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Review

Diabetes Type 2 and Kisspeptin: Central and Peripheral Sex-Specific Actions

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Kisspeptin (KP) plays a major role in the regulation of reproduction governed by the hypothalamic–pituitary–gonadal (HPG) axis. However, recent findings suggest that the KP system is present not only centrally (at the level of the hypothalamus), but also in the peripheral organs crucial for the control of metabolism. The KP system is sexually differentiated in the hypothalamus, and it is of particular interest to study whether sex-specific responses to type 2 diabetes (DM2) exist centrally and peripherally. As collection of data is limited in humans, animal models of DM2 are useful to understand crosstalk between metabolism and reproduction. Sex-specific variations in the KP system reported in animals suggest a need for the development of gender specific therapeutic strategies to treat DM2.

Highlights

Kisspeptin (KP) is a key molecule for the regulation of the hypothalamic–pituitary–gonadal axis and is also involved in the integration of metabolic cues to allow reproductive functions.

KP systems are altered both centrally and peripherally in animal models of diabetes type 2 (DM2), which may account for both reproductive and metabolic dysfunctions in this disease.

Alterations in the KP system appear to be sex and organ specific in rat models of DM2.

Data collected in both sexes in rats suggest that gender differentiated pharmaceutical approaches should be considered to develop new therapeutic strategies for DM2.

Global Epidemics of Obesity and Diabetes

The human population is struggling with a worldwide epidemic of obesity. Most common causes of this metabolic disruption are: positive energy balance, sedentary lifestyle, and limited physical activity (https://www.who.int/nmh/publications/ncd-status-report-2014/en/).

Another disease that results from obesity is DM2, accounting for nearly 90% of all cases of diabetes [1]. DM2 is characterized by elevated blood glucose, insulin resistance (IR), and pancreatic islet β cell dysfunction [2].

Besides primary metabolic health problems occurring in people with obesity and DM2, there are numerous secondary physiological alterations including damage to the cardiovascular system, eyes, kidneys, nerves, and reproductive system (e.g., disruptions of the menstrual cycle, premature child birth, miscarriages in women, decrease in testosterone concentrations in men, and fertility impairment both in men and women) [3,4].

Moreover, certain aspects of glucose homeostasis and energy balance are regulated differently between sexes [5]. There are also sex differences in the development of DM2, with women favoring fat tissue storage, and men tending to mobilize adipose tissue burning [6]. Additionally, women also have greater insulin sensitivity compared to men. Finally, sex differences in body fat distribution exist that appear to be largely a result of differences in sex hormones between men and women [7].

KP, a Possible Link between Reproduction and Metabolism

There is a lack of synthetic knowledge considering the interplay between metabolism and reproduction, however, the peptide KP could be a missing link. KP was first discovered as a metastasis inhibitor and named metastin [8]. Later, this peptide was shown to be a key molecule for the regulation of the hypothalamic-pituitary-gonadal (HPG) axis, as the absence of KP or of its functional receptor resulted in hypogonadotropic hypogonadism (HH); a condition characterized by low sex steroid and gonadotropin concentrations [9,10]. Moreover, KP is now considered to be the most potent stimulator of gonadotropin-releasing hormone (GnRH) secretion (see Figure I in Box 1 for a description of the HPG axis, which controls reproduction).

In mammals, two major populations of KP-synthesizing neurons exist in the anterior preoptic area (POA) and the arcuate nucleus (ARC) of the hypothalamus, respectively. In rodent hypothalamus,

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Box 1. Central Control of Reproduction by Peripheral Hormones

Reproduction is governed by gonadotropin releasing hormone (GnRH) released from hypothalamic neurons. This hormone stimulates the release of gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH), into blood from the pituitary gland. LH and FSH then act on the gonads – ovaries and testes to promote their maturation, gametogenesis, and production of steroid hormones (Figure I). Steroid hormones exert positive and negative feedback at the hypophyseal and hypothalamic levels but their influence on GnRH neurons is mostly indirect and requires the involvement of interneurons. The HPG axis is also undergoing a central fine-tuned regulation by different metabolic cues released by peripheral organs including fat, pancreas, stomach, and liver (Figure I).

