Available online at www.sciencedirect.com

Metabolism

www.metabolismjournal.com

# Roles of Leptin in Reproduction, Pregnancy and Polycystic Ovary Syndrome: Consensus Knowledge and Recent Developments

*María Jesús Vázquez*[1], *Antonio Romero-Ruiz*[1], *Manuel Tena-Sempere*[*]

*Department of Cell Biology, Physiology and Immunology, University of Córdoba, Spain*
*CIBER Fisiopatología de la Obesidad y Nutrición, Instituto de Salud Carlos III, Spain*
*Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC)/Hospital Universitario Reina Sofia, 14004 Córdoba, Spain*

ARTICLE INFO

*Keywords:*
Leptin
Reproduction
Puberty
Pregnancy
PCOS

ABSTRACT

As an essential function for perpetuation of species, reproduction, including puberty onset, is sensitive to the size of body energy stores and the metabolic state of the organism. Accordingly, impaired energy homeostasis, ranging from extreme leanness, such as in anorexia or cachexia, to morbid obesity has an impact on the timing of puberty and is often associated to fertility problems. The neuroendocrine basis for such phenomenon is the close connection between numerous metabolic hormones and nutritional cues with the various elements of the so-called hypothalamic-pituitary-gonadal (HPG) axis. Yet, despite previous fragmentary knowledge, it was only the discovery of the adipose-hormone, leptin, in 1994 what revolutionized our understanding on how metabolic and reproductive systems closely interplay and allowed the definition of the neurohormonal causes of perturbations of puberty and fertility in conditions of impaired body energy homeostasis. In this article, we aim to provide a synoptic view of the mechanisms whereby leptin engages in the regulation of different elements of the HPG axis, with special attention to its effects and mechanisms of action on the different elements of the reproductive brain and its proven direct effects in the gonads. In addition, we will summarize the state-of-the-art regarding the putative roles of leptin during gestation, including its potential function as placental hormone. Finally, comments will be made on the eventual leptin alterations in reproductive disorders, with special attention to the polycystic ovary syndrome (PCOS), a disease in which reproductive, metabolic and neuroendocrine alterations are commonly observed. All in all, we intend to provide an updated account of our knowledge on the physiological roles of leptin in the metabolic regulation of the reproductive axis and its eventual pathophysiological implications in prevalent reproductive disorders, such as PCOS.



## 1. Introduction: Metabolic Gating of Reproductive Function

Reproduction is a sophisticated biological function that enables perpetuation of species. The reproductive system is under the control of complex regulatory networks, which allow maximal reproductive efficiency but also adaptation to environmental and endogenous conditions. In mammals and other vertebrates, these reproductive signals integrate at different levels of the hypothalamic-pituitary-gonadal (HPG; also termed gonadotropic)

* Corresponding author.
E-mail address: fi1tesem@uco.es (M. Tena-Sempere).
[1] Equally contributed and should be considered as joint first authors.

http://dx.doi.org/10.1016/j.metabol.2014.10.013
0026-0495/

axis [1–3], which is primarily defined by three major sets of factors: the hypothalamic decapeptide, gonadotropin-releasing hormone (GnRH), pituitary gonadotropins, LH and FSH, and gonadal hormones, of steroid and peptidergic nature [1,2]. These elements are linked by feed-forward and feedback regulatory loops, which are sensitive to numerous internal and external modifiers, thus ensuring the adjustment of reproductive hormone secretion and gonadal function to the different developmental periods and environmental conditions [4].

While reproduction is essential for survival at the species level, it is an energy-costly function that is dispensable at the individual level. Accordingly, when body homeostasis is perturbed, reproductive function is suppressed as a mean to secure energy reserves for indispensable functions of the organism. Thus, the maturation and function of the HPG axis are sensitive to the magnitude of body fuel stores and under the regulation of numerous nutritional and metabolic factors [5,6]. For instance, thresholds fat reserves are indispensable to complete pubertal development and to attain reproductive capacity in adulthood. This phenomenon is very relevant in the female, because fertility is coupled to pregnancy and lactation, which are highly energy demanding [7]. Nonetheless, the close link between metabolism and reproduction is present in both sexes, and conditions of metabolic impairment have also an impact of male puberty onset and testicular function [8]. Moreover, it is not only the lack of energy resources but also situations of persistent energy excess, such as morbid obesity, that are associated to reproductive dysfunction.

