Kisspeptin as a link between metabolism and reproduction: Evidences from rodent and primate studies

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Changes in metabolic status gate reproductive activity by still incompletely deciphered mechanisms. Many neuropeptides have been shown to be involved in restraining hypothalamic gonadotropin releasing hormone (GnRH) release under conditions of negative energy balance. Broadly, on the basis of their effect on feeding, these can be grouped as orexigenic and anorexigenic neuropeptides. Reciprocally correlated, in response to changes in systemic concentrations of metabolic hormones, the secretion of orexigenic neuropeptides increases while that of anorexigenic neuropeptides decreases during conditions of food restriction. Recently, kisspeptin signaling in hypothalamus has appeared as a pivotal regulator of the GnRH pulse generator. Kisspeptin apparently does not affect feeding, but in light of accumulating data, it has emerged as one of the major conduits in relaying body metabolic status information to GnRH neurons. The present review examines such data obtained from rodent and primate models, which suggest kisspeptin-Kiss1r signaling as a possible pathway providing a link between metabolism and reproduction.

Abbreviations: KP, Kisspeptin; GnRH, Gonadotropin Releasing Hormone; ARC, Arcuate Nucleus; NPY, Neuropeptide Y; AgRP, Agouti Related Protein; GALP, Galanin-like Peptide; MCH, Melanin-Concentrating Hormone; POMC, Proopiomelanocortin; CART, Cocaine- and Amphetamine-Related Transcript; CRH, Corticotrophin-Releasing Hormone.

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1. Introduction

In mammals, it is well established that fertility is gated by metabolic status [1,2]. Metabolic fuel deficiency delays the onset of puberty in pre-pubertal animals [3,4], while in post-pubertal animals hampers pulsatile gonadotropin releasing hormone (GnRH) release with concomitant hypogonadotropic hypogonadism [1,2,5], and the inhibition of sexual behavior [6]. Nutrient intake, after a brief period of food restriction, normalizes the malfunctioning hypothalamic-pituitary-gonadal (HPG) axis, reinstating the process of reproduction [7]. Nevertheless, the mechanistic links between nutrition and the HPG axis, by which food restriction curtails reproduction and food intake transposes it, need to be further elucidated.

Food restriction-associated HPG axis suppression is ultimately caused by a reduction in the release of GnRH from the hypothalamus [8–11]. Alterations in the secretion of many neuropeptides have been shown to be involved in suppressing hypothalamic GnRH release under conditions of negative energy balance [12–14]. Broadly, on the basis of their effect on feeding, they can be grouped as orexigenic and anorexigenic peptides. The orexigenic group includes appetite stimulating...
neuropeptides such as neuropeptide Y (NPY), agouti related protein (AgRP), galanin-like peptide (CALP), and melanin-concentrating hormone (MCH) [15–19], while the anorexigenic group is comprised of appetite inhibiting neuropeptides, among which are products of the proopiomelanocortin (POMC) precursor, cocaine- and amphetamine-related transcript (CART), and corticotrophin-releasing hormone (CRH) [20–23]. The majority of the neuronal systems secreting orexigenic and anorexigenic neuropeptides are concentrated in the arcuate nucleus (ARC) (with the exception of CRH neurons, which are mostly populated in the paraventricular nucleus but are interconnected with the ARC [24,25]), a hypothalamic area critically involved in metabolism and energy homeostasis [16]. The functioning of these neurons is sensitive to circulating concentrations of peripheral metabolic hormones, including ghrelin, insulin, and leptin [26–28]. Leptin and ghrelin are secreted by adipocytes and gastric cells, respectively, and these hormones act reciprocally to signal metabolic status to the brain [26,28].

