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Kisspeptin Modulates Reproduction in Ruminants

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Abstract

Kisspeptin, a neuropeptide encoded by the KiSS1 gene and its cognate, KiSS1R are the key regulators of reproduction in animals. Kisspeptin, also known as metastin, is a potent secretagogue of gonadotropin-releasing hormone (GnRH). It stimulates the GnRH neurons in the brain and generates pulses for GnRH thereby its secretion and release, and this in turn stimulates the release of LH and FSH. Owing to its importance in reproductive biology, the kisspeptin-KiSS1R system is presently regarded as an essential gatekeeper of reproduction in animals. Besides central nervous system, role of Kisspeptin during the process of placentation and pregnancy has been established recently. Therefore, kisspeptin-KiSS1R system potentially plays diverse roles in animal reproduction. Here, we review the role and physiological significance of kisspeptin in the reproduction of ruminants.

Keywords: *Kisspeptin, KiSS1, metastin, KiSS1R, reproduction, ruminant, GnRH, LH*

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INTRODUCTION

Kisspeptin (KP), also known as metastin, has recently been reported to be a master player in animal reproduction [1–2]. Kisspeptin is a potent secretagogue of gonadotropin releasing hormone (GnRH). It was first identified as a product of a metastasis suppressor gene (KiSS-1) in malignant melanomas [3].

Kisspeptin is basically the endogenous ligands for a G-protein-coupled receptor 54 (GPR54, also presently known as KiSS1R). The parent kisspeptin is a peptide of 145-amino acid long and this peptide has undergone proteolytic breakdown *in vivo* from the carboxyl-terminus region resulting production of several shorter peptides like kisspeptin of 54 amino acids (KP-54), kisspeptin of 14 amino acids (KP14), kisspeptin of 13 amino acids (KP-13) or kisspeptin of 10 amino acids (KP-10) [4].

All of these peptides have a common carboxyl terminal amidated 10-amino acid sequence, which is reported to have the equal potency to bind the KiSS1R. Hence, KP-10 is considered to be potent enough to exhibit all biological properties of the parent and other kisspeptin peptides.

DERIVATION OF THE NAME 'KISSPEPTIN'

Out of all kisspeptin fragments, the largest one, KP-54 was first identified for its ability to suppress the metastatic potential of malignant melanoma cells and it was, therefore, termed as 'metastin' [5]. As kisspeptin-54 fragment was first discovered in Hershey, Pennsylvania, USA, hence it was named after Hershey's famous chocolate "Kisses". However, there exists a scientific background for the nomenclature of the gene of kisspeptin, KiSS1, as the inclusion of 'SS' in the name also indicates that the gene has a suppressor sequence.

Kisspeptins are now a group of family of peptides that comprised of an Arg-Phe-NH2 motif at the C-terminus, which is a typical characteristic of the RF-amide peptide superfamily [6].

DISTRIBUTION OF KISSPEPTIN-KISS1R SYSTEM

Distribution of kisspeptin has been best described in rodents and humans, where expression of both receptor (KiSS1R) and ligand (KiSS1) are the highest in placenta, with additional wide distribution throughout

the central nervous system (CNS). In the CNS; hypothalamus, pituitary, cerebellum, cortex and brainstem are the sites where KP and KiSS1/KiSS1R are expressed abundantly [4].

In addition, they are also reported to be expressed in pancreas, liver, adipose tissue, small intestine, peripheral blood lymphocytes, testes, lymph nodes, aorta, coronary artery and even in umbilical cords [7–8]. Recent evidences showed that kisspeptin neurons are present in the arcuate nucleus (Arc), periventricular nucleus (PeN) and the anteroventral periventricular nucleus (AVPV) of the CNS [9]. Kisspeptin stimulates the GnRH neurons in the CNS thereby producing pulse generation for preovulatory GnRH/LH surge in female animals [9].

MODE OF KISSPEPTIN ACTION

Activation of endogenous KiSS-1 gene in the hypothalamus is reported to take place during commencement of pubertal process and such activation of KiSS-KiSS1R system in the CNS has been found to be sufficient to trigger the neuroendocrine events leading to the onset of puberty [9].

