Kisspeptins and the metabolic control of reproduction: Physiologic roles and physiopathological implications

Kisspeptines et le contrôle métabolique de la reproduction : rôles physiologiques et implications physiopathologiques

M. Tena-Sempere a,*,b,c

a Department of Cell Biology, Physiology and Immunology, University of Cordoba, 14004 Córdoba, Spain
b CIBER Fisiopatología de la Obesidad y Nutrición, 14004 Córdoba, Spain
c Instituto Maimónides de Investigaciones Biomédicas, 14004 Córdoba, Spain

Available online 2 April 2010
Presented by Jacques Young

Résumé

Dans cette présentation, nous avons tenté de faire un point sur les connaissances acquises sur les kisspeptines, le système de neuropeptides récemment identifié qui joue un rôle clé dans le contrôle de l’axe gonadotrope et la régulation métabolique de la survenue de la puberté et de la fertilité. La synthèse des travaux expérimentaux rapportée ici, essentiellement réalisés dans des modèles de rongeurs, soutient l’hypothèse que les neurones hypothalamiques Kiss1 canalisent au niveau central les informations métaboliques vers les centres gouvernant la fonction reproductrice par une probable voie leptine-kisspeptine-GnRH qui impliquerait Crtc1 et/ou mammalian target of rapamycin (mTOR) en tant que médiateurs.

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Mots clés : Kiss1 ; Kisspeptine ; mTOR ; Leptine ; GnRH

Abstract

In this presentation, we have provided a succinct state-of-the-art of our knowledge on kisspeptins, the newly identified neuropeptide system with key roles in the control of the gonadotropic axis, in the metabolic regulation of puberty onset and fertility. The experimental evidence reviewed herein, gathered mostly in rodent models, supports the contention that hypothalamic Kiss1 neurons do operate as a central conduit for conveying metabolic information onto the centers governing reproductive function, through a putative leptin-kisspeptin-GnRH pathway, which is likely to involve Crtc1 and/or mTOR as molecular mediators.

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Keywords: Kiss1; Kisspeptin; mTOR; Leptin; GnRH

It is well known that acquisition of reproductive capacity at puberty and its maintenance during adulthood are gated by the state of body energy reserves, especially in the female, where the organism must be able to cope with the considerable energy drainage imposed by pregnancy and lactation [1]. Accordingly, conditions of metabolic stress and energy insufficiency, such as malnutrition or strenuous exercise, are frequently coupled to disturbed reproductive maturation and/or infertility [1]. In addition, obesity is also commonly linked to altered puberty onset and reproductive impairment. Such an impact of the body energy status on the reproductive axis is thought to be conveyed through a number of neuropeptide hormones and metabolic cues, whose nature and mechanisms of action have begun to be deciphered only in recent years.

Among the central signals responsible for the neuroendocrine control of the gonadotropic axis, kisspeptins, the products of

* Corresponding author.
E-mail address: f1tesem@uco.es.
Kiss1 gene that operate via the G protein-coupled receptor, GPR54, have emerged very recently as essential gatekeepers of puberty onset and fertility [2]. This indispensable role is mainly conducted at central (hypothalamic) levels, where kisspeptins have been shown to participate in the regulation of key reproductive phenomena, including sexual differentiation of the brain, the pubertal activation of the GnRH system, the feedback control of gonadotropin secretion and the pre-ovulatory surge of gonadotropins, among others [2,3]. Indeed, kisspeptins have been now characterized as (one of) the most potent elicitors of GnRH/gonadotropin secretion in different mammalian (and non-mammalian) species [2–4]. These pivotal functions have led to the proposal that identification of kisspeptins, as essential players in the reproductive brain, is (probably) the most seminal finding in reproductive biology since the cloning of GnRH back in early 1970s [4].