The kisspeptinergic neuronal system, another neuronal system located in the ARC [29–35], does not appear to affect feeding [36,37], but in light of accumulating data has been unveiled as one of the major conduits in transferring metabolic status related information to GnRH neurons. Parenthetically, kisspeptinergic neurons have been acknowledged to contain leptin receptors [33]. Kisspeptin (KP) gene (Kiss1 mRNA) expression in the ARC is at nadir in animal models of hypoleptinemia [33,37–40], while leptin infusion significantly ameliorates this expression [33,38,40]. In short-term fasting situations, which is characterized by disrupted GnRH release with resulting hypogonadotropic hypogonadism [9,10,41,42], Kiss1 as well as KP receptor (Kiss1r) expression is affected [35,37,39,40]. KP administration rescues fasting induced hypogonadotropic hypogonadism in rats [37], while the HPG axis response to KP, both in initiation and quantity, is attenuated by fasting in monkeys [43]. Moreover, expression of both Kiss1r as well as Kiss1 have been detected in a number of peripheral tissues (including the pituitary, pancreas, and adipose tissue) concerned with energy homeostasis and reproduction [44–47]. KP has also been acclaimed to affect secretion of metabolic hormones, including aldosterone, adiponectin, insulin, growth hormone, oxytocin, and prolactin [48–55]. All these observations suggest a potential role for KP in connecting metabolic status with reproductive function. Herein, we will review the currently available evidence obtained from rodent and primate studies implicating KP-Kiss1r signaling as a possible central mechanism, which adjusts reproductive function according to energy availability.

2. Biology of KP and Kiss1r

About 16 years ago, the KiSS1 gene was isolated as a human melanoma metastasis suppressor gene by Lee et al., [45] using differential display and subtractive hybridization techniques in human melanoma cells. They observed that KiSS1 expression was confined only to sound cells while transfection with KiSS1 cDNA inhibited metastasis of melanomas without affecting proliferation and migration properties of the cells. They, therefore, named the gene as metastasis suppressor sequence “KiSS1”. The name KiSS was coined due to the famous “chocolate kisses” of Hershey, the town in Pennsylvania, home to the institute and investigators who discovered KiSS1 [56]. Like melanoma, similar properties of KiSS1 were subsequently noted in human breast carcinomas [57].

Interestingly, KiSS1 was first believed to be found on chromosome 6 [45]. However, later radiation hybrid mapping and fluorescence in situ hybridization confirmed the presence of the KiSS1 gene to the long arm of chromosome 1, where it exists as a single locus on 1q32, but its anti-metastatic activities are dependent on an additional sequence on chromosome 6 [58].

The gene encoding KP is known as KiSS1 in human and Kiss1 in all animals [59]. KP appertains to the RF-amide superfamily of peptides, which are punctuated by an Arg-Phe-NH2 terminal signature [44,46,47]. The KiSS1 gene encodes a precursor peptide of 145-amino acids, which by post-translational modification is proteolytically processed into shorter biologically active C-terminal amidated products that all belong to the KP family of peptide hormones. The main members of the KP family of peptide hormones are KP54, KP14, KP13, and KP10 (numbers indicating amino acids length) [44,46,47]. Processing of the rat and mouse Kiss1 gene has been noted to produce a mature peptide of 52, rather than 54, residues in length [60]. Binding and functional assays showed that KP-54, -14, and -13 as well as KP-10 had the same affinity and efficacy on the Kiss1r receptor, indicating that the C-terminal decapeptide shared by the all KPs is the minimum amino acid sequence mandatory both for binding and activation of Kiss1r [44,46,47].

In 1999, GPR54 (also named AXOR12 or hOT7T175 [46,47], but now globally recognized as KISS1R1 in human and Kiss1r in all other animals [59]) the receptor for KP was identified initially as an orphan G-protein coupled receptor in rat brain tissue by Lee et al., [61]. A few years later, the human ortholog of rat Kiss1r was identified and the encoding gene was localized to chromosomal position 19p13.3 [46,47]. Kiss1r is a 396 amino acid protein, which shares significant identity in the transmembrane region with rat galanin receptors GalR1 (45%), GalR3 (45%), GalR2 (44%), and the rat opioid receptor DOR (37%). Despite these structural similarities with galanin receptor, galanin was unable to bind or activate Kiss1r [61].

Upon binding with KP, Kiss1r is coupled to G proteins of the Gq/11 subfamily forming a complex that, when activated, results in the release of intracellular calcium stores and activation of phospholipase C-β. Other intracellular transduction pathways recruited by Kiss1r after activation include accumulation of inositol-1,4,5-trisphosphate, hydrolysis of phosphatidylinositol 4,5-bisphosphate, release of arachidonic acid and phosphorylation of extracellular signal-regulated kinases 1/2 and p38 mitogen-activated protein kinases [44,62]. Moreover, KP also induces stress fiber formation in GPR54-expressing cells through Rho activation [44], and recently, KP-13 was noted to induce reduction of the insulin response to exendin-4 independent of Gi proteins in pancreatic β-cells [53].