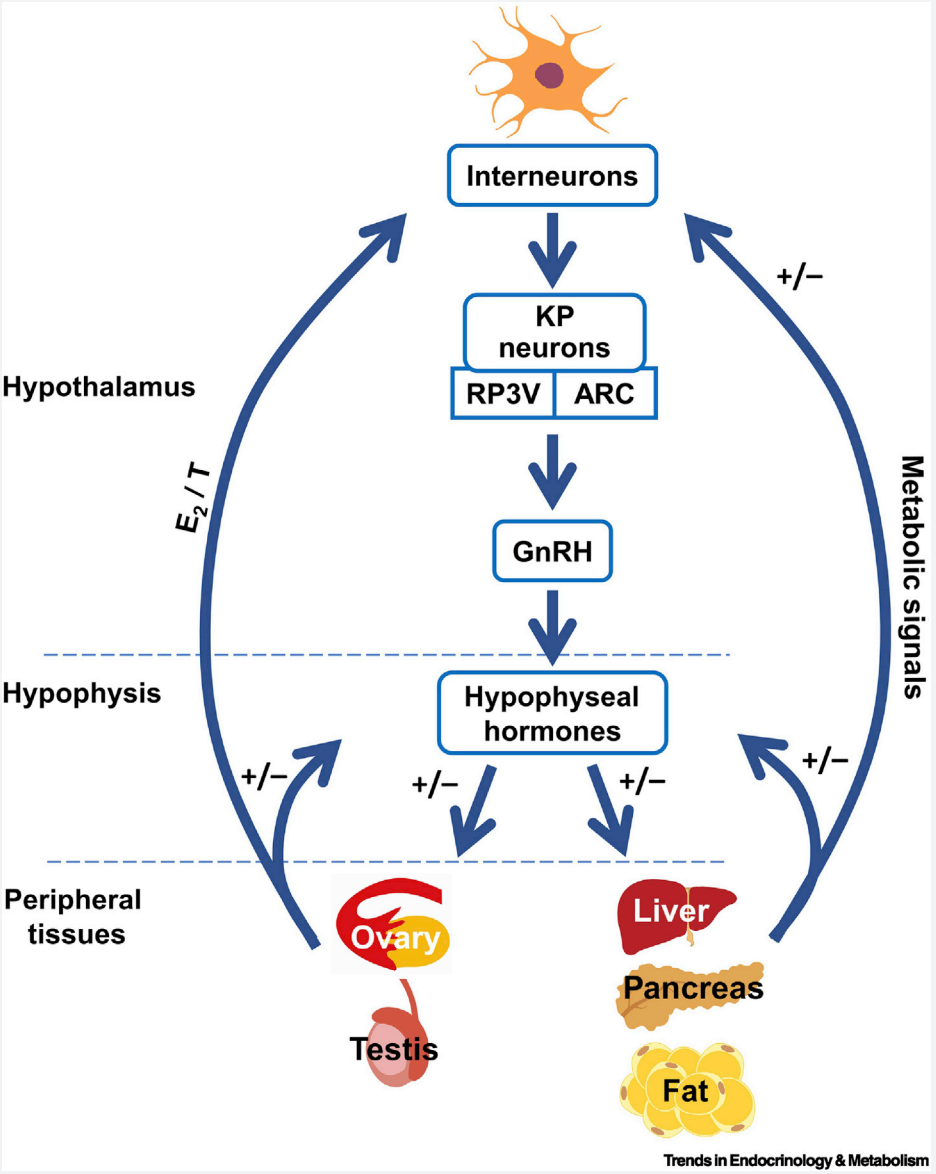

Figure I. Interactions between the Hypothalamic–Pituitary–Gonadal Axis and KP.

Abbreviations: ARC, arcuate nucleus of the hypothalamus; E_2, estradiol; KP, kisspeptin; RP3V, rostral periventricular area of the third ventricle; T, testosterone.

KP neurons are found in two main populations of neurons located in the rostral periventricular area of the third ventricle (RP3V) and in the ARC [11]. Both KP cell populations are also present in humans, with the majority of neurons located in the infundibular nucleus (Inf) [12,13]. While the first group of cells is required for the preovulatory surge of GnRH and subsequently luteinizing hormone (LH), the second one projects onto GnRH terminals and is important for pulsatile LH release. In the RP3V, KP synthesis is enhanced by estradiol (E_2), while in the ARC it is inhibited [14].

