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Estradiol effects on hypothalamic AMPK and BAT thermogenesis: A gateway for obesity treatment?

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ABSTRACT

In addition to their prominent roles in the control of reproduction, estrogens are important modulators of energy balance, as evident in conditions of deficiency of estrogens, which are characterized by increased feeding and decreased energy expenditure, leading to obesity. AMP-activated protein kinase (AMPK) is a ubiquitous cellular energy gauge that is activated under conditions of low energy, increasing energy production and reducing energy wasting. Centrally, the AMPK pathway is a canonical route regulating energy homeostasis, by integrating peripheral signals, such as hormones and metabolites, with neuronal networks. As a result of those actions, hypothalamic AMPK modulates feeding, as well as brown adipose tissue (BAT) thermogenesis and browning of white adipose tissue (WAT). Here, we will review the central actions of estrogens on energy balance, with particular focus on hypothalamic AMPK. The relevance of this interaction is noteworthy, because some agents with known actions on metabolic homeostasis, such as nicotine, metformin, liraglutide, olanzapine and also natural molecules, such as resveratrol and flavonoids, exert their actions by modulating AMPK. This evidence highlights the possibility that hypothalamic AMPK might be a potential target for the treatment of obesity.

Contents

Abbreviations: 3 V, third ventricle; ACC, acetyl-CoA carboxylase; AgRP, agouti-related peptide; AMPK, AMP-activated protein kinase; ARC, arcuate nucleus of the hypothalamus; β3-AR, beta3 adrenergic receptor3; BAT, brown adipose tissue; CaMKK2, Ca2 +/calmodulin-dependent protein kinase kinase 2; CNS, central nervous system; CPT1, carnitine palmitoyltransferase 1; DMH, dorsomedial nucleus of the hypothalamus; E2, estradiol; ERα, estrogen receptor alpha; ERβ, estrogen receptor beta; FAS, fatty acid synthase; GLP-1, glucagon-like peptide-1; IO, inferior olive nucleus; LHA, lateral hypothalamic area; LKB1, liver kinase B1; NPY, neuropeptide Y; PVH, paraventricular nucleus of the hypothalamus; PGC1α, peroxisome-proliferator-activated receptor-gamma co-activator 1 alpha; PGC1β, peroxisome-proliferator-activated receptor-gamma co-activator 1 beta; PP2Cα, protein phosphatase 2C alpha; PPARγ, peroxisome proliferator-activated receptor γ; POA, preoptic area; POMC, proopiomelanocortin; PSNS, parasympathetic nervous system; RPa, raphe pallidus nucleus; SNS, sympathetic nervous system; TH/-s, thyroid hormone/—s; UCP-1, uncoupling protein 1; VMH, ventromedial nucleus of the hypothalamus; WAT, white adipose tissue.

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1. Introduction

Obesity causes thousands of deaths per year worldwide, directly and indirectly due to comorbidities including cancer, cardiovascular disease and T2D, and yet it is the most preventable epidemic (Clemmensen, Muller, Finan, Tschop, & DiMarchi, 2016; Dietrich & Horvath, 2012a, 2012b; Tschop et al., 2016; Tuduri, Lopez, Dieguez, Nadal, & Nogueiras, 2016). However, in spite of significant investments in education and public engagement, government-led policies are relatively ineffective. This is shown in the *World Health Organization* (WHO)'s latest report, which states that 13% of adults globally are obese. In healthy individuals, maintaining normal weight is a matter of lifestyle. However, such apparent simplicity also necessitates an understanding of how the body manages what, how, when and why we eat, as well as how we expend calories.

The progression of obesity relies on a persistent state of positive energy balance (Dietrich & Horvath, 2012a; Farooqi & O'Rahilly, 2006; Friedman, 2003; López, Nogueiras, Tena-Sempere, & Dieguez, 2016). For this reason, it seems reasonable that the majority of attempts of treating obesity have focused on reducing appetite (Dietrich & Horvath, 2012b). However, to date, all drugs exclusively targeting food intake have failed because any reduction achieved has been matched by a compensatory drop in energy expenditure (Dietrich & Horvath, 2012b). In this scenario, it is demanding to gain a more profound knowledge of the major homeostatic modifiers of energy balance, and how these might contribute to the metabolic complications of obesity. During the last two decades, quite substantial efforts have been devoted to the identification of the major metabolic roles of several neuropeptides and transmitters, as well as multiple peripheral hormones (Gautron, Elmquist, & Williams, 2015; Loh, Herzog, & Shi, 2015; López et al., 2016; Schneeberger, Gomis, & Claret, 2014; Scott, Xu, Elias, & Williams, 2014), not only in the regulation of feeding, but also in the modulation of energy utilization. Significant attention has been paid to clarify the roles of signals from metabolic tissues, such as the pancreas, the adipose tissue and the gut (Allison & Myers, 2014; Scott, Tan, & Bloom, 2013). Notwithstanding that, *"classical"* endocrine organs, such as the adrenals, the thyroid and the gonads have been long known to secrete hormones that play key roles in the control of metabolism and energy balance (Brown, Gent, Davis, & Clegg, 2010; Clegg, 2012; Fliers, Klieverik, & Kalsbeek, 2010; López, Alvarez, Nogueiras, & Diéguez, 2013; López & Tena-Sempere, 2015; Martínez-Sánchez et al., 2014; Mauvais-Jarvis, 2015; Mauvais-Jarvis, Clegg, & Hevener, 2013; Mullur, Liu, & Brent, 2014; Palmer & Clegg, 2015). This review aims to provide an overview about the role of estrogens acting on the central nervous system (CNS) to regulate energy homeostasis, with particular attention on brown adipose tissue (BAT) thermogenesis and appetite.