Expression and co-expression of Kiss1r and its cognate ligand precursor, Kiss1, has been documented in several central as well as peripheral tissues [47]. Kiss1 mRNA is expressed in several brain regions including the hypothalamus, a key area for regulation of both reproduction and
metabolism [32,35,45,63,64]. Within the hypothalamus, KISS1/Kiss1 mRNA is highly expressed in the ARC and the anteroventral periventricular nucleus [32,35,45,64]. It is also highly expressed in several peripheral tissues, such as placenta, pituitary, and pancreas. Moreover, low levels of KISS1/Kiss1 mRNA are also noted in the small intestine, thymus, spleen, lung, stomach, testis, kidney, liver, adrenal gland, and adipose tissue [39,45,49,52]. KISS1R/Kiss1r is also highly expressed in central (midbrain, hypothalamus, thalamus, hippocampus, amygdala, cortex, frontal cortex, pons and striatum) and peripheral (pituitary gland, liver, intestine, pancreas, and placenta) tissues of rodents and primates including humans [32,35,44,46,61,65–67].

3. Evidences demonstrating KP as a link between metabolism and reproduction

3.1. Presence of KP secreting neurons in the hypothalamic ARC

Kiss1 mRNA expressing cells have been consistently detected in ARC of several species including both non-primates and primates [29–32,34,35,37,68–71]. The hypothalamic ARC, known as infundibular nucleus in man, is an aggregation of neurons in the medio basal hypothalamus, adjacent to the third ventricle and the median eminence [16]. Positioned outside the blood-brain barrier, the neuronal networks in the ARC are directly bathed by systemic metabolic factors (such as leptin, insulin, and ghrelin, etc), and therefore, are ideally placed to be responsible for transmitting metabolic status related information into the brain [16,26–28].

The ARC acts both as a feeding and satiety center [16]. The feeding center contains orexigenic neurons, which stimulate appetite – important neuronal populations present in this region are NPY, MCH, AgRP, and GALP. The majority of these neurons are located in the ventromedial aspect of the ARC [15–19]. Alternatively, the satiety center neurons appear to populate the ventrolateral division of the ARC. This area contains anorexigenic neurons such as POMC and CART, which stifle appetite [20–23]. In addition to having transynaptic connection with one another, the ARC neuronal systems have extensive reciprocal connections with other hypothalamic regions, including the paraventricular nucleus, lateral hypothalamic areas, and dorsomedial hypothalamic nucleus, that are important in the regulation of food intake [25,72,73]. Furthermore, neural projections from the ARC make direct contact with GnRH neurons [68,74,75] and GnRH neurons contain receptors for neuropeptides produced in ARC [30,66,68,76,77]. Therefore, the ARC contains a complex neurocircuit that can serve to integrate changes in food intake/energy balance with the regulation of reproductive function.

Kisspeptinergic neurons, unlike the other neuronal systems of feeding and satiety in the ARC, do not appear to affect food intake [36,37], but are responsive to circulating metabolic factors. In particular, the adipocytic hormone leptin has been recently acknowledged to modulate ARC Kiss1 expression [33,37–40,78]. Indirect relay of metabolic information by KP to the neuroendocrine reproductive axis is also possible. Many studies have demonstrated Kiss1r expression not only on GnRH neurons [30,66,68,76] but also in numerous discrete areas of the hypothalamus [32,35,46,61,64,65,79,80], suggesting that KP affects GnRH neurons both directly and indirectly [80,81]. Indeed, Backholer et al. [78] have shown the presence of reciprocal input to the neurons of feeding (NPY) and satiety (POMC) from KP neurons in the ARC of the sheep. KP-immunoreactive varicose fibers were seen in close apposition to both POMC and NPY cell bodies, and vice versa. This anatomical evidence suggests that KP cells affect the function of neurons involved in metabolic homeostasis. Indeed, KP infusions modulated expression of both POMC and NPY mRNA [78]. However, Castellano et al. [37] found no effect of KP infusion on the expression of NPY, AgRP, CART, and POMC genes in the rat. Nevertheless, further work is needed to determine whether KP administration affects secretion of NPY and POMC in vitro or in vivo. Recently, KP has been documented to directly excite POMC neurons, while indirectly inhibit NPY neurons [82].

