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Application of kisspeptin in domestic animal reproduction

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Abstract
Kisspeptin id the peptide molecule synthesised naturally in the animals' body. The Hypothalamic-Pituitary-Gonadal (HPG) axis controls all stages of reproduction. Kisspeptins are several structurally related amidated peptides, which are derived from the differential proteolytic processing of a common precursor of 145 amino acids encoded by the *KISS1* gene. Recent studies found that it can turn on productions of LH mainly after stimulating secretion of GnRH and help in oocyte maturation and ovulation. This can help in improvement of farm economy by establishing better reproductive traits. This review describes mode of action of kisspeptins and its application in animal reproduction.

Keywords: Kisspeptin, domestic animal, hypothalamic-pituitary-gonadal

Introduction
Reproduction in the animals is the most important factor that not only affect the dairy farm profitability and the development of national economy but also it improves the living standard of rural and urban societies. Animal reproduction it directly or indirectly related to the economic parameters *viz*. milk production, reproductive culling, breeding cost and income through selling the calves. For flawless milk yield and optimal economic output, the cattle should give a calve at 12 months interval [1]. To accomplish this, there should not be a problem in a herd from the aspect of reproduction. There are numerous reproductive abnormalities which affect reproductive performance of animals.

The Hypothalamic-Pituitary-Gonadal (HPG) axis controls all stages of reproduction. The hypothalamus produces gonadotropin-Releasing Hormone (GnRH), which travels to the anterior pituitary and stimulates Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH) secretion. Slow GnRH pulsatility favours FSH secretion and fast pulse frequencies support LH secretion [2]. LH and FSH, in turn control gametogenesis, and steroidogenesis. Gonadal steroids, in turn, modify GnRH neuronal function via negative and positive feedback action [3]. It has recently been revealed that hypothalamic Kisspeptin acts upstream of GnRH and mediates sex steroid feedback and metabolic input on the reproductive axis. This neuropeptide is required for puberty onset and maintenance of normal reproductive function, as loss-of-function mutations of kisspeptin receptor gene (*KISS1R*) are associated with pubertal failure [4]. It is observed that brain control over the release of the gonