determine the influence of E2 and their receptors in regulating food intake and body weight in the CNS were performed by intra-nuclear microinjections of estradiol benzoate (E2) (Wade and Zucker, 1970). Due to the difficulty in precisely placing cannulae or producing lesions in small, complex hypothalamic regions, findings obtained from these studies are somewhat controversial. For example, E2 implanted in the PVN decreased food intake and body weight in ovariectomized (OVX) rats in the absence of peripheral estrogenic stimulation. Moreover, the anorexigenic effects of subcutaneous E2 were blunted in rats with PVN lesions (Butera and Beikirch, 1989). However, subsequent studies failed to reproduce these phenotypes in rats with PVN