Therefore, on the basis of currently available evidence, direct interpretation of metabolic information by KP neurons and transmission of this information to the reproductive or feeding axis is very plausible. Reciprocal input from neuronal systems of the feeding and satiety centers to Kiss1 expressing cells is also possible, which may affect Kiss1 expression as well as KP release. Parenthetically, NPY knockout mice have defective expression of Kiss1 [40], suggesting that an intact NPY neuronal system is necessary for correct functioning of kisspeptinergic neurons. Likewise, recently co-expressions of other important neuropeptides have been detected on the kisspeptinergic neurons, namely dynorphin A and neuropeptide B [83]. Whether KP neurons have receptors for NPY, POMC, CART, GALP, and AgRP or receive synaptic input from these neuronal systems requires attention. In this regard some evidence has already been provided showing that KP neurons receive reciprocal connections from POMC and NPY in ewe [78].

3.2. Alteration of the hypothalamic KP-Kiss1r system in paradigms of energy imbalance

The link between metabolism and reproduction is of a central origin, primarily at the level of the hypothalamus, and is pivotal in regulating GnRH neuronal drive to the reproductive axis. This is evident from studies that have demonstrated that pituitary gonadotrophs retain normal responsiveness to GnRH under conditions of energy imbalance [8–11,84–86]. A key question that remains unanswered is the identity of the neuronal mechanism through which changes in metabolic status modulate the activity of GnRH neurons. In this section, we examine the evidence that suggests the involvement of KP in modulating the reproductive system in different paradigms of altered energy homeostasis (Table 1) [35,37,40,43,87–91]. In some of these paradigms, sources of metabolic fuels decrease (fasting), while in others (such as obesity and diabetes) more than sufficient reserves of metabolic fuels are available, but the body cannot utilize them.

3.2.1. Fasting
Fasting is a metabolic fuel deficient condition, characterized by deficiency of not only various macronutrients crucial for
normal growth but also of calories [1,2]. During a fasting situation, many changes occur in the body's neuroendocrine physiology. These changes primarily lead to processes that generate glucose from body reserves of glycogen and non-carbohydrate sources (fat and protein) [1,2]. Metabolic deficiency during fasting conditions also activates mechanisms to minimize less essential biological processes in order to allocate more energy for essential processes. Reproduction is the most obviously affected process under conditions of negative energy balance [1–11]. Food restriction induced suppression of reproduction is characterized by a decrease in release of GnRH, rather than a suppression of pituitary sensitivity to GnRH [8–11]. However, how food restriction affects neural mechanisms that control the intermittent GnRH discharge is poorly understood.

In rats, a 72 h fast has been noted to delay the pubertal awakening of the HPG axis, in part, through lowered hypothalamic expression of Kiss1 [37]. This finding suggests that for normal pubertal activation of the HPG axis, an adequate supply of metabolic fuel is essential, which in turn conveys its impact to the reproductive axis via KP neurons. It is now well established that puberty begins with an increase in release of GnRH, rather than a suppression of pituitary sensitivity to GnRH [8–11]. Food restriction induces neural mechanisms that control the intermittent GnRH discharge is poorly understood.

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Table 1 – Summary of the hypothalamic Kiss1 and Kiss1r mRNA expression in various experimental metabolic paradigms, and the HPG axis responsiveness to KP challenge under these metabolic conditions.

<table>
<thead>
<tr>
<th>Metabolic Paradigm</th>
<th>Kiss1 mRNA</th>
<th>Kiss1r mRNA</th>
<th>HPG axis response to KP</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>↓</td>
<td>↓, ↑</td>
<td>↓, ↑</td>
<td>[35,37,40,43]</td>
</tr>
<tr>
<td>IIH</td>
<td>↓</td>
<td>?</td>
<td>=</td>
<td>[87,88]</td>
</tr>
<tr>
<td>lactation</td>
<td>↓</td>
<td>=</td>
<td>=</td>
<td>[89,90]</td>
</tr>
<tr>
<td>STZ induced diabetes</td>
<td>↓</td>
<td>=</td>
<td>=</td>
<td>[38]</td>
</tr>
<tr>
<td>Diet induced obesity</td>
<td>↓</td>
<td>?</td>
<td>?</td>
<td>[91]</td>
</tr>
<tr>
<td>-do-</td>
<td>↑</td>
<td>?</td>
<td>?</td>
<td>[40]</td>
</tr>
<tr>
<td>ob/ob mouse</td>
<td>↓</td>
<td>=</td>
<td>?</td>
<td>[33,91]</td>
</tr>
<tr>
<td>NPY knock out rat</td>
<td>↓</td>
<td>↓</td>
<td>?</td>
<td>[40]</td>
</tr>
<tr>
<td>MSG-induced hypothalamic lesion</td>
<td>↓</td>
<td>?</td>
<td>?</td>
<td>[39]</td>
</tr>
</tbody>
</table>

