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Review

Connecting metabolism and reproduction: Roles of central energy sensors and key molecular mediators

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ABSTRACT

It is well established that pubertal activation of the reproductive axis and maintenance of fertility are critically dependent on the magnitude of body energy reserves and the metabolic state of the organism. Hence, conditions of impaired energy homeostasis often result in deregulation of puberty and reproduction, whereas gonadal dysfunction can be associated with the worsening of the metabolic profile and, eventually, changes in body weight. While much progress has taken place in our knowledge about the neuroendocrine mechanisms linking metabolism and reproduction, our understanding of how such dynamic interplay happens is still incomplete. As paradigmatic example, much has been learned in the last two decades on the reproductive roles of key metabolic hormones (such as leptin, insulin and ghrelin), their brain targets and the major transmitters and neuropeptides involved. Yet, the molecular mechanisms whereby metabolic information is translated and engages into the reproductive circuits remain largely unsolved. In this work, we will summarize recent developments in the characterization of the putative central roles of key cellular energy sensors, such as mTOR, in this phenomenon, and will relate these with other molecular mechanisms likely contributing to the brain coupling of energy balance and fertility. In doing so, we aim to provide an updated view of an area that, despite still underdeveloped, may be critically important to fully understand how reproduction and metabolism are tightly connected in health and disease.

Contents

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1. Metabolic control of reproduction: Fitting energy stores, puberty and fertility

"*We are what we eat*". The basis for this popular assertion pervades all aspects of animal physiology, including reproduction. Indeed, while reproduction is essential for the survival of the species, it is dispensable at the individual level, since reproduction is an energy-costly function that can only be efficiently faced when sufficient energy resources guarantee the metabolic demands imposed by pregnancy and lactation. Moreover, specific aspects of male reproduction, such as territoriality and dominance, are also critically dependent on proper metabolic and energy status. Accordingly, conditions of energy insufficiency and metabolic impairment are commonly associated to halted puberty onset and perturbed fertility. These responses can be regarded as a failsafe mechanism, whereby energy re-allocation takes place to support indispensable body functions at the individual level. Yet, such *adjustment* (namely, suppression on puberty and fertility in adverse metabolic conditions) must be done in a precisely controlled manner, since persistency of reproductive suppression would compromise the perpetuation of species, especially in nutritionally-adverse environments. Furthermore, compelling evidence indicates that not only the lack of energy stores but also situations of persistent energy excess, such as morbid obesity, are associated to reproductive dysfunction; overweight will likely become one of the major threats for human reproduction in the coming years.

But how is reproduction metabolically gated? Because of its paramount evolutionary importance in all species, the reproductive system is controlled in mammals and non-mammalian species by complex, and often over-lapping regulatory circuits that are responsible for coupling reproductive efficiency and the environmental and endogenous (including nutritional) conditions. These reproductive networks form the hypothalamic–pituitary–gonadal (HPG) axis: also termed gonadotropic axis (Pinilla et al., 2012; Schwartz, 2000; Tena-Sempere and Huhtaniemi, 2003). Three major groups of signals compose this neuroendocrine system, namely, (*a*) the gonadotropin-releasing hormone (GnRH), a decapeptide produced by a scarce population of neurons, mostly located in the anterior basal forebrain in rodents and primates; (*b*) the pituitary gonadotropins, LH and FSH; and (*c*) gonadal hormones, including sex steroids and peptide factors (Schwartz, 2000; Tena-Sempere and Huhtaniemi, 2003). In this system, a major hierarchical role is held by GnRH neurons, which operate as major regulatory hub and key output pathway for the brain control of the downstream elements of the gonadotropic axis. Anyhow, the three levels of the HPG system are modulated by different endogenous and exogenous signals, which modify the output of each level. In turn, the primary elements described earlier regulate each other via feed-forward and feedback regulatory loops, so that GnRH stimulates pituitary gonadotropins, which increase gonadal function, while gonadal hormones predominantly inhibit upstream elements of this axis. The dynamic interplay among these factors allows the precise adjustment of reproductive function to the stage of development and the internal and external environments (Fink, 2000).