Kisspeptin is reported to stimulate the neuroendocrine-reproductive axis, while steroid hormones differentially regulate the abundance of KiSS-1-kiSS1R in different nuclei of CNS as depicted in the previous literature. Endogenous KP stimulates the GnRH neurons present in the CNS, resulting in pulse generation of GnRH, thereby GnRH release in to the system. The resultant GnRH induces the release of LH and FSH from pituitary in the circulation. In turn, the gonads (ovary in female and testis in male) respond to gonadotropins by secreting sex steroids, which then regulate the kisspeptin neurons through positive or negative feedback mechanism.

PHYSIOLOGICAL FUNCTIONS OF KISSPEPTIN

Kisspeptin Induces LH Surge

Kisspeptin stimulates GnRH neurons in the brain to release endogenous GnRH, which in turn generates the LH surge and due to the latter, dominant follicle of the ovary ovulates. Constant intravenous infusion of Kp-10 for 8 h beginning 30 h after progesterone withdrawal is reported to stimulate an earlier LH surge that results increased circulatory progesterone concentrations [10]. Interestingly, intravenous infusion of Kp-10 was also found to stimulate the LH surge in anestrous ewes [11–13]. Blocking of KiSS1R with its antagonist is reported to attenuate the estradiol induced LH surge [12]. Hence, it was concluded that the action of KP on LH release in sheep was via an effect on GnRH release from the hypothalamus and not as direct action of KP on pituitary gonadotropes [11–13].

Exogenous KP was also found to increase the release of endogenous LH in cultured ovine pituitary cells, but hypothalamo-pituitary disconnected ewes did not respond to Kp-10 treatment [13]. Expression of Kp is reported to be increased in caudal ARC during the late follicular phase of ewes [14]. Similarly, the KiSS1 mRNA positive cells were found more abundantly in the middle and caudal ARC and POA during the late follicular phase [15]. Kisspeptin is found to be involved in generation of the GnRH surges in the brain, and consequentially the LH, release as revealed in several studies [11, 16].

Kisspeptin Action in Anestrous Animals

Intravenous administration of KP-10 stimulates ovulation in ewes during the nonbreeding season [10], but the KP expression was higher in the breeding season than the nonbreeding season [10]. An increased KP contacts with GnRH neurons was also observed during the breeding season in ewes [14].

Smith *et al.* also found that the number of KP positive cells were higher in the ARC during the breeding season than the nonbreeding season in ovariectomized ewes [13]. The number KP positive neurons in the ARC and percentage of KP positive neurons in both the ARC and preoptic area are reported to be increased in ovariectomised estradiol treated ewes following the transition to short day exposure [17].

Li *et al.* observed greater KP-10 response in terms of GnRH and LH release in seasonally anestrous ewes than luteal ewes during the breeding season [18]. Abundances of transcripts encoding KiSS1R in GnRH neurons was found to be higher during the

nonbreeding season than during the breeding season in ewes, and expression of KiSS1R in GnRH neurons was reduced post-KP-10 treatment in ewes during the non-breeding season but not by steroid treatment of ovariectomised ewes [18]. These results clearly showed that the alterations in KP release are associated with the season in ewes.

Kisspeptin Action in Prepubertal Animals

Decreased negative feedback inhibition of LH by estradiol is required for initiation of pubertal process in all the mammals; and ruminants are in no way exception to this. Kisspeptin and neurokinin B has been reported to be co-expressed in the brain during the pubertal process and therefore both of them may have some role to play in the process of commencement of puberty in ruminant species. This is also supported by the administration of neurokinin B agonist in prepubertal ewes exhibiting a distinct LH pulse immediately after its administration [19], though no differences in the number of neurokinin B cells in ARC was observed between the prepubertal and post puberty ewes [19].

Redmond *et al.* observed the number of KiSS1 positive cells in the POA increased from 25 to 35 weeks of age in ewe lambs, although the number of KiSS1 positive cells did not appear to be related to increases in LH pulse frequency [20]. However, Redmond *et al.* did report an increase in KiSS1 positive cells in the middle ARC that was associated with increased frequency of LH pulses [20]. Intravenous administration of KP at hourly interval in prepubertal ewe lambs was reported to induce LH surges with elevated progesterone levels and thereby ovulation [20]. These evidences clearly suggest the role of KP in the process of commencement of puberty.