Abbreviations: ↑ Increase; ↓ Decrease; = No effect; ? currently unknown.

increased Kiss1r mRNA expression (Fig. 2) [37], with higher LH response to exogenous KP challenge, while in monkeys a 48-h fast was used, which causes a decrease in the expression of Kiss1r mRNA (Fig. 2) [35], with lower HPG axis response to exogenous KP [43].

The nature of the metabolic signals produced during fasting conditions that affect KP signaling is not known. Important factors in this regard could include adiponectin, cortisol, ghrelin, glucose, insulin, leptin or other metabolically vital biochemical factors as shown in Fig. 3 [41,42,54,93,94]. Glucose is a crucial oxidizable fuel that functions as metabolic

![](image1.png)

**Fig. 1 – Changes in mean (± SEM) plasma testosterone (T) before and after KP10 and vehicle (V) treatments in:**

Adapted with permission from Wahab et al., [43,87].
Fig. 2 – Possible mechanism for food restriction induced suppression of the HPG axis in rats, mice, and rhesus monkeys. Hypothalamic Kiss1 and Kiss1r mRNA expression decreases (↓) while GnRH1 mRNA expression remains normal (±) during acute fasting in mice and monkeys. This reduction in the hypothalamic Kiss1 and Kiss1r expression may contribute to the suppression of the HPG axis in two ways: first, by a decrease in the Kiss1peptinergic drive to the HPG axis; and second, through a reduction in the sensitivity of the GnRH neuronal network to endogenous KP stimulation during fasting conditions. In contrast, in rat expression of Kiss1 decreases while expression of Kiss1r increases during fasting situation. Therefore, the suppression of the HPG axis in rat may be due to decrease in Kiss1peptinergic drive to the HPG axis and not because of change in the HPG axis sensitivity to KP.

signal to regulate LH release [94–96]. But glucose does not appear to be responsible for affecting GnRH-Kiss1r signaling because in acute hypoglycemia induced by insulin administration, GnRH neuronal sensitivity remains preserved to exogenous KP treatment (Fig. 1B) [87]. This characteristic appears to be specific for KP because GnRH neuronal sensitivity to N-methyl-D-aspartate (NMDA) administration is attenuated both in fasting [97] and insulin-induced hypoglycemia (IIH) [87]. This notion suggests that excitatory amino acids (EAA) signaling is modulated by both fasting and IIH, while KP signaling is regulated by factors resulting from fasting, which may not be generated in IIH or if generated may not be to a level sufficient to alter GnRH-Kiss1r sensitivity to KP. Most likely candidates in this regard are leptin and cortisol, both of which are capable of modulating Kiss1 expression [33,37–40,78,88]. Whether leptin or cortisol can affect GnRH-Kiss1r sensitivity requires further examination. In this regard, we are investigating GnRH neuronal sensitivity to KP in short and long-term exposure to cortisol. More recently, ghrelin has been shown to decrease the expression of Kiss1 in the hypothalamus [98]. This effect has been shown to be a result of food restriction induced hyperghrelinemia and also exogenous ghrelin administration [98]. These observations suggest that ghrelin induced down regulation of hypothalamic Kiss1 expression may be one of major contributing factors in fasting induced suppression of the HPG axis.

3.2.2. Lactation
Lactation is a physiological model of hyperphagia. During lactation, negative energy balance, resulting from a large energy drain due to milk production, causes suppression of cyclic ovarian function [99,100]. Moreover, during lactation the alteration in reproductive activity is additionally caused by the suckling stimulus suppressing gonadotropin release [101–104]. In all species for which there are adequate data, suckling clearly inhibits normal pulsatile release of LH [103–105]. As LH pulses occur in response to the pulsatile secretion of GnRH from the hypothalamus [106,107], it is inferred that the suckling stimulus inhibits the normal pattern of hypothalamic release of GnRH [101,102,108]. The decrease in pulsatile stimulus with advancing lactation (related to the growth of the young and their use of alternative food sources) or artificial removal of the nursing pups, reverses many of the adaptations associated with the suckling stimulus, including the increase in frequency of pulsatile LH release [109,110]. The mechanism by which lactation alters the pulsatile GnRH release is not understood, but is upstream of GnRH neurons because total hypothalamic content of GnRH mRNA does not change during lactation [111,112].