KP neurons from the ARC have been renamed KNDy neurons as they coexpress KP, neurokinin B (NKB), and dynorphin (DYN) in most mammalian species [11]. However, there are species and sex differences in expression of KNDy peptides in these neurons (Table 1). It has been proposed that GnRH pulse generation is initiated in the KNDy neuronal network by an interplay of stimulatory NKB signals and inhibitory DYN inputs, which drives the secretion of KP to master GnRH release [11].

The interplay between reproduction and metabolic cues is likely to occur in the ARC where several neuronal populations controlling food intake and lipid metabolism have been described, such as neuropeptide Y (NPY), proopiomelanocortin (POMC), and somatostatin (SST) [15,16]. Moreover, KP effects on metabolism seem to be sexually differentiated. *Kiss1r* knockout (KO) mice are characterized by altered metabolic phenotype with increased adiposity and reduced energy expenditure [17]. However, only mature female *Kiss1r* KO mice have higher body weight and increased white adipose tissue mass [18]. Additionally, a short period of fasting decreases *Kiss1* and *Kiss1r* mRNA in the hypothalamus of C57BL/6J male mice [19]. Finally, ovariectomized E_2-replaced, high-fat-diet-induced obese DBA/2J mice show a decrease in *Kiss1* mRNA and in the number of KP-immunoreactive cells in the hypothalamus [20]. These data indicate that KP expression can be affected by metabolic factors, thus KP could be considered a sensor of the metabolic status necessary to initiate a successful reproduction.

Feature	Human	Rats	Refs
Localization of KP-ir neurons in the hypothalamus	POA and Inf	RP3V and ARC	[12–14,21,22]
Sexual dimorphism of KP-ir neurons	At the level of RP3V and Inf females > males	At the level of RP3V females > males At the level of ARC females = males	[21–25]
KNDy peptides NKB-ir/KP-ir colocalization	There are sex and age differences in KP expression in NKB neurons. The overall incidences of KP-ir and NKB- ir cell bodies: postmenopausal women > aged men > young men. The percentage of KP perikarya containing NKB–ir: similar in postmenopausal women, aged men, and young men Percentages of NKB-ir perikarya with KP-ir: postmenopausal women > aged men > young men	NKB-ir is present in KP-ir neurons in the ARC of males and females NKB-ir in KP neurons: females > males Almost complete colocalization of *Kiss1* and NKB-ir neurons in the ARC of females	[12,24–27]
DYN-ir/KP-ir colocalization	Poor evidence for the presence of DYN-ir in KP-ir neurons in the Inf of young men	DYN-ir in KP-ir neurons in the ARC – unknown	[26,28,29]

Table 1. Comparison of Sex Differences between Humans and Rats Related to KP and KNDy Neurons in the Hypothalamus

HPG Axis and Reproductive Disorders in DM2

In general, metabolic disorders can lead to alterations in sex hormone concentrations in both men and women [30]. In men the negative impact of DM2 on testosterone concentrations have been reported [31], which stems from a reduction in the total number of Leydig cells and a decrease in androgen biosynthesis [32,33]. Similarly, concentrations of testicular testosterone are lower in DM2 male rats [32,34,35]. The amplitude and/or frequency of pulsatile LH secretion is also reduced in obese and DM2 men [36], while conflicting results (reduction [34], or no change [32,34] in LH concentrations) have been reported in DM2 rats. Obesity and DM2 also influence semen quality with a decrease in sperm volume and sperm cell number [37]. Similarly to men, DM2 affects the female reproductive system, and early menopause or premature ovarian insufficiency are associated with increased risk of DM2 [38].