Kisspeptin and Estrous Cycle

Circulatory kisspeptin levels have recently been characterized in crossbred cows [1]. The mean plasma kisspeptin concentration during different days of the estrous cycle was reported to be different ($P<0.01$) [1]. Mondal *et al.* reported three distinct peaks of kisspeptin during entire bovine estrous cycle [1]. A peak of kisspeptin on a day before the occurrence of preovulatory LH surge was observed [1]. The peak level was decreased steadily to reach the basal level on day 4, which again rose sharply and registered the second peak of lesser amplitude on day 6 of the cycle.

The plasma kisspeptin level showed an increasing trend again to exhibit another low amplitude peak on day 12 of the cycle. On the basis of the plasma kisspeptin profiles obtained during estrous cycle, it was observed that some pulsatility in kisspeptin secretions in peripheral circulation was present during cyclicity in cows. Appearance of the first peak of kisspeptin on a day before preovulatory LH surge may probably be required for preovulatory surge of LH that leads to ovulation, as kisspeptin is reported to be a potent gonadotropin secretagogue in animals [21]. The other two peak concentrations of kisspeptin during early (day 6) and late luteal (day 12) phases of the reproductive cycle may be required to increase blood FSH for follicular wave emergence, as transient increase of FSH is reported to be essential for emergence of follicular waves in bovine [22].

Kisspeptin during Pregnancy

Mondal *et al.* reported that with the advancement of pregnancy, plasma kisspeptin concentrations also showed an increasing trend [1]. The level of circulatory kisspeptin has been reported to be more than 4.5 times and 8 times higher during mid and late than early stage of pregnancy, respectively. Similarly, placental kisspeptin content has also been reported to be increased four and seven folds from early to mid and late pregnancy, respectively. These findings clearly indicate that the source of high plasma kisspeptin during the pregnancy in bovine species is the placenta. Kisspeptin has also been reported to be a placenta-derived hormone in humans and its concentrations increases as pregnancy advances [23].

Results of the recent experiment on rats revealed that KiSS1 and KiSS1R mRNA are abundantly present in the rat placenta with expression increasing over the final third of pregnancy [24].

Kisspeptin and Lactation

Abundances of mRNA for KiSS1 in the ARC and KiSS1R in AVPV has been reported to be reduced in rats during lactation [25], which explains the possible mechanism for the reduction of LH secretion during lactation. The suckling stimulus may probably be responsible for the suppression of KiSS1 mRNA expression in the ARC. Catecholamines and γ-Aminobutyric acid may also be the factors for the inhibitory inputs to the kisspeptin neurons in the brain. Also, the suckling-induced reduction in kisspeptin-KiSS1R system may be explaining the mechanism so as to why an estrous cycle is totally off when the animals are lactating.

Metabolic Regulation by Kisspeptin

Recent studies suggest that response of kisspeptin is dependent on several factors like age, body weight, nutritional status and metabolic activities, and also on neuroendocrinological signaling of the animal system. As a significant percentage of KiSS1 neurons of ARC also express the leptin receptor [12], it is expected that leptin, a satiety factor, can also regulate KiSS1 neurons in the arcuate nucleus. Malnutrition is reported to reduce gonadotropin secretion and also expression of KiSS1.

Exogenous administration of kisspeptin has been found to reinstate reproductive function [26]. Though much information is not available on the role of kisspeptin in regulation of metabolic activities in animals, the available above mentioned findings clearly indicate the possible role of KP-KiSS1R system in regulation of reproduction.

CONCLUSIONS

The kisspeptin, KiSS1 and its receptor KiSS1R that consist the KP-KiSS1R system has attained special attention in animal reproduction due its well defined function on the onset of puberty through generating pulsatility of GnRH in the brain.

The KP-KiSS1R system has recently been explored in the bovine ovary and placenta that revealed promising results indicating circulatory kisspeptin as a biological marker for pregnancy. Besides, the system has a significant role during cyclicity and metabolic activities of animals. Hence, KP-KiSS1R system is an inevitable part of animal biology particularly for optimum reproduction.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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