Hypothalamic KP-Kiss1r signaling may provide an overt central mechanism that links the suckling stimulus to GnRH neuronal function. Lactation leads to a profound reduction in expression of Kiss1 mRNA and its product, KP, in the ARC in lactating ovariecotomized rats [89]. The lactating ovariecotomized rats retain responsiveness to exogenous KP because LH secretory responses to central KP administration in lactating mothers are similar to those in nonlactating rats [89]. This preserved response of GnRH neurons is unique for KP because lactating rats do not secrete GnRH in response to depolarizing effects of NMDA [113,114], indicating that GnRH neurons become refractory to excitatory stimulation of EAA. In contrast to these observations, Roa et al., [90] demonstrated that although, intracerebral injections of high doses of KP were able to elicit LH secretory responses in lactating mothers, the magnitude of these responses was significantly attenuated as compared to non-lactating controls. Thus, a significant impact of lactation on the GnRH neuronal sensitivity to KP in terms of gonadotropin secretion was demonstrated. Altogether, these findings suggest that diminution in Kiss1 gene expression associated with lactation may lead to decreased synthesis and secretion of KP, which in turn could diminish the pulsatile secretion of GnRH and would be mechanistically relevant for the observed inhibition of the HPG axis during lactation. Currently, signals responsible for the suppression of Kiss1 expression during lactation are unknown, but it is reasonable to speculate them as an amalgam of central and peripheral factors that are involved in mediating the increase in food intake during lactation.
3.2.3. Obesity

*Ob*/*ob* mouse, lacking the leptin gene, is characterized by severe obesity and hypogonadotrophic hypogonadism [115,116]. A possible causative hypothalamic mechanism for this abnormality of reproductive function in *ob*/*ob* mouse was recently observed to be associated with disruption of hypothalamic KP- Kiss1r signaling. *Ob*/*ob* mouse has reduced expression of the *Kiss1* gene [33]. In *ob*/*ob* mouse, exogenous injections of leptin reverse the adverse effect of obesity on reproductive organs, and rescue fertility in both males and females [115,116]. Moreover, leptin infusion significantly ameliorates Kiss1 expression [33], pinpointing KP neurons as the missing link for the effects of leptin on neuroendocrine reproductive axis in obese animals and human. In contrast, caloric restriction does not rescue reproductive function in the *ob*/*ob* mouse, which indicates that obesity *per se* is not responsible for causing infertility during leptin deficient conditions, and again highlights that leptin is necessary for reproductive function [117].

3.2.4. Diabetes

Streptozotocin (STZ)-treated rat, a widely used model of type I diabetes, is characterized by hypoinsulinemia with resulting hyperglycemia due to destruction of the insulin-producing beta cells of the islets of Langerhans in the pancreas [118]. The STZ induced diabetic animals are also characterized by hypogonadotrophic hypogonadism [119–121]. In diabetic rats, numerous studies have demonstrated that hypothalamic GnRH content and secretory capacity is conserved [120,121], suggesting that the causative agent for gonadotropin deficiency in the diabetes lies upstream of GnRH neurons, though there are conflicting data about the pituitary responses. Howland and Zebrowski [85,86] and Frenkel and colleagues [84] observed normal functioning of pituitary glands in diabetic rats versus control, whereas others observed an impaired LH and FSH response to GnRH [122,123]. A more comprehensive explanation for these observations was provided by Castellano et al., [38] and George et al., [124], demonstrating that LH response to KP administration remains normal in the diabetic rat and human diabetic patients. As LH pulses occur following GnRH pulses, therefore, GnRH neuronal response to KP and pituitary response to GnRH remain intact, and the primary defect, which is causing hypogonadotropism, must be upstream of GnRH neurons. This defect involves, more likely, a decrease in excitatory drive to the GnRH neurons, and Kiss1 expression is at a nadir in diabetic rats, while Kiss1r expression is normal [38]. Hypoleptinemia in the diabetic model has been proposed to be most possible factor...
responsible for decreased expression of Kiss1 because leptin infusion significantly increased Kiss1 expression while insulin and IGF failed to do so [40].