Compelling evidence is also mounting that the hypothalamic kisspeptin/GRP54 system may also participate in the coupling of body energy status and reproductive maturation (puberty) and function [1,3,5]. Thus, Kiss1 expression at the hypothalamus has been shown to be under the regulation of metabolic cues, as conditions of negative energy balance and metabolic stress are able to induce variable degrees of inhibition of Kiss1 mRNA levels at the hypothalamus in pubertal and adult rodents [1]. In turn, the state of hypogonadotropism and/or lack of puberty induced by chronic subnutrition or metabolic stress (e.g., in uncontrolled diabetes) could be rescued (at least partially) by administration of exogenous kisspeptin [1]. This evidence strongly suggests that kisspeptin neurons at the hypothalamus operate as sensors and neuroendocrine conduits for conveying metabolic information onto reproductive centers, likely GnRH neurons.

A wealth of experimental data has pointed out that the adipose hormone, leptin, is involved in the modulation of Kiss1 expression by nutritional and metabolic factors, as suggested by studies in rats and mice, where leptin has been shown to enhance hypothalamic Kiss1 mRNA levels [1]; a finding replicated in hypothalamic/neuronal cell lines. Such a leptin-kisspeptin pathway provides a tenable explanation for the fact that leptin is capable to influence GnRH secretory function, but its receptors are not expressed in GnRH neurons [1]. Admittedly, other hormonal signals and neuropeptides involved in metabolism and energy homeostasis, such as ghrelin, NPY, IGF1, and melanocortins, have been suggested to modulate Kiss1 expression; yet, their roles in the metabolic control of the kisspeptin system remain ill defined.

Of note, our knowledge on the molecular mechanisms whereby leptin (and eventually other metabolic signals) regulates Kiss1 expression at the hypothalamus has recently been enlarged with the identification of the putative roles of Crtc1 and mTOR in this phenomenon. Thus, the Creb1-regulated transcription coactivator-1 (Crtc1) has been shown to be involved in mediating (at least part of) leptin effects on the hypothalamic Kiss1 system, in line with the fact that Crtc1 KO mice are not only obese and hyperphagic, but also infertile. Such a phenotype is likely related to the ability of leptin to dephosphorylate (and activate) Crtc1, which in turn stimulates the recruitment of Crtc1 to Kiss1 gene promoter and the expression of Kiss1 mRNA at the hypothalamus [6]. In addition, the hypothalamic signaling system involving the mammalian target of rapamycin (mTOR), which has been proposed as transducer for leptin effects on energy homeostasis and food intake, appears to be also involved in the control of the Kiss1 system, as blockade of central mTOR (i) disrupted the normal timing of puberty in female rats, (ii) prevented the permissive effects of leptin in terms of puberty onset, and (iii) resulted in the suppression of Kiss1 mRNA levels, mainly at the arcuate nucleus [7].

In sum, in this presentation we have provided a succinct state-of-the-art of our knowledge on the important roles and mechanisms of action of kisspeptins, the newly identified neuropeptide system with key roles in the control of the gonadotropic axis, in the metabolic regulation of puberty onset and fertility. The experimental evidence revised herein, gathered mostly in rodent models, supports the contention that hypothalamic Kiss1 neurons do operate as a central conduit for conveying metabolic information onto the centers governing reproductive function, through a putative leptin-kisspeptin-GnRH pathway, which is likely to involve Crtc1 and/or mTOR as molecular mediators. Admittedly, key aspects of this ‘metabolic’ network involving the Kiss1 system, such as its different peripheral regulators and central effectors, remain to be fully elucidated. Nonetheless, the proposed hypothalamic circuitry, responsible for transmitting metabolic information onto the reproductive axis through Kiss1 neurons, may explain, at least in part, the tight physiological connection between the state of energy reserves of the body and its capacity to reproduce, thereby providing a tenable mechanism for the well-known alterations of puberty onset and fertility linked to conditions of disturbed energy balance in humans, ranging from anorexia nervosa to morbid obesity.

Conflict of interest statement

The author has not declared any conflict of interest.

References