

# Interaction Between Energy Homeostasis and Reproduction: Central Effects of Leptin and Ghrelin on the Reproductive Axis

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## Abstract

Reproductive maturation and function are sensitive to the metabolic state of the organism and the magnitude of body fuel reserves; hence, conditions ranging from energy insufficiency to morbid obesity impact the timing of puberty and are frequently linked to fertility problems. This phenomenon is the result of the close interplay between a diversity of nutritional cues and metabolic signals (including hormones) with different elements of the so-called hypothalamic-pituitary-gonadal (HPG) axis. In this review, we will focus our attention on the 'reproductive' roles of 2 key metabolic hormones, namely, the adipose signal, leptin, and the gut hormone, ghre-

lin. These 2 factors, which have been proposed to operate as functional antagonists in the control of metabolism and energy homeostasis, are also provided with important, and in many cases opposite, roles in the regulation of puberty onset and gonadal function. We will provide herein an update view of the reproductive effects of leptin and ghrelin, with a major emphasis on the actions of these 2 key hormones upon the central elements of the HPG axis, including their putative effects on Kiss1 and other reproductive neuronal networks. This will help to understand the mechanisms whereby reproductive function is gated and dynamically regulated by metabolic signals at different key developmental stages, such as puberty and adulthood.

## Introduction: Reproductive Function is Modulated by Metabolic Signals during the Lifespan

Reproduction, as the physiological process that enables any given organism to generate new organisms of the same kind, is essential for the perpetuation of species and, therefore, it is under the control of sophisticated regulatory networks. These networks and signals impinge at different levels of the so-called hypothalamic-pituitary-gonadal (HPG) or gonadotropic axis [1,2]. The core of this neurohormonal system is formed by the hypothalamic decapeptide, gonadotropin-releasing hormone (GnRH), pituitary gonadotropins, LH and FSH, and gonadal hormones of steroid and peptidergic nature [1,2]. These major elements are connected by feed-forward and feedback regulatory loops that are essential for the proper control of reproductive hormone secretion and gonadal function throughout the lifespan [3].

Despite its paramount importance for the survival of species, reproduction is an energy-demanding

function that is dispensable at the individual level. Hence, conditions that perturb organism homeostasis, in which indispensable body functions must be preserved, often result in reproductive impairment. In this context, it is well known that the maturation and function of the HPG axis are sensitive to the magnitude of body energy reserves and to the effects of different nutritional and metabolic factors [4,5]. As a clear example, critical thresholds of fat reserves need to be reached in order to attain complete pubertal development and reproductive capacity in adulthood. While this phenomenon is especially relevant in the female, because of the substantial energy investment that needs to be faced during pregnancy and lactation [6], such a tight association is actually detectable in both sexes, so that conditions of metabolic stress can perturb puberty onset and gonadal function also in males [7]. Moreover, not only energy deficit but also conditions of persistent energy excess, such as morbid obesity, are also frequently associated to reproductive alterations, whose pathophysiological mechanisms remain ill defined.