In the last two decades, we have witnessed a substantial enlargement of our understanding of the signals involved in the metabolic control of reproduction, which are multiple and likely operate at different levels of the gonadotropic system. In one hand, numerous peripheral factors, responsible for transmitting metabolic information to the HPG axis, have been recognized. Intriguingly, apart from hormones arising for *classical* endocrine organs (*e.g.*, insulin), *non-classical* endocrine tissues, such the adipose and the gut, seem to play prominent roles because of their capacity to secrete key metabolic signals that operate also as relevant modulators of the reproductive system, such as leptin and ghrelin (Fernandez-Fernandez et al., 2006; Hill et al., 2008; Tena-Sempere, 2007). On the other hand, it has been recognized in the last decades that a substantial component of the metabolic control of the HPG axis occurs at central levels, ultimately by the (mostly indirect) regulation of GnRH neurons in the hypothalamus (Acosta-Martinez, 2012; Castellano et al., 2010; Elias, 2012; Elias and Purohit, 2012; Hill et al., 2008; Pinilla et al., 2012; Xu et al., 2012). In this context, recent studies have unveiled the prominent roles of different neuronal populations (*e.g.*, Kiss1- or nitric-oxide [NO]-neurons) and nuclei (*e.g.*, the ventral premammilary nucleus [PMV]) in transmitting the metabolic information of peripheral hormones to GnRH neurons. Yet, the molecular mechanisms whereby such a connection between peripheral signals and central transmitters occurs remain ill defined. In this work, we will provide an updated account of our current knowledge on the roles of specific cellular energy sensors and related molecular mechanisms in bridging energy homeostasis and reproduction, acting at central (brain) levels. For sake of introduction, the major roles of some key peripheral hormones and central transmitters in such a physiological phenomenon will be briefly discussed in the coming sections.

2. Hormonal signals for the metabolic control of reproduction: Roles of leptin, insulin and ghrelin

Despite the *ancient* intuitive knowledge connecting body weight (and hence energy reserves) and fertility, it is probably not until 1990s when the endocrine signals and molecular mechanisms serving this key function begun to be systematically characterized. No doubt, a milestone in this area was the identification and characterization of the biological actions of the adipose hormone, leptin, which allowed to define its indispensable role in the metabolic regulation of puberty and fertility. As extensively revised elsewhere, leptin was discovered in 1994 as a major secretory product of the white adipose tissue, which functions as signal of energy abundance, as it is produced in proportion to the amount of body fat stores (Halaas et al., 1995). Hence, its circulating levels inform of the actual size of energy reserves to different body systems, including the reproductive axis (Ahima et al., 2000; Casanueva and Dieguez, 1999; Fernandez-Fernandez et al., 2006; Tena-Sempere, 2007).

Despite some initial debate on the actual nature of its reproductive effects (*i.e.*, whether they are permissive or stimulatory), it is now well established that leptin acts an essential threshold factor for the metabolic control of puberty and fertility (Ahima et al., 2000; Casanueva and Dieguez, 1999; Cheung et al., 1997; Fernandez-Fernandez et al., 2006; Tena-Sempere, 2007). Thus, attainment of appropriate leptin levels is indispensable for normal pubertal progression and maintenance of fertility; yet, leptin alone cannot trigger early puberty or hyper-stimulate the HPG axis *per se*. The mechanisms whereby leptin conducts such permissive action are multifaceted and yet to be fully characterized. In any event, compelling experimental evidence has set the notion that, as is also the case for its regulatory effects on food intake and energy expenditure, the hypothalamus is the primary site of action of leptin in the control of reproductive function, where leptin can modulate GnRH output. However, as described in Section 3, GnRH neurons seem to be devoid of functional leptin receptors, thus requiring the participation of intermediate pathways and signals for transmitting the actions of leptin to this key neuronal population.

Another systemic hormone with a major role in the regulation of reproduction is the pancreatic hormone, insulin (Pralong, 2010). Of note, insulin, which is also an anorectic signal, operates as major regulator of leptin production, and their levels and biological actions are frequently closely connected. In fact, insulin has been shown to play a modulatory role of the HPG axis also, with predominant stimulatory actions; indeed, conditions of low or null insulin levels are commonly associated with suppressed gonadotropins and