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Mystic Effects of Kisspeptin in Reproduction of Livestock

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A B S T R A C T

The commencement of puberty has been interesting topic for reproductive endocrinologists for years. Yet its fundamental physiological mechanisms have stayed mysterious until recently. The findings and understanding of the effects put forth by the peptide hormone kisspeptin have shed light on this research area. Kisspeptin (Kp), a family of neuropeptides which is produced chiefly by neuronal clusters at discrete hypothalamic nuclei, are vital regulators of GnRH neurons. Studies have found a role for Kp to release growth hormone (GH), prolactin and luteinizing hormone (LH) from cattle, rat and monkey pituitary cells. Kisspeptin neuronal system directs both pulsatile GnRH secretion that stimulates folliculogenesis, spermatogenesis and steroidogenesis and the GnRH surge that activates ovulation in females Kisspeptin and related substances could therefore be valuable for the development of novel strategies for the management of fertility in farm animals. To this end, the present review aimed to summarize the current research on kisspeptin and its importance in domestic animals.

Introduction

Kisspeptin (Kp), also known as Metastin is a neuropeptide, produced chiefly in the hypothalamus from Kiss1 gene, Kisspeptin is a peptide hormone comprised of 145-amino acid residues. Kisspeptin was discovered by Lee *et al.*, (1996) who identified Kiss1 gene for inhibiting cancer cell metastasis in humans. Kiss1 was baptized for the home of the legendary Hershey chocolate Kiss (Hershey, Pennsylvania, USA) where the gene was discovered (Gottsch *et al.,* 2004). Kp has also been caught up in the assimilation of metabolic control of reproduction where it stimulates gonadotropin-releasing hormone (GnRH) release and subsequent secretion of luteinizing hormone. G-protein-coupled receptor (Kiss1r or GPR54), a strong associated receptor of kisspeptin. Principally brain controls gonadal activities by synthesizing gonadotropin-releasing hormone (GnRH) by neurons in the hypothalamus into the portal vessels. This GnRH acts on anterior pituitary to secrete gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Gonadotropins stimulate the gonads to secrete steroid hormones such as Estrogen and Progesterone in females and androgens in males. The significance of Kisspeptin and G protein-coupled receptor 54 concerning fertility was motioned by the seminal discovery in 2003 of human pedigrees with GPR54 mutations that failed to go

through puberty (Seminara *et al.,* 2003). Kisspeptin and GPR54 were identified within the brain stem, hypothalamus, pituitary, spinal cord, ovary, liver, prostate, pancreas, aorta, intestine, coronary artery, placenta and umbilical vein (Roseweir *et al.,* 2009). Kisspeptin-GPR54 signaling is obligatory for the pubertal commencement of Gonadotropin-releasing hormone (GnRH) neurons and reproductive function, both of which play a vital role in the rheostat for the hypothalamic pituitary gonadal (HPG) axis encompassing follicular development, ovulation, spermatogenesis and steroidogenesis (Roseweir *et al.,* 2009). The three most important components of HPG axis i.e. Hypothalamus, Anterior pituitary, and Gonads are linked via feed-forward loops whereby GnRH stimulates the secretion of gonadotropins and these, in turn, support gonadal maturation and function (Figure 1). This review aimed mainly to summarize the importance of kisspeptin in domestic animals.

