



ISSN: 2456-2912

VET 2023; 8(2): 76-80

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Received: 08-12-2022

Accepted: 19-01-2023

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## Role of Kisspeptin on the reproductive system of livestock and pet animals

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**DOI:** <https://doi.org/10.22271/veterinary.2023.v8.i2b.493>

### Abstract

The livestock species economically enhance the quality of life of farmers and industries and reproduction is the only way to progress in the next generation. Kisspeptin (Kp) is a neuropeptide that acts on the reproductive system and is associated with reproductive disorders in mammals. The different forms of Kp are present but only kp-14 are more prominent to use due to their short length. The Kp. is act with the orphan G-protein coupled receptor 54 (GPR54) ligands and activates the hypothalamic-pituitary-gonadal axis (HPG) to release GnRH and reproductive hormones. Even the Kp. is a reproductive neuropeptide, it's limited to a few species to conduct the research and needs to perform more research on various species. The Kp may act powerful supplement in animal reproductive techniques and this review focuses on the livestock and pet animal reproductive system regulated by Kp.

**Keywords:** Buffalo, cattle, cat, goat, camel and mare, pig and sheep

### Introduction

The mammalian reproduction system is regulated by the number of peptides including Kisspeptin (Kp). Kp was first discovered in malignant melanoma cells of humans and acts as a potential suppressor gene in malignant tumors (Lee *et al.*, 1996) [1]. The kp is 165 amino acid length is the proteolytically inactive form and the short forms of kp-54, -14, -13, and -10 are synthesized proteolytically active with common sharing of Arg-Phe-NH<sub>2</sub> large family (Kotani *et al.*, 2001) [2] and which bind to G- protein-coupled receptor encoded by Kp 1R (GPR54) (Stafford *et al.*, 2002) [3]. The importance of kp in the reproduction system is identified due to mutation in the Kp 1R leads to the isolated hypogonadotropic hypogonadism in humans (De *et al.*, 2003) [5] and infertility in mice due to knock-down of the Kp 1R gene (Seminarat *et al.*, 2003) [6]. Exogenous injection of Kp in different modes can enhance the release of gonadotrophin of LH in a number of species. The kp neurons act on the GnRH and activate for secretion of gonadotrophin in Mice (Messenger *et al.*, 2005) [7], Gilts (Lents *et al.*, 2008) [8], Mare (Wilborn *et al.*, 2008) [10, 34], Cattle (Ezzat *et al.*, 2010) [9, 42], Goats (SAITO *et al.*, 2011) [11], Men (George *et al.*, 2011) [12], Women (Dhillon *et al.*, 2007; Jayasena *et al.*, 2014) [14, 15], Ewes (Wang *et al.*, 2012) [13], Dogs (Albers-Wolthers *et al.*, 2014) [16], Buffalo (Pottapenjera *et al.*, 2018) [17]. The kp and its receptor are expressed in the ovaries of many species (Roman *et al.*, 2012; Hu *et al.*, 2017; Terao *et al.*, 2004; Iwata *et al.*, 2017) [18, 19, 20, 21], mainly expressed in granulosa cells of rats and predominantly expressed in mice oocytes (Chakravarthi *et al.*, 2018) [22]. Exogenous administration of kp ultimately leads to the oocyte maturation variety of species and ovulation occurs (Ruohonen *et al.*, 2022; Gaytan *et al.*, 2014; Taniguchi *et al.*, 2017; Chakravarthi *et al.*, 2021) [26]. Assisted Reproductive Technologies (ART) can use Kp one of the reproductive regulators to indirectly affect oocyte maturation in humans and animals (Masumi *et al.*, 2022) [27]. The role of Kp in the production of gonadotrophins may be species-specific because in dogs it enhances the release of FSH and LH (Albers-Wolthers *et al.*, 2014) [16], but most of the species can enhance only LH (Whitlock *et al.*, 2011) [28, 36]. Since the last 28 years onwards literature about Kp is revealed that it is a neuropeptide that regulates the reproductive system of mammals but few shreds of evidence showed that can use in ART. This review can explain the vital role of Kp on the reproductive system in the manner of species wise.