Data Obtained from DM2 Experimental Models

As collection of data is limited in humans, animal models of DM2 could help to understand crosstalk between metabolism and reproduction. These models include genetically induced DM2, such as Lep ob/ob mice, which are deficient in leptin [39–41], Lepr db/db mice and Zucker Diabetic Fatty (ZDF) rats, which are deficient in the leptin receptor [42,43]. There are also polygenic models of obesity and DM2; for example: C57BL/6J obesity-prone mice that develop obesity and glucose intolerance and moderate IR (however, they rarely develop hyperglycemia and/or islet atrophy when fed an obesogenic diet) [44]; C57BL/6N mice that develop hepatosteatosis, hyperglycemia, and hyperinsulinemia following 3 weeks on an HFD [45,46]; New Zealand Obese (NZO) mice that develop moderate hyperphagia, leptin resistance, and pancreatic and hepatic defects and DM2 [47]; TALLYHO/Jng mice that are characterized by moderate obesity, β-cell hypertrophy, hyperplasia with hyperinsulinemia, severe dyslipidemia, and hyperglycemia and IR [48]; and KK mice that spontaneously develop diabetic characteristics, including obesity, hyperinsulinemia, IR, and diabetic nephropathy [49]. The above-mentioned genetic models of DM2 are valuable; however, in humans the development of this disease is mostly the result of interplay between different genes and the environment [50]. To study the influence of environmental factors in the laboratory, animal models are commonly used where diet-induced obesity using HFD and/or high-carbohydrate diets, or a combination of both is followed by streptozotocin (STZ) injections [51]. In such models, severe metabolic alterations are found; for example, increased weight, percentage of body fat, glucose intolerance, IR, cholesterol, triglyceride, and leptin concentrations, and abnormal functioning of the pancreatic islets of Langerhans, which may lead to the development of DM2 [52]. The HFD/STZ model involves a combination of HFD to induce hyperinsulinemia, IR, and/or glucose intolerance followed by subsequent injection of a low dose of STZ, a toxin that severely damages pancreatic cells [51]. These two stressors in this animal model aim to mimic the pathology of DM2 observed in humans. The key advantage of this approach is that it allows us to observe the development of DM2 that occurs in most humans, leading from induction of adult-onset obesity to glucose intolerance, IR, the resulting compensatory insulin release, and finally STZ-induced partial β cell death [50]. Additionally, depending on the amount of residual functional β cell mass, the HFD/STZ model might be suitable to study the final stage of DM2 [51]. Finally, it is also useful for testing of antidiabetic compounds [53,54].

In animal models of DM2, an increase in body weight is observed both in female and male DM2 animals [52,55,56]. This increase appears to be sexually differentiated in our animal model, as DM2 females gained less weight related to control animals than males gain.

In our rat model of DM2, blood glucose and insulin concentrations are higher in DM2 males and lower in DM2 females compared to controls [35,55,56]. Observed alterations reflect different stages of development of the disease between experiments conducted in male and female rats. In the early stage of DM2, the pancreas produces insulin, but target tissues are not able to respond to it, and IR is reached, but in late stage of diabetes development, a decrease in insulin can also be observed [57]. Additionally, higher cholesterol and triglyceride concentrations in both sexes in

DM2 animals have been reported. Finally, leptin concentrations remain similar in DM2 and control rats [35,55,56].

Thus, metabolic outcomes in DM2 females and males were therefore very similar in our animal model despite DM2 sex-specific patterns of gonadal steroid fluctuations: higher E_2 concentrations were seen in DM2 females and lower T in DM2 males related to controls [35,56].

Higher concentrations of E_2 in DM2 females are associated with an increased duration of proestrus phase and a decreased length of diestrus stage. DM2 females are also characterized by higher rates of irregular estrous cycle [56]. In the nonobese rat model of DM2, Goto-Kakizaki rats, reduced reproductive capacity has also been reported, as females show a delay in the transition from proestrus to estrus phases [58].

Therefore, our rat model mimics the metabolic outcomes in diabetic patients. However, metabolic profiles obtained in DM2 animals may vary depending on dose of STZ administration, and time at which hormones are measured, which indicates the severity and different stages of DM2 development [51,59].

KP System Alterations in Peripheral Organs of DM2 Animals

KP System in Gonads

KP system in gonads is affected by DM2 in rats (Figure 1A), with *Kiss1r* mRNA being highly expressed in testes of DM2 rats, while no difference is detected for *Kiss1* mRNA between treated and control groups of male rats. No differences are observed in female rats regarding both *Kiss1* and *Kiss1r* mRNA in ovaries between DM2 and control groups [60]. Of note, the stage of the estrous cycle is not taken into consideration during the analysis of ovaries, which may buffer any small significant variation occurring at a specific time of the cycle. As studies performed on STZ-induced diabetic rats and mice have focused mainly on the histology of ovaries and testes, ours is the first to report changes in the KP system in this metabolic condition. *Kiss1* mRNA and KP are detected in Leydig cells from mice