Although our knowledge of the basis of the above phenomena remains incomplete, solid evidence has unveiled that the mechanisms for the *metabolic* regulation of the reproductive system are likely multifaceted, and operate at different levels of the HPG axis. Notwithstanding this, it has been recognized that an important component of this metabolic regulation occurs at central levels, by the direct and/or indirect modulation of hypothalamic GnRH neurons [3,9–14]. It is also well known that a wide range of peripheral signals are responsible for transmitting metabolic information onto the reproductive centers in the brain. These include different hormones, of various tissue sources. Of note, while it was long known that metabolic hormones from *classical* endocrine organs, such as insulin, glucocorticoids and thyroid hormones, modulate the reproductive axis, during the last decades it has been recognized that hormones from *non-classical* endocrine tissues, such as the adipose and the gut, play a key role as metabolic regulators of the reproductive system [5,7,13,15,16]. Among the latter, there is unanimous recognition of the essential function of the adipose hormone, leptin, in the control of different aspects of the development and function of the HPG axis [16]. In this work, we provide a summary of our current knowledge of the reproductive roles of leptin, with special emphasis on the mechanisms whereby this metabolic factor, whose discovery is commemorated in this Special Issue, operates at different levels of the reproductive system to modulate its pubertal activation, fertility and gestation.

## 2. Leptin and the Metabolic Control of Puberty and Fertility: General Considerations

Although the connection between body energy stores and fertility was assumed since Old Ages on the basis of intuitive knowledge, the scientific formulation of such a link crystallized only in the 1970s, with the proposal of the critical fat mass hypothesis by Frisch and co-workers. Yet, this initial hypothesis told little about the actual mechanisms whereby energy homeostasis and metabolic signals modulate reproductive maturation and function; knowledge that has expanded significantly only recently. In fact, we can consider that, to a great extent, progress in this area has been tightly connected with the identification and characterization of the biological actions of the adipose hormone, leptin, and particularly, of its indispensable role in the metabolic regulation of puberty and fertility. As extensively revised elsewhere in this Special Issue, leptin was identified in 1994 as a major secretory product of the white adipose tissue (WAT) [17]. Identification of leptin revolutionized not only our understanding of the physiological mechanisms for the control of energy balance and body weight; because of its role as signal of energy abundance, leptin plays the essential function as neuroendocrine integrator linking the magnitude of body fat stores to different neuroendocrine axes, including the reproductive system [5,7,15,18–20]. This is due to the fact that leptin is secreted in proportion to the amount of WAT; hence, its circulating concentration informs of the actual size of fat stores to different body systems. Accordingly, in conditions of negative energy balance or nutrient restriction, leptin levels are substantially decreased, as extensively documented in different species [21–23].

In the context of the reproductive axis, short after its identification, it was documented that leptin is an indispensable factor in the metabolic control of puberty and fertility [5,7,15,18,24]. The paramount relevance of leptin in reproductive control is illustrated by the impact of conditions of leptin insufficiency on reproductive maturation and function, as reported in humans with low or absent leptin levels, as well as in rodent models lacking leptin or its receptor, such as the *ob/ob* mouse, the *db/db* mouse and the *fa/fa* Zucker rat [5,15,25]; in all these, defective leptin signaling is associated to delay or absence of puberty and compromised fertility [25,26].

As indicated above, the reproductive dimension of leptin was demonstrated soon after its identification, thus providing molecular evidence for the link between fat stores and puberty onset and fertility, as proposed by the Frisch hypothesis. Yet, despite the recognition of this net positive effect of leptin on the HPG axis, the nature of such action, and whether it is stimulatory (i.e., can trigger puberty) or merely permissive (i.e., can allow puberty to progress if threshold levels are achieved, but cannot *per se* trigger puberty), was the subject of considerable interest and debate in the *early days* of leptin studies. Thus, initial pharmacological work in rodents evidenced that leptin may advance the onset of female puberty; this would suggest that leptin is a primary stimulatory signal of the reproductive system, which could evoke on its own the pubertal activation of the HPG axis [27,28]. Notwithstanding this initial work, later studies testing the effects of leptin administration to rodents and humans with leptin deficiency clearly documented that appropriate leptin levels are indispensable for normal pubertal progression; yet, leptin cannot trigger early puberty *per se* [29].

The above observations are fully compatible with a role of leptin as major permissive, but not stimulatory, signal in the metabolic control of puberty [24,26,29–31]. Thus, threshold leptin levels must be achieved in order to proceed through