### Buffalo

The LH surge is increased due to the administration of Kp but no longer sustains the peak and the Kp is enhance the follicular growth and a follicular number of the Murrah buffalos up on the age of animals (Pottapenjara *et al.*, 2018)<sup>[17]</sup>. The Kp and Kp1r expression can change the follicular development stage of the estrous cycle and expression is higher in the case of cyclic compared to the acyclic buffaloes. (Mishra *et al.*, 2022)<sup>[32]</sup>. The serum Kp concentrations are statistically non-significant in the ovulatory buffalos and anovulatory, almighty may lead to the restoration of the reproduction cycle in buffalos (Gahlot *et al.*, 2022)<sup>[31]</sup>. The Kp effect on buffalo oocyte maturation was first reported in India and standardized concentration with 10 µg/ml and achieved optimum oocyte maturation (73.21%), increasing concentration decreased the maturation (68.77%). In the case of first polar body extrusion also Kp was positively correlated (Rajesh *et al.*, 2018)<sup>[29]</sup>. The Kp has autocrine action and local interaction with hormones and modulates the FSH, LH, and E2 receptors on oocytes. E2 hormone is subduing action on the oocyte maturation with a positive effect on maturation and a negative effect on nuclear maturation of the oocyte (Rajesh *et al.*, 2020)<sup>[31]</sup>. There is no effect of Kp on buffalo bull semen parameters in a different season (Shahzad *et al.*, 2021)<sup>[33]</sup>.

### Cattle

The dose wise of peripheral injection of Kp strongly stimulates the production of LH and GH in cows up to maximum level (Whitlock *et al.*, 2008, Kadokawa *et al.*, 2008)<sup>[34, 17]</sup>. Intramuscular administration of Kp can release a high concentration of LH and FSH compared to intravenous injection but didn't show any effect on the basal level of GH concentration. The LH and FSH production is greater in bulls than cows in both the routes of Kp injection (Whitlock *et al.*, 2011)<sup>[28, 36]</sup>. The regulatory effect of Kp-10 has significant value in the case of the proliferation of epithelial cells differentiated from the absence of Kp-10 culture of the first trimester of bovine epithelial cells (Martino *et al.*, 2015)<sup>[38]</sup>. The follicular size is changed to the luteal phase based on Kp and indirectly carried out the ovulation. The addition of Kp in IVF media without any steroid hormones can produce a high percentage of cleavage and blastocyst rate. Kp neuropeptide regulates the *in vitro* production of bovine embryos without the addition of LH and FSH (Soares *et al.*, 2018). Downregulate of miRNA-1246 expression due to Kp, leads to the synthesis of progesterone in cattle (Guo *et al.*, 2022)<sup>[52]</sup>.

### Goat

The Kp acts on the HPG axis and enhances the production of reproductive hormones. The ARC region of the brain contains the Kp, neurokinin B, and dynorphin A neurons which continuously express and coordinate within among them leading to pulsatile secretion of the GnRH in vasectomized goats (Wakabayashi *et al.*, 2013)<sup>[39]</sup>. The C6 is analogue of Kp which plays a vital role in the production of LH, FSH, advanced puberty, and ovulation of the goat breeds irrespective of the breeding season and PMSG can be replaced by C6 for better breeding of goats (Decourt *et al.*, 2016; Decourt *et al.*, 2019)<sup>[41, 40]</sup>. The Kp-10 restorative the LH and FSH response 20 to 30 minutes but not PR and GH in the luteal phase of female goats. The same effect carried out by GnRH initiates the release of PR and GH but is more potent than the Kp-10 (Hashizume *et al.*, 2010)<sup>[42]</sup>.

### Camel and mare

The Kp expression is differentiated sexual dimorphisms in the breeding and non-breeding seasons of the camel. The brain sectional studies indicated the ARC and POA region's Kp expression and neurons' High-density are positively correlated with breeding season of camel (Hassan *et al.*, 2019)<sup>[43]</sup>. The Kp-induced LH secretion via GnRH in Kp-high treated compared untreated llama groups in the same way ovulation rate is positively influenced by the Kp act as induced ovulatory group of llama (Carrasco *et al.*, 2020)<sup>[45]</sup>. The Kp neurons are expressed in the preoptic area of the brain around 28% and its expression is positively regulated ovulation with enhanced activity of beta nerve growth factor (NGF) via iv injection in female dromedary camel (Hassan *et al.*, 2022)<sup>[46]</sup>. GnRH-dependent Kp activates the pituitary cell population to release LH (Magee *et al.*, 2020)<sup>[47]</sup>. The iv injection of Kp in the mare can lead to a threshold level of the GnRH, it enhances the release of LH and FSH in the diestrous period of the mare. The histology of the POA area had 33.7% of Kp immunoreactive cell expression associated with gonadal secretion in diestrus mare (Magee *et al.*, 2009)<sup>[44]</sup>.