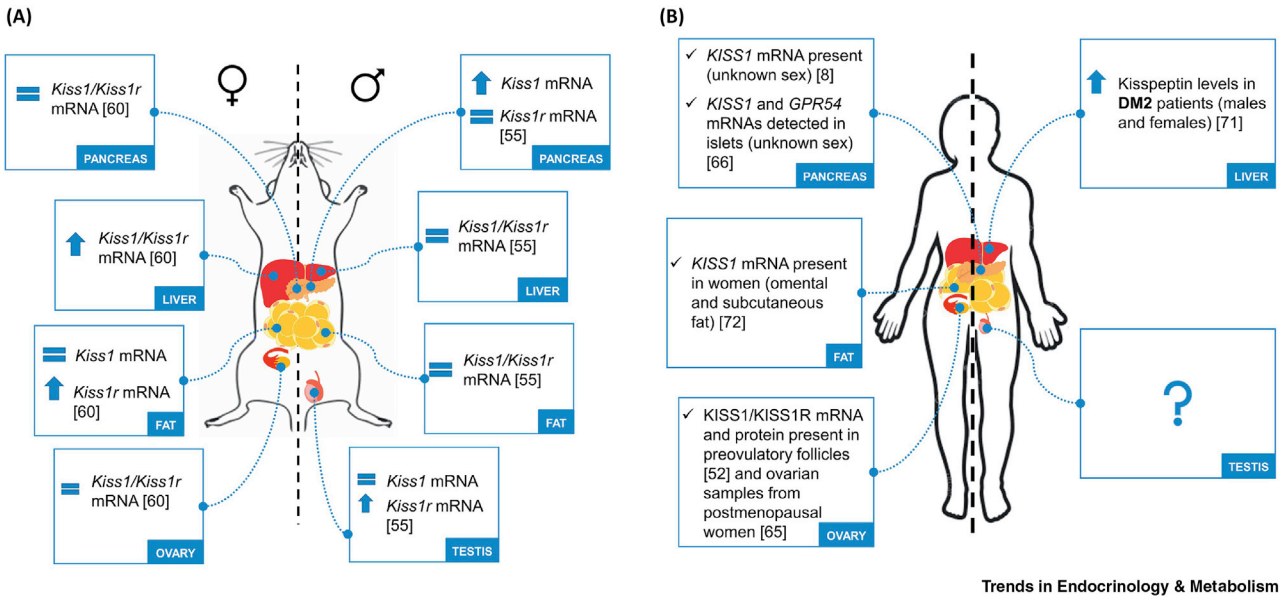

Figure 1. Comparison of Sex-Specific Responses in the Metabolic Profile of Rats.
(A) experimentally induced DM2 and changes in expression of *Kiss1/Kiss1r* system mRNA in peripheral organs involved in regulation of metabolism and reproduction. In contrast to animal studies, so far no human data on the expression of KISS1/KISS1R mRNA are available from healthy patients in exception of the liver (B). Symbols: ↑, increase; ↓, decrease; =, no change. See also [8,52,55,60,65,66,71,72].

[61,62], which are involved in testosterone synthesis. The increased *Kiss1r* mRNA in testes and decreased testosterone concentrations in DM2 male rats may account for the reproductive abnormalities in those animals. KP is also detected in growing and preovulatory follicles, and corpora lutea of ovaries [63], and locally produced KP in ovaries could play a role in the control of ovulation. So far, no difference has been found in *Kiss1* and *Kiss1r* mRNA levels in the ovaries of DM2 rats but again the stage of the estrous cycle has not been taken into account. It would be of particular interest to examine KP immunoreactivity in gonads in a DM2 model to investigate possible changes that may help to explain alterations in reproductive function of these animals. Of interest, KISS1/KISS1R mRNA and peptides are expressed in mural granulosa cells and cumulus cells collected from preovulatory follicles of oocyte women donors [64] and ovarian samples from postmenopausal women [65] (Figure 1B). So far, there are no data available on possible alterations in the KP system in gonads in women and men suffering from DM2.