3.3. Modulation of hypothalamic KP secretion by the metabolic hormone leptin

As discussed above, hypothalamic Kiss1 expression is modulated by leptin infusion in various metabolic paradigms of altered energy balance [33,38,40,78]. Leptin is a peptide hormone. It is secreted by white adipose tissue. It is one of the major indicators of body metabolic reserves. Systemic leptin levels are directly proportional to the mass of fat in body [125]. Circulating leptin levels are sensitive to acute changes in food intake. Leptin levels decrease in food deprivation conditions as compared to normal fed conditions [126–129].

Leptin links body metabolic status-related information with various neuroendocrine functions including the neuroendocrine regulation of reproduction [26,125,130–132]. Starvation induced hypoleptinemia leads to decrease in puberty onset [134]. Leptin replacement via exogenous infusion significantly increased pubertal progression [904].

Leptin acts on the HPG axis indirectly because GnRH axis while leptin infusion has been illustrated to reverse the starvation induced suppression of the HPG axis [93,130,131]. Leptin is also essential for the attainment of reproductive ability at time of puberty onset, as ob/ob mice do not undergo puberty [115,116]. However, elevation of circulating leptin levels through exogenous administration does not cause precocious GnRH release in prepubertal rhesus monkeys [133], suggesting that leptin plays a permissive role in the initiation of puberty in rhesus macaques. As mentioned earlier, ob/ob mice are infertile [115,116]. Similarly, human subjects with congenital defects in the leptin signaling pathway show abnormalities in the proper functioning of the reproductive axis including the lack of activation at time of puberty onset [134]. Leptin replacement via exogenous administration has been documented to permit reproductive function commencement in these subjects [135–137].

Leptin acts on the HPG axis indirectly because GnRH neurons do not express ObRb, the putative leptin receptor [131,138,139]. One of the most important mechanisms of leptin actions on the reproductive axis has recently been unveiled. Leptin has been shown to act on the reproductive axis via hypothalamic kisspeptinergic neurons [33]. About 40% of kisspeptinergic neurons in the ARC nucleus express leptin receptors [33]. In situations of metabolic fuels deficiency, hypoleptinemia leads to decrease in Kiss1 mRNA expression in the hypothalamus [33,35,37,40] while exogenous leptin infusion significantly ameliorates Kiss1 mRNA expression [33,40]. Taken together, these findings suggest that leptin directly acts on the hypothalamic KP secreting neurons to modulate the HPG axis performance (Fig. 3) [33]. Indirect action of leptin on KP secreting neuron is also possible because leptin receptors also express on other hypothalamic neurons [131] which have connections with kisspeptinergic neurons [78,82].

3.4. Expression and action of Kiss1 and Kiss1r in peripheral tissues implicated in energy homeostasis and reproduction

Comprehensive analysis of Kiss1 and Kiss1r expression has revealed that the signaling duo are highly expressed in two types of organs: (1) those which are concerned with energy homeostasis and (2) those governing reproduction. The hypothalamus and the pituitary, which are involved in control of both energy balance and reproduction, express Kiss1 and Kiss1r [35,44–47,64,140–145]. In addition, expression of both ligand and receptor genes has been observed in the pancreas, placenta, adipose tissue, adrenal gland, and intestine [39,44,46,47,49,52,53,61]; these are tissues, which are mainly concerned with energy homeostasis. Similarly, Kiss1 and Kiss1r genes are also expressed in the gonads, which drive reproduction [146–148]. The actions of KP-Kiss1r in the physiology of these peripheral tissues are currently not understood, but the effect of KP on the endocrine output (Table 2 [44,48,49,52–55,149,150]) of these tissues may give us clues to potential importance of KP’s presence.

