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Review article

Connecting metabolism and gonadal function: Novel central neuropeptide pathways involved in the metabolic control of puberty and fertility

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ABSTRACT

Albeit essential for perpetuation of species, reproduction is an energy-demanding function that can be adjusted to body metabolic status. Reproductive maturation and function can be suppressed in conditions of energy deficit, but can be altered also in situations of persistent energy excess, e.g., morbid obesity. This metabolic-reproductive integration, of considerable pathophysiological relevance to explain different forms of perturbed puberty and sub/infertility, is implemented by the concerted action of numerous central and peripheral regulators, which impinge at different levels of the hypothalamic-pituitary-gonadal (HPG) axis, permitting a tight fit between nutritional/energy status and gonadal function. We summarize here the major physiological mechanisms whereby nutritional and metabolic cues modulate the maturation and function of the HPG axis. We will focus on recent progress on the major central neuropeptide pathways, including kisspeptins, neurokinin B and the products of POMC and NPY neurons, which convey metabolic information to GnRH neurons, as major hierarchical hub of our reproductive brain.

1. Neuroendocrine control of reproduction: the intricate regulation of the HPG axis

Reproduction is indispensable for perpetuation of the species. Accordingly, strong evolutionary pressure has allowed selection of optimal reproductive strategies for each animal class, fitting exquisitely the individual, species and environmental demands. Indeed, in mammals, the acquisition of reproductive capacity at puberty and its subsequent maintenance in adulthood is subjected to the precise regulation and coordinated interaction of numerous central and peripheral signals that permit the precise matching of reproductive efficiency to endogenous and exogenous conditions. Such an integration takes place at key levels of the so-called hypothalamic-pituitary-gonadal (HPG) axis, also known as reproductive or gonadal axis (Pinilla et al., 2012; Tena-Sempere and Huhtaniemi, 2003). This complex neurohormonal system is primarily composed of (i) a small group of hypothalamic neurons that synthesize and release, in a pulsatile manner, the decapeptide, gonadotropin-releasing hormone (GnRH); (ii) the anterior pituitary or adenohypophysis, where gonadotrope cells are stimulated by GnRH to synthesize and release both gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH); and (iii) the gonads, i.e., testes and ovaries, which, in response to gonadotropins, generate gametes from puberty onwards and are responsible for the synthesis and release of gonadal hormones, of steroid and peptidergic nature (Pinilla et al., 2012; Tena-Sempere and Huhtaniemi, 2003). These elements are connected also by feedback regulatory loops, whereby peripheral hormonal signals (e.g., gonadal steroids) modulate the upstream elements of the HPG axis. These regulatory circuits become organized at early developmental periods and are responsible, in conjunction with other endogenous factors and exogenous cues, of the dynamic regulation of the reproductive system during the lifespan.

Within this neuroendocrine axis, GnRH neurons are considered the key hierarchical element, since they act as the final (direct or indirect) integrators of different central and peripheral regulatory signals, and the major output pathway for the brain control of the downstream elements of the HPG axis and, ultimately, of gonadal function. Hence,

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the maturation of the HPG axis (including puberty onset) and its proper functioning later on life critically depend on the adequate function of GnRH neurons and their precise regulation. On the latter, it is known that the synchronized release of GnRH bursts is the result of the integral function of the so-called GnRH pulse generator, an hypothalamic network originally proposed by Knobil (1980), which comprises not only GnRH neurons themselves, mainly located in the preoptic area (POA), but also numerous hypothalamic afferents, including both excitatory and inhibitory signals, whose nature has been only partially elucidated in the last decades (Terasawa et al., 2010; Maeda et al., 2010; Ojeda et al., 2010). These include, different neuronal transmitters, ranging from excitatory and inhibitory amino acids to various neuropeptides, among which kisspeptins have emerged recently as fundamental GnRH regulators. In addition to neural afferents, GnRH neurons receive also regulatory inputs from non-neuronal sources, such as glia (Ojeda et al., 2000) and endothelial cells (Prevot et al., 2000; Knauf et al., 2001). This is well illustrated by the fact that GnRH nerve terminals interact at the median eminence (ME) with glial structures belonging to either astrocytes or tanycytes; the latter are specialized ependymoglial cells that line the ventral portion of the third ventricle (Prevot, 2002). Thus, it is the balance, and eventual interplay, between neuronal and non-neuronal afferents to GnRH cells that dictates GnRH neurosecretion.

As clear reflection of this complexity, in recent years, the transcriptional substrate of such regulatory networks has begun to be exposed, with the identification of numerous genes, arranged into functionally connected hubs and pathways, which are essential for the precise control of reproductive function (Ojeda et al., 2006; Seminara and Crowley, 2001; Mitchell et al., 2011). This is epitomized by the model of genetic control of puberty that Ojeda and co-workers proposed one decade ago, using system biology approaches (Roth et al., 2007). According to this model, puberty is controlled by a set of genes, hierarchically organized within functionally connected networks, where GnRH is the final effector. The highest level of network control is provided by transcriptional regulators that operate upon key subordinate genes, such as those operating within kisspeptin, GABAergic and glutamatergic neurons, as well as in glial cells, which in turn act as upstream modulators of GnRH neurosecretion (Ojeda et al., 2006).