KP System in Fat, Liver, and Pancreas

Male and female DM2 rats express *Kiss1* and *Kiss1r* mRNA in tissues involved in the control of metabolism, with the lowest levels in fat compared to liver and pancreas (Figure 1A). Moreover, comparison of *Kiss* and *Kiss1r* mRNA levels between DM2 and control rats revealed sex specific differences in liver, pancreas, and fat. It appears that female hepatic and fat tissues are more sensitive to DM2 condition than male tissues are (Figure 1A).

Our data confirm *Kiss1* expression in pancreas reported earlier in humans [8] and mice [66] (Figure 1B). Moreover, in murine islets, KP and *Kiss1r* are colocalized in both α and β cells [66]. Additionally, both *in vitro* studies on human and murine islets [8,66] and *in vivo* data from experiments performed on monkeys [67] and rats [68] indicate that KP increases glucose-induced insulin secretion, without any effect on basal secretion. It has also been found in experiments in murine, porcine, and human islets that KP acts directly on β cells to potentiate insulin secretion stimulated by glucose [68–70]. Additionally, KP enhances insulin secretion from murine islets in a dose-dependent manner through a Gβγ-dependent pathway [70]. Based on above data and experiment showing that the intracerebroventricular administration of KP in rats has no effect on insulin levels, a peripheral site of action for KP has been suggested [68]. The results also suggest that the *Kiss1* system in DM2 males is deficient and therefore unable to modulate insulin concentrations.

Much less is known regarding role of KP in regulation of metabolism in females. It is known that DM2 females have alterations in hepatic and fat KP systems [71]. However, interesting findings on sex differences have come from *Kiss1r* KO studies. It has been shown that only *Kiss1r* KO animals have greater body weight, hyperinsulinemia, increased adiposity, elevated fasting basal glucose concentration, and impaired glucose tolerance [17]. Importantly, observed obesity is not due to hyperphagia, but reduced metabolism, as *Kiss1r* KO females are characterized by dramatically decreased energy expenditure. Unfortunately, IR, which is observed in DM2, has not been measured in this experimental model. In the liver of hyperglucagonemic diabetic animals (in HFD-induced diabetes and genetic leptin receptor-deficient db/db mice) KP levels were increased [71]. *In vitro* experiments have confirmed that glucagon treatment increases *Kiss1* mRNA and protein levels in murine hepatocytes. Similarly, increased liver and plasma KP levels have been reported in women and men with DM2 [71] (Figure 1B). These data indicate that the control of insulin, glucagon, and glucose secretion modulated by peripheral KP systems is impaired in DM2 mammals. Moreover, a trihormonal regulatory circuit between pancreatic α cells, hepatocytes, and β cells has been proposed. According to this model, activation of the liver glucagon receptor stimulates insulin secretion by increased hepatic glucose production and hyperglycemia. Liver glucagon action may also inhibit insulin secretion by stimulating KP production. Thus, in pancreatic β cells in DM2 patients, the glucose-sensitive insulin secretion can be stimulated by hyperglycemia but inhibited by KP. The above findings indicate a potential role of KP antagonism as a therapeutic tool to improve β cell function in DM2 patients [71].

Finally, the KP system in fat is only affected in DM2 females, which have higher *Kiss1r* mRNA expression than controls (Figure 1A). *Kiss1* mRNA is also present both in omental and subcutaneous fat;

however, a positive correlation between body mass index and *KISS1* mRNA levels has been reported in omental adipose tissue, but not in subcutaneous fat in women [72] (Figure 1B). Reported variations may have been buffered in our study, as the stage of the estrous cycle was not considered. This could be an important factor since *Kiss1* mRNA expression in adipose tissue is sensitive to sex steroids [73], and by pooling females, we might obscure significant estrous-cycle-dependent variations.