4. Conclusions and future recommendations

In summary, hypothalamic kisspeptinergic neurons are positioned in such a way to integrate information, regarding nutritional status, from heterogeneous sources (central as well as peripheral) and relay this to the neuroendocrine reproductive axis. There are three possible pathways by which kisspeptinergic neurons may convey metabolic status related information to GnRH neurons (Fig. 2): (1) direct perception of metabolic information and passage of this to GnRH secreting cells; (2) interpretation of metabolic information from orexigenic and anorexigenic neurons and transmission of this to GnRH neurons; (3) indirect relay of metabolic information to GnRH neurons through afferent interneuronal systems having synaptic contact with GnRH neurons. Additionally, KP drive may also generate stimulatory cues to certain metabolic hormones.
The nuts and bolts of the neurocircuitry, that connects metabolic status-related information with kisspeptinergic neurons or carries it from KP neurons to GnRH neurons and/or metabolic efferent pathways, are required to be fully explored. In this regard, the precise interaction between kisspeptinergic neurons and orexigenic or anorexigenic neurons in the ARC also needs to be studied. Currently, there is evidence for input from KP secreting cells to POMC and NPY cells in sheep (Fig. 2) [78], but whether these neurons express Kiss1r or send reciprocal output to kisspeptinergic neurons should be properly investigated. Similarly, other hypothalamic neuronal systems altered during energy challenge may also be important. Recently, KP has been documented to directly excite POMC neurons while indirectly inhibit NPY neurons [82]. KP has been also shown to affect glutamate and GABA secretion [151].

Among peripheral metabolic effectors, available data have evidenced that leptin is a significant up regulator of hypothalamic Kiss1 expression [33,37–40,78]. Further work is needed to clarify the possible mechanisms by which leptin modulates Kiss1 expression because leptin receptors are present on kisspeptinergic neurons as well as on other neuronal circuits no doubt having some interaction with KP secreting neurons [33]. Despite this True et al. [152] recently showed that physiological doses of leptin do not restored the negative energy balance induced decrease in Kiss1 mRNA and LH to control levels. They have concluded that leptin is not a critical signal for KP or LH restoration during short-term fasting of 48 h. Also, the role of metabolic factors other than leptin in modulating Kiss1 expression needs to be determined. Leptin infusion, though significantly augments Kiss1 expression in animal models of metabolic disruptions, does not fully restore it. In this regard other adipokines (particularly adiponectin and resistin), thyroid hormone, insulin, and gut hormones are likely to be important. Likewise, it is critical to understand role of factors generated during energy challenge such as cortisol, which is capable of suppressing Kiss1 expression [88].

Recent observation that KP stimulates reproductive hormone secretion in the human male with mild biochemical hypogonadism and type 2 diabetic patients with hypogonadism [124] suggests that KP can be a potential hormone replacement therapy for reproductive hormone deficiency in human patients of metabolic disorders. However, further larger clinical trails are required before KP can be widely recommended as hormonal therapy for human hypogonadotropic hypogonadism patients. More importantly, clinical studies on the assessment of the long-term efficacy and safety of KP are needed. Of note, the findings of animal experiments suggest that leptin is a key upstream regulator of KP in conditions of negative energy balance [33,37–40,78]. Therefore, clinical studies on the effect of combine KP and leptin infusion in human patients of leptin deficiency with reproductive abnormalities will be worth.

Kiss1 and Kiss1r expression in these tissues in conditions of energy challenge could be enlightening to the knowledge of the specific role of KP in these tissues. Indeed, in adipose tissue Kiss1 mRNA expression is regulated by fasting-associated metabolic signals and also by gonadal steroids [39], but how this is related to the performance of reproductive axis requires attention. Moreover, the effect of KP on secretion of metabolic hormones would pinpoint it as a regulator of metabolism and energy homeostasis, but again correlation of this action with reproduction is not clear at the moment and requires further work.

It is pertinent to mention that certain physiological conditions, like puberty and pregnancy, are characterized by an increase in the basal metabolic rate of body [153]. In the foregoing conditions, the activity of KP-KISS1R system is also greatly enhanced [154,155]. The role of KP has been comprehensively studied in the metabolic regulation of puberty [37,154], where, more likely, KP is linking metabolism with pubertal initiation. However, the metabolic importance of such a tremendous increase in peripheral KP levels during pregnancy [138] remains elusive. Clearly, more work is needed to understand any potential role of KP in pregnancy-associated metabolic perturbations.

KP-Kiss1r signaling is critical in the regulation of the reproductive axis in mammals, including rodents and primates, in situations of metabolic challenge. As to whether it is just another redundant pathway or the master conduit for relaying such information to GnRH neurons, the current pace of research is soon likely to unravel. Further establishment of the physiological role of KP signaling in linking reproduction and energy metabolism will likely make central/peripheral Kiss1-Kiss1r signaling potential drug target for treatment of reproductive problems that occur in metabolic disorders. Indeed, very recently KP restores reproductive hormone secretion in human diabetic patients with hypogonadism [124].

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Conflict of interest

Disclosure: Authors have nothing to disclose.

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