2. Brown adipocytes: master regulators of energy balance

At thermoneutrality, the *obligatory thermogenesis* (the heat production automatically caused by the metabolic rate) maintains body temperature, and no other homeostatic thermoregulatory mechanisms are required (Cannon & Nedergaard, 2004; Contreras et al., 2015; López et al., 2013; Silva, 2006). However, when ambient temperature goes below this level the body activates heat-saving mechanisms, such as vasoconstriction, piloerection, rounded positions and decreased locomotor activity. However, if those strategies are non-efficient at long-term, additional thermogenic mechanisms are activated. This additional heat, produced on demand, is called *facultative or adaptive thermogenesis* (Cannon & Nedergaard, 2004; Contreras et al., 2015; López et al., 2013; Silva, 2006). Shivering is the timeliest and most primitive way to increase heat production; however its long term efficiency is low. In mammals, including humans, the major place for facultative thermogenesis is the BAT (Cannon & Nedergaard, 2004; Contreras et al., 2015; Nedergaard, Bengtsson, & Cannon, 2007; Silva, 2006). Morphologically, cells in the BAT consist of multi-locular lipid droplets and wide presence of mitochondria, in which uncoupling protein 1 (UCP1, also called thermogenin) is expressed. In typical mitochondria, the energy resulting from the electron movement through the respiratory chain is used by ATP synthase to produce ATP from ADP (Boyer, 1997; Futai, Noumi, & Maeda, 1989; von, Wiedenmann, & Dimroth, 2009) (for extensive review). In BAT mitochondria, UCP1 provides an optional pathway for the protons back into the mitochondrial matrix, bypassing ATP synthase and producing heat (Cannon & Nedergaard, 2004; Nicholls & Locke, 1984; Silva, 2006).

Thermogenesis in BAT is controlled by the sympathetic nervous system (SNS), which releases noradrenaline (NA), activating the β3-adrenergic receptor (β3-AR), which is highly expressed in brown adipocytes (Cannon & Nedergaard, 2004; Contreras et al., 2015; Nedergaard et al., 2007; Silva, 2006; Villarroya & Vidal-Puig, 2013; Whittle, Lopez, & Vidal-Puig, 2011). β3-ARs are coupled to G protein activating adenylate cyclase (AC) that increases cAMP levels, and subsequently activates protein kinase A (PKA). On one hand, PKA activates p38 mitogen-activated protein kinase (MAPK), which induces gene transcription, protein synthesis and cell growth and differentiation. PKA also increases the activity of lipolytic enzymes, such as adipose triglyceride lipase (ATGL), hormone sensitive lipase (HSL) and monoacylglycerol lipase (MGL) that hydrolyze triglycerides (TAGs) augmenting the cytosolic free fatty acids (FFAs) levels, that are imported through carnitine palmitoyltransferase 1A (CPT1A) into the mitochondria, where they are used as fuel (Cannon & Nedergaard, 2004; Contreras et al., 2015; Nedergaard et al., 2007; Silva, 2006; Villarroya & Vidal-Puig, 2013; Whittle et al., 2011).

For a long time, BAT was considered as a tissue relevant only to rodents, hibernating mammals and newborn humans (Cannon & Nedergaard, 2004). However, current evidence demonstrates that BAT is also present in adult humans. Using different approaches including positron emission tomography (PET) studies alongside ^{18}fluorodeoxyglucose (^{18}FDG) uptake, BAT was found in defined, but dispersed, areas in the body of adult humans, distributed mainly in the cervical, supraclavicular, perirenal, intercostal and periaortic regions (Cypess et al., 2009; Marken Lichtenbelt et al., 2009; Nedergaard et al., 2007; Virtanen et al., 2009; Zingaretti et al., 2009). Despite the initial enthusiasm following the identification of BAT in adult humans, further data demonstrated that human BAT is mainly composed by beige/brite adipocytes cells rather than brown cells (Jespersen et al., 2013; Wu et al., 2012), which can also be found under some conditions in the white adipose tissue (WAT). The process in which precursor cells placed in WAT become beige/brite cells instead of white adipocytes is called *browning* (Contreras et al., 2015; Nedergaard & Cannon, 2014).

3. Hypothalamic control of BAT: the key role of the VMH

The brain integrates peripheral signals informing on changes in external environmental temperature. This provides a coordinated output response by regulating thermogenesis that is carried out in several brain regions, with the hypothalamus playing an important role (Bellefontaine & Elias, 2014; Contreras et al., 2015; Cornejo et al., 2016; López et al., 2016; Morrison, Madden, & Tupone, 2014; Morrison & Nakamura, 2011; Richard, Monge-Roffarello, Chechi, Labbe, & Turcotte, 2012; Scott et al., 2014). Hypothalamic neurons with relevant functions in thermoregulation are located in the arcuate (ARC), dorsomedial (DMH), paraventricular (PVH) and ventromedial (VMH) nuclei, as well as in the lateral hypothalamus (LHA) and preoptic (POA) areas (Contreras et al., 2015; Cornejo et al., 2016; López et al., 2016; Morrison & Nakamura, 2011; Morrison et al., 2014; Richard et al., 2012).

The VMH has long been related with the regulation of thermogenesis in BAT (Contreras et al., 2015; López et al., 2016; Morrison & Nakamura, 2011; Morrison et al., 2014; Richard et al., 2012). Anatomical data show that VMH neurons are functionally linked to brainstem areas,