Previous *in vitro* experiments have also indicated an action of KP on lipid metabolism [74], as isolated rat adipocytes (fat-storing cells in adipose tissue) and mouse 3T3-L1 cells (the most commonly studied adipogenic cell line) express mRNA and peptide for *Kiss1* and *Kiss1r* genes. Moreover, multiple actions of KP-10 have been shown: (i) inhibition of proliferation, viability, and adipogenesis in 3T3-L1 cells and decreased expression of PPAR-γ and CEBPβ genes, involved in differentiation processes and adipogenesis; (ii) increased lipolysis in rat adipocytes and 3T3-L1 cells by enhancing the expression of perilipin (the protein associated with the surface of lipid droplets in adipocytes, essential for the mobilization of fats in adipose tissue) and hormone-sensitive lipase (the rate-determining enzyme for lipolysis); (iii) modulation of lipogenesis; and (iv) decreased glucose uptake and adiponectin secretion and stimulation of leptin secretion from rat adipocytes. This leads to the conclusion that KP-10 may slow the process of lipid accumulation via decreasing lipogenesis and increasing lipolysis. In the light of experiments performed on *Kiss1r* KO animals, it would be of particular interest to study sex-specific action of KP on metabolic functions. It has been found that *Kiss1r* KO females are characterized by greater body weight, hyperinsulinemia, increased adiposity, elevated fasting basal glucose concentrations, and impaired glucose tolerance [17]. Observed obesity is not due to hyperphagia, but reduced metabolism, as *Kiss1r* KO females have markedly decreased energy expenditure. Of particular interest for the current review, *Kiss1r* KO males are characterized by normal body weight and glucose tolerance. It is also reported that adiposity, hyperinsulinemia, and decreased metabolism are already seen at a younger age in *Kiss1r* KO females. Impaired glucose tolerance appears later in adulthood when body weight is significantly increased. Thus, an early life decrease in metabolism and energy expenditure may underline the later occurrence of the obese phenotype of adult *Kiss1r* KO females [75]. As this phenotype can arise from defective signaling in the brain, and/or peripherally, it is important to study KP signaling at both levels.

Hypothalamic KP System in DM2 Animals and Influence of DM2 on KNDy Neurons

In our animal model, KP hypothalamic mRNA was lower in DM2 females compared to controls, while *Kiss1r* mRNA levels did not differ (Figure 2A). Opposite results were obtained in DM2 males, having similar *Kiss1* but higher *Kiss1r* mRNA levels than controls (Figure 2A). Of note, analysis was performed on total hypothalamus using RT-PCR, without discrimination between RP3V and ARC regions. Alterations in the KP system may depend on the severity of DM2 stage. Castellano and colleagues demonstrated a decrease in *Kiss1* mRNA hypothalamic expression using a male rat model of severe long-term DM2 induced by STZ (4 weeks after STZ and severe hyperglycemia $\geq$450 mg/dl) [76]. We had a less severe stage of DM2, as our experiments were performed up to 2 weeks after STZ injections and animals had lower concentrations of glucose. The different responses to DM2 in females and males may reflect altered sex steroids concentrations in both sexes as mentioned earlier. Regarding peptides immunodetected in KNDy neurons, no difference was seen in females, while DM2 males had higher numbers of KP-, NKB-, and DYN A-immunoreactive neurons compared to controls [35,56] (Figure 2B). These differences on the impact of DM2 on these peptides are reminiscent of results published in control rats showing sex differences in the number of KP-ir and NKB-ir that were more abundant in the caudal ARC of females. Of note, neurons expressing only NKB, but not KP, were more numerous in males [25]. Except our data, no previously published paper documented KP/NKB/DYN levels in the hypothalamus of DM2 animals. Moreover, no data are available concerning possible changes in KP system and KNDy neurons from tissue of DM2 human subjects (Figure 2C,D).

Somatostatin (SST) and KP Interactions in the ARC of DM2 Animals

As SST is a neuropeptide involved in the central regulation of metabolism, through the growth hormone/IGF-1 system, and reproduction, it could represent an important modulator for KP neurons. Indeed, these latter are well-known integrative hubs of several endocrine factors for the control of