Moreover, compelling evidence has recently demonstrated that, together with *classical* transcriptional regulation, the neuroendocrine control of the HPG axis is also subjected to the precise control of various epigenetic mechanisms. In this context, pioneering work by Ojeda and colleagues recently revealed that increases in hypothalamic methylation (which is conventionally a mark of decreased gene expression) of the promoters of silencers belonging to the Polycomb group (PcG), such as Eed, releases a repressive brake on key puberty-controlling genes (such as Kiss1; see also Section 3), which is essential for the proper timing of pubertal maturation (Lomniczi et al., 2013, 2015). In the same vein, initial genome-wide association studies (GWAS) and expression analyses, in humans and rodents, respectively, suggested that regulatory mechanisms involving microRNAs (miRNAs) may play a relevant role in the control of puberty onset (Elks et al., 2010; Sangiao-Alvarellos et al., 2013); a contention that has been very recently substantiated by the work of Messina and co-workers, which has unambiguously demonstrated that a switch in expression of specific miRNAs in GnRH neurons during the infantile-to-juvenile transition is determinant to drive changes in GnRH neurosecretion that lead to the pubertal activation of the HPG axis (Messina et al., 2016).

Over this complex neuroendocrine substrate, numerous endogenous signals and environmental cues impinge on the major elements of the HPG axis to tightly couple reproductive maturation and function to other relevant body systems, ranging from growth and stress responses to metabolism and energy homeostasis (Roa and Tena-Sempere, 2014; Li et al., 2015). In this review, we aim to provide a comprehensive overview of the major neuroendocrine mechanisms whereby metabolic information is relayed (and modulates) the centers governing the HPG axis, with a particular focus on the roles and modes of action on key neuropeptide mediators.

2. Connecting metabolism and gonadal function: sensing via peripheral metabolic hormones

Reproductive function is a costly process in terms of energy consumption that, while essential for survival of the species, is dispensable at the individual level. Hence, the maturation and function of the reproductive axis are tightly connected with (and highly sensitive to) the energy status of the organism and sophisticated mechanisms may have been selected during evolution to allow specific inhibition of the reproductive axis in unfavourable energetic conditions. Indeed, appreciation of this close relationship between the magnitude of body energy reserves and fertility dates back to Palaeolithic Ages, when fecundity icons were often represented as overweight women. Yet, it was not until the 1960s and 70s that this connection was formulated on a scientific basis, with the proposal by Frisch and colleagues of the critical fat mass hypothesis (Frisch and Revelle, 1970), which claimed the need to reach a certain threshold of body (fat) mass as a physiological requirement for attainment of menarche and for maintaining reproductive function in adulthood. Admittedly, generation of that hypothesis was not devoid of potential flaws (Scott and Johnston, 1982), and in general, it fell short in recognizing important aspects of the metabolic-reproductive interplay, as it mostly focused on the impact of negative energy balance conditions in girls. Yet, the experimental and clinical work leading to this hypothesis clearly emphasized the link between body energy reserves and reproductive function, and set the scene for the study of the physiological substrate and putative mediators of such interaction. Moreover, it laid the basis for the analysis of the impact of different metabolic disorders (ranging from anorexia to obesity and metabolic syndrome) on puberty and fertility, and their underlying mechanisms; an area of increasing interest due to the escalating prevalence of metabolic and reproductive pathologies worldwide (Castellano and Tena-Sempere, 2016).

Analyses of the neuroendocrine pathways responsible for conveying the metabolic information to brain reproductive centers have focused not only on the central mediators, but importantly also in the peripheral hormones that allow the central sensing of metabolic status by such reproductive circuits (Castellano and Tena-Sempere, 2016). In this context, compelling evidence has now set the important role that different hormonal signals from the adipose tissue, pancreas and gastrointestinal tract play in transmitting metabolic information to the neural elements involved in the control of reproduction. As paradigmatic example, the physiological actions of two of such metabolic hormones, namely, leptin and insulin, in the control of the HPG axis will be briefly summarized in this section. Both signals share features regarding their major effects and mode of action in the reproductive brain, and clearly illustrate how peripheral metabolic factors dynamically modulate the HPG axis.

A major breakthrough in our understanding of the endocrine signals and mechanisms involved in the metabolic control of puberty and fertility occurred in 1994, when the adipose hormone, leptin, was identified (Vazquez et al., 2015). Leptin, the product of the *Lep* gene, was found to be secreted by the adipocytes and to be present in the circulation, in both rodents and humans, at levels directly related to the amount of body fat stores (Casanueva and Dieguez, 1999). In terms of metabolic control, leptin acts as an anorexigenic and thermogenic factor at the hypothalamus to adjust energy requirements, fat reserves and food intake; conditions of energy insufficiency cause a decrease in leptin levels that enhances feeding and decreases energy expenditure. Notwithstanding these predominant central effects, direct peripheral actions of leptin on key metabolic tissues, such as the muscle, liver, pancreas and adipose, as well as on non-metabolic organs, have been documented (Muoio and Lynis, 2002).

In fact, soon after its identification, it became evident that leptin has a wider spectrum of biological actions, as it operates as a pleotropic