Metabolic influences on neuroendocrine regulation of reproduction

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Purpose of review
Reproduction is a tightly regulated function in which many mechanisms contribute to ensure the survival of the species. Among those, due to the elevated energy requirements of reproduction, metabolic factors exert a pivotal role in the control of hypothalamic-pituitary-gonadal axis. Although this control may occur at multiple levels of the axis, the majority of interactions between metabolic and reproductive systems take place in the hypothalamus. In this article, we present an overview of the state-of-the-art knowledge regarding the metabolic regulation of reproduction at the central level. We aim to identify the neuroanatomical location where both functions interconnect by discussing the likelihood of each component of the neuronal hierarchical network controlling gonadotropin-releasing hormone release to be first-order responders to metabolic cues, especially the peripheral metabolic signals leptin, insulin, and ghrelin.

Recent findings
Latest evidence suggests that the primary action of leptin, insulin, and ghrelin to regulate reproduction is located upstream of the main central elicitors of gonadotropin release, Kiss1 and gonadotropin-releasing hormone neurons, and neuroanatomically separated from their metabolic action.

Summary
The study of the neuronal interactions between the mechanisms governing metabolism and reproduction offers the platform to overcome or treat a number of prevailing metabolic and/or reproductive conditions.

Keywords
hypothalamus, kisspeptin, leptin, metabolism, reproduction

INTRODUCTION

Reproduction is one of the most energy demanding endeavors of any species and, hence, tight connections between the mechanisms controlling metabolism and reproductive integrity have developed during evolution. Metabolic cues from peripheral tissues and environmental cues translate information reflecting fuel storage and food availability to the central regulators of reproduction, thus assuring the appropriate timing of gestation and survival of the offspring. Sufficient energy stores are critical for the attainment of reproductive maturation and maintenance of fertility in adulthood [1]. Indeed, situations of energy depletion such as anorexia nervosa, excessive exercise, or diabetes –but also extreme energy surplus (e.g., severe obesity) – lead predominantly to delayed or absent pubertal onset in adolescents and hypogonadism in adults, which is usually characterized by hypothalamic amenorrhea [2,3]. Indeed, peripheral metabolic cues and reproductive hormones may act on different targets to regulate food intake and reproduction at multiple levels, for example, at the level of the pituitary [4▪,5▪,6]; however, there is a key central node that coordinates these two functions and that is common to both: the hypothalamus. In this article, we offer a comprehensive review of the latest advances in the identification and characterization of the neuroendocrine mechanisms that bridge metabolism and reproduction in the hypothalamus in mammals, focusing on the mechanism(s) of action of leptin, insulin, and ghrelin as the three major representatives of peripheral metabolic cues.

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