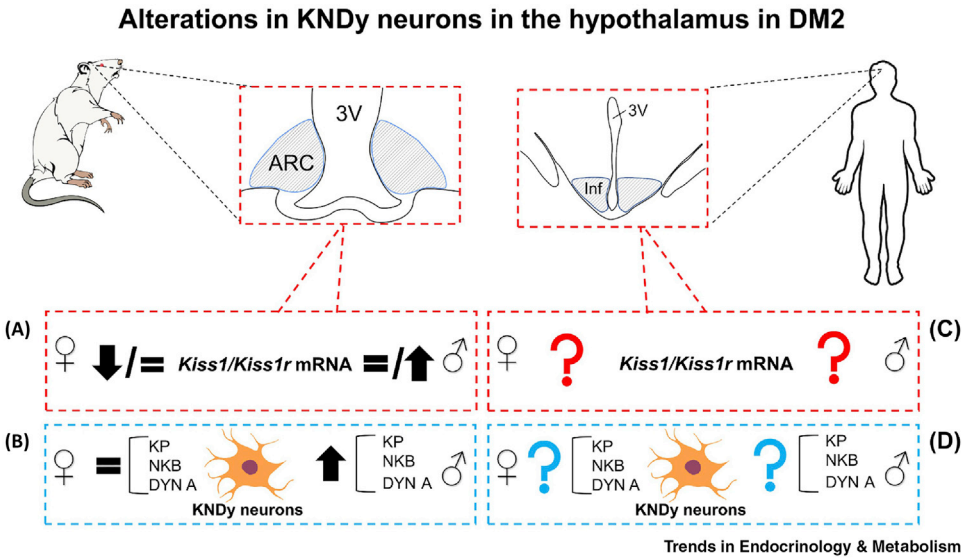

Figure 2. Changes in Hypothalamic Expression of KP System in Diabetic Male and Female Rats.
(A) *Kiss1/Kiss1r* mRNA measured in whole hypothalamus by RT-PCR. (B) Number of KP-, NKB-, and DYN A-immunoreactive neurons assessed in the ARC. No parallel data are available from women and men with type 2 diabetes mellitus (C and D). Symbols: ↑, increase; ↓, decrease; =, no change. Abbreviations: 3V, third ventricle; ARC, arcuate nucleus of the hypothalamus; DYN A, dynorphin A; Inf, infundibular nucleus; KP, kisspeptin; NKB, neurokinin B.

GnRH neurons. Moreover, strong relationships between SST neurons and KP neurons have been described in both lean female and male rats [77]. In spite of the high percentage of KP neurons with SST appositions (comprised between 80% and 100%) no significant differences are observed between DM2 and control animals in both sexes. No differences are seen between DM2 and control animals regarding the number of SST appositions per KP neuron in both sexes, despite a slightly higher level of SST apposition number per KP neuron in DM2 males compared to controls (unpublished data). This lack of differences may stem from an increase of both KP and SST hypothalamic content, as previously reported in obese subjects [78]. This may have buffered any variation occurring in the anatomical relationships between the two neuronal populations. It is also possible that DM2 does not affect the interactions between the two populations but has a deleterious influence on SST receptors involved in the transduction of SST effects to KP neurons.

Concluding Remarks and Future Directions

Animal models of DM2 mimic the metabolic outcomes observed in human patients. In our rat model: (i) similar metabolic profiles in DM2 females and males are seen; (ii) DM2 is associated with impaired sex steroid concentrations in both sexes; and (iii) sex-specific hormonal response to DM2 can account for specific differences in the response of KNDy neurons in male and female animals. However, many questions regarding the peripheral and central action of KP remain unresolved (see Outstanding Questions).

KP is a successful therapeutic target in human reproduction, including treatment of delayed and precocious puberty, subfertility, and contraception [79]. Data also suggest its potential use in diabetic patients, as KP-10 given to men with DM2 and central hypogonadism increases testosterone secretion [80]. Studies on animal models have demonstrated that KP may be involved in the regulation of insulin secretion, proving that *in vivo* experiments are needed to explore KP actions in the peripheral organs involved in the control of metabolism. In this regard, further studies are needed to reveal interactions between KP and insulin in DM2 patients.

Outstanding Questions

Does development of DM2 lead to alterations of both central and peripheral KP systems? May these alterations be associated with reproductive deficits observed in DM2 subjects?

Is the response of KNDy neurons to DM2 sex differentiated? Does estrogen exert a protective role on KNDy neurons during DM2 development in females?

Is KP influence on metabolic functions sexually differentiated? Does KP refrain lipid accumulation through decreased lipogenesis and increased lipolysis? Is this KP effect sex-specific?

Does DM2 influence the central modulation of KP neuron activity by SST?

Finally, the sex-specific variations observed in rats provide important data to develop new pharmaceutical tools and to conceive new sex-differentiated therapeutic strategies to palliate DM2 effects in humans.

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Disclaimer Statement

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