Kisspeptin action on LH and Gonadotropin

In situ hybridization (ISH) and immunohistochemistry (IHC) are the foremost modus operandi for ascertaining GPR54, GnRH gene or protein expression and its localization. Kiss1 neurons were found in the Preoptic area (POA) and Arcuate nucleus (ARC) regions with a superior cell density in ARC by ISH in ewes (Smith *et al.,* 2007). Kisspeptin fuels the release of GnRH and consequent secretion of LH. Intravenous administration of Kp-10 to ovariectomized (OVX) ewes, stimulated the concentration of circulating LH and upsurge of GnRH concentrations in Cerebrospinal Fluid (CSF) (Caraty *et al.,* 2007). Central administration of Kp-10 augmented GnRH concentrations in the cerebrospinal fluid and increased LH concentrations in the plasma of sheep (Messager *et al.,* 2005). Furthermore, Kisspeptin-10 (Kp-10) stimulated circulating concentrations of LH in Holstein cows and ovariectomized Jersey cows, and interestingly the sensitivity of LH to exogenous Kp-10 stimulation seems to be enhanced with lactation (Whitlock *et al.,* 2010). Kisspeptin expression is structured by steroids as the quantity of Kp positive cells in the ARC increased in OVX ewes paralleled to intact ewes, the contradictory being found in the preoptic area (POA) Kp neurons (Smith et al.2007). Furthermore, the number of Kp positive cells in the arcuate nucleus (ARC) were reduced in OVX ewes on treatment with estrogen or progesterone (Smith *et al.,* 2007). Fascinatingly, single nucleotide polymorphisms in the Kiss1 gene were associated with increased litter size in goats (An *et al.,* 2013). The LH response to Kp-10 was greater in the late-follicular phase when matched with the luteal phase during the breeding season (Smith *et al.,* 2011), and the influence of Kp-10 on LH but not FSH, secretion, was more during the anoestrous season than in the luteal phase during the breeding season (Smith *et al.,* 2009a).

Consociates and actions of kisspeptin on GnRH neurons

Kp-IR fibers were acknowledged in the POA region in ewes, where the GnRH neurons exist (Franceschini *et al.,* 2006). Additionally, Kp-IR fibers were found to encompass from the ARC into the external neurosecretory segment of the Median Eminence (ME) (Pompolo *et al.,* 2006) in both females (ewes: Smith et al 2011) and males (goat: Ohkura *et al.,* 2009b). These terminals might be the basis for the kisspeptin that has been documented in the ewe hypophyseal portal blood (Smith *et al.,* 2008). Kisspeptin might have a non-synaptic action at the ME level to initiate GnRH release. Electron microscopy has publicised that the axon terminals of kisspeptin neurons do in fact are in close contact with GnRH axon terminals in goats (Matsuyama *et al.,*

2011) and rats (Uenoyama *et al.,* 2011). Hence, even though kisspeptin neurons may relate with either cell bodies or the axon terminals of GnRH neurons, the earlier is unlikely to be the foremost site of kisspeptin action in males.

GnRH neurons directly act on Kisspeptin to commence a sustained depolarization event. The capability of GnRH neurons to retort to kisspeptin signals is progressively synchronized, with the percentage of responsive GnRH neurons rising from 25% in the pre-pubertal period to more than 90% in adults. This elevation in GnRH responsiveness during the pre-pubertal period echoes an increase in Kiss1 gene expression (Han *et al.,* 2005). Central Infusion of a GPR54 antagonist gridlocked or attenuated both pulsatile LH secretion (Goodman *et al.,* 2012) and the E2-induced LH surge (Smith *et al.,* 2011) in ewes. Functional inactivation of GPR54 by chronic administration of potent GPR54 agonists totally eliminated LH pulses in male (Ohkura *et al.,* 2011) and female goats (Wakabayashi *et al.,* 2011), these studies clearly depicts that kisspeptin plays a crucial role in the control of both the pulsatile and surge modes of GnRH secretion.