### Sheep

Kp enhances the rudimental level production of GnRH and LH, and a double dose increases the production certain level (Caraty *et al.*, 2013)<sup>[48]</sup>. The histological studies of ewe's brain confirmed that expression of Kp neurons was high in the region ARC and had a steroid effect on ovaries (Goodman *et al.*, 2007)<sup>[49]</sup>. The Kp is increasing the oocyte maturation rate of sheep. The addition of other reproductive hormones (FSH, LH, and E2) in IVM media supplemented with oocytes clearly demonstrated that not only does Kp act on oocyte maturation but also rise the first polar body extrusion and cumulus cell expansion rate (Byri *et al.*, 2017)<sup>[50]</sup>. The Kp-treated granulosa cell of RNA sequence revealed that expression of the different kinds of miRNA and mRNA is associated with the mechanism of steroid hormone regulation, cell proliferation, and physiological functions of ovarian granulosa cells in Tan sheep (Dai *et al.*, 2022)<sup>[52]</sup>. The different kinds of doses and modes of Kp injection can change the gonadotropic hormone response and cause ovulation in noncyclical female ewes (Caraty *et al.*, 2007)<sup>[51]</sup>.

### Pig

The Kp regulate the reproductive system almost in all species except for some difference in pig due to the little genetic variation of kp (Lents *et al.*, 2019)<sup>[53]</sup>. The porcine hypothalamus and ovary of Kp specimens are expressed with 40 KDs protein and along with its receptor of KP1R is around 15 KDs (Basini *et al.*, 2018)<sup>[54]</sup>. The direct action of Kp on the 6 months old barrow anterior pituitary (AP) cells in *in-vitro* studies showed that the release of LH from AP cells was dependent on the Kp nevertheless week life span of LH (Suzuki *et al.*, 2007)<sup>[57]</sup>. The Kp enhances the production of reproductive hormones besides the fact that it is an adverse effect on hatched blastocyst stage. The porcine IVM embryos encountered significant results in presence of Kp and it encouraged the expression of apoptosis and pro-apoptosis of genes (*BAK1*) at the hatched blastocyst on the feeder layer (Saadeldin *et al.*, 2012)<sup>[55]</sup>. The electric pulse and ethanol-activated oocytes with the addition of Kp and 6-dimethylamino purine (6-DMAP) coordinate together with an increase in the cleavage and blastocyst formation rate compared to the control groups of porcine developmental competence of early embryos (Saadeldin *et al.*, 2018)<sup>[56]</sup>.

## Cats and Dogs

The neurons of Kp are distributed around 56% and 23% in ovariectomized dogs and cats respectively. Pulsatile secretion of GnRH and LH is responsible for the action of Kp neurons on GnRH neurons (Rumpler *et al.*, 2020) <sup>[58]</sup>. The Kp is one of the most conserved parts in the cat hypothalamus mainly located in the periventricular and infundibular nuclei of the cat (Amelkina *et al.*, 2019) <sup>[59]</sup>. The reproductive disorders in cats can be cleared by using Kp as a drug and it elevates the LH concentration for up to 30 minutes in dogs (Terse *et al.*, 2021) <sup>[60]</sup>. The fluctuation of LH concentration depends upon the Kp, along with the estrous cycle of the dogs, and in reproductive endocrinology, Kp is playing a dynamic role (Albers-Wolthers *et al.*, 2016) <sup>[61]</sup>.

## Conclusion

The number of neuropeptides is having control of the reproductive system but since the last 30 years onwards the Kp is attained a special focus on the regulation of reproduction in mammals. The role of Kp is still not clearly emphasized in many species of animals. One thing that literature is clearly occupied is that Kp neurons are acting on the GnRH and enhance the production of gonadotrophins, especially LH in cattle, buffalo, humans, dogs, pigs, sheep, goats, camel, mares, and mice. The vital role of Kp is unclear in follicular dynamics, maturation of oocytes, ovulation, and embryogenesis of mammals. This review emphasized some aspects of the Kp effect on the reproductive system in a species manner. The known role of Kp in the reproductive system is under the budding stage only need to discover more about it and Kp can rule the reproductive system of mammals.

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