Deeds of kisspeptin on reproductive function

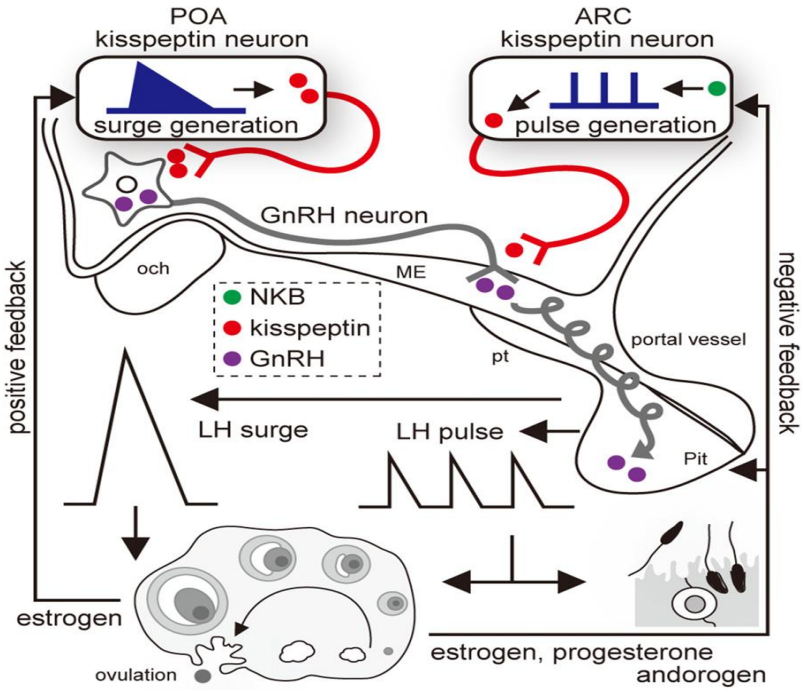
Kisspeptin and puberty: The commencement of puberty is triggered by the stimulation of neurons in the forebrain which harvest a neuroendocrine substrate to stimulate GnRH (Saito *et al.,* 2012). Studies in mammals specified that kisspeptin and GPR54 were crucial controllers of puberty due to the programmed increased in Kiss1 mRNA, GPR54 mRNA (only in females), which had been witnessed in the anteroventral periventicular nucleus (AVPV), the POA, and the ARC areas which would cause an upsurge in GPR54 sensitivity to kisspeptin (possibly due to increase in receptors at the cell surface). Studies on Kiss1R knockout mice illustrated that they do not attain the process of puberty and agonize severe shortfalls in their reproductive function in adulthood, e.g., sexual immaturity, smaller gonads, absence of spermatogenesis, low concentrations of gonadotropins and sex steroids, impaired ovulation, and therefore, irregular or absent cycling (Holmes. 2014). Male and female rodents show a remarkable rise in the hypothalamic expression levels of Kiss1 mRNA during puberty (Navarro *et al.,* 2004). Stimulation of the kisspeptin system facilitates increased pulsatile and surge modes of GnRH from GnRH neurons then GnRH rouses the reproductive axis fetching about pubertal maturation via hypophyseal portal circulation to fuel the fabrication and release of gonadotropins such as luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (Kadokawa *et al.,* 2008a). It has been proposed that such changes in the expression levels of KISS1 mRNA possibly reflect not only in upsurge of neuronal activity during puberty, but also a possible mediation of kisspeptin on the neuroendocrine events prompting the commencement of puberty (Dungan *et al.,* 2006). Close to puberty, and as a consequence of the increased adipose tissue in the body, greater amounts of leptin are on the rampage from the adipocytes, leading to higher levels of this hormone in blood (Vigil *et al.,* 2013). Recent studies suggest that leptin surge would endorse kisspeptin secretion from kisspeptinergic neurons, and the latter hormone would bind to its GPR54 receptor in the GnRH-releasing neurons. Once stimulated, these would secrete higher amounts of GnRH, enhancing the release of FSH and LH from the adenohypophysis. Therefore it can be suggested that kisspeptin is a key factor triggering puberty

Kisspeptin mechanism on hypothalamic pituitary gonadal axis: Estrogen receptor-α (ERα), Progesterone receptor (PR) and androgen receptor (AR) are expressed by

Kisspeptin neurons, and therefore pose a potential relay feedback effects on the GnRH neuron (Hashizume *et al.*, 2010). Researchers found that ovariectomy (OVX) and estrogen replacement in animals affected kisspeptin expression in the different region of the hypothalamus called by "Differential estrogen regulation" (Adachi *et al.*, 2007).

Basically, there are two modes of GnRH secretion: a) estrogen-induced ovulatory surge of GnRH/LH, b) pulsatile, basal GnRH/LH releasing modes. The prototype is well-developed in rodents. On one hand, the Kiss1 neurons in the AVPV are directly roused by estrogen effects via ERα (predominant in females). These neurons through GPR54 which is expressed on the cell bodies will stimulate GnRH neurons. This positive feedback of estrogen effects on AVPV Kiss1 neurons climaxes in the GnRH/LH surge, which generates the pre-ovulatory LH surge, which in turn triggers ovulation. On the other hand, the pulsatile GnRH/LH release from ARC kisspeptin neurons (present in both female and male) energies tonic secretion of gonadotropin which mainly controls folliculogenesis and steroidogenesis. Additionally, it appears that positive feedback occurs at the level of GnRH cell bodies, with estrogen-responsive cells in the AVPV projecting directly to GnRH neurons, whereas negative feedback occurs primarily at the GnRH terminal level by an indirect (inter-neuronal) pathway (from estrogen-sensitive neurons in the ARC) (Smith*et al.*, 2010).

Figure.1 A schematic illustration of the novel hypothalamic-pituitary-gonadal (HPG) axis. The two populations of kisspeptin neurons in the preoptic area (POA) and arcuate nucleus (ARC) are suggested to be located upstream of the gonadotropin-releasing hormone (GnRH) neurons in the HPG axis and to control the surge and pulse modes of GnRH/luteinizing hormone (LH) secretion, respectively. Neurokinin B (NKB) likely plays a role in the pulse-generating mechanism of the ARC kisspeptin neurons. ME, median eminence; och, optic chiasm; Pit, pituitary; pt, pars tuberalis



(Okamura *et al.*, 2013)

Kisspeptin: reproductive research in ruminants

Kp-10 was infused intravenously at 480 nmol/h for 8h in progesterone-primed cyclic ewes (Caraty *et al.,* 2007). It appeared to increase LH surge within 2h after initiation of Kp-10. These results recommend that kisspeptin may be used as a brand new tool for synchronization of ovulation. The immediate upsurge in LH secretion stirred by peripheral administration of the Kiss-1 peptide to OVX ewes appeared to imitate a straight action on the hypothalamus (Arreguin-Arevalo *et al.,* 2007). Meanwhile, sheep are short-day breeders, Melatonin, a photoperiodic hormone triggers their reproductive activity. Throughout the non-breeding season/ anoestrus, GnRH secretion is by both steroid-independent and steroid-dependent mechanisms (Smith. 2009). Captivatingly, the estrogen hold on Kiss1 mRNA and kisspeptin protein expression within the ARC were superior throughout the non-breeding season in ewes (Smith *et al.,* 2008). Hence, the core candidate to facilitate changes in feedback effect of estrogen seems to be Kisspeptin cells (Smith, 2009). In addition, a seasonal allowance in Kiss1 expression in OVX ewes in ARC region, significantly specifies that kisspeptin is basically convoluted in the seasonal change control in their reproductive function (Smith*et al.,* 2007). In cattle, kisspeptin along with luteinizing hormone (LH), also excites growth hormone (GH) in OVX cows, which were injected with kisspeptin10 (Kp10) in different doses. In vitro analysis indicated that kisspeptin was relevant to the release of growth hormone (GH) and prolactin (PRL) as well as the release of gonadotropin in ruminants (Hashizume *et al.,* 2010). One study showed that Kp10 treatment stimulated LH secretion from anterior pituitary cells in bovines (Ezzat *et al.,* 2010). In OVX goats, the peripheral infusion of Kp10 stimulates GnRH neurosecretion into hypophyseal portal circulation and the action of kisspeptin on LH releasing is mediated by GnRH.

It is concluded as compared to last decade, emerging research confirms that the kisspeptin neuronal system shows a significant role as the gatekeeper of reproduction and thereby governs the secretion of GnRH secretion. Kiss1 genes primarily appear in the hypothalamus of ruminants and other mammals to deliver negative and positive feedback directive of GnRH exudation by gonadal steroids. Secretion of the kisspeptin hormone exerts neuroendocrine effects of elementary importance in the activation of the hypothalamic-hypophyseal-gonadal axis. In ruminants, the kisspeptin cells in the ARC are poised to play a role in the steroid negative feedback control of GnRH. Detection of kisspeptin may additionally offer therapeutic potential. The kisspeptin system has provided a new window to develop substitute treatments for disorders of reproduction branded by low gonadotrophins or anovulation and also for the development of high potency analogs parallel to those already in place for GnRH that may be helpful for conditions during downregulation of reproductive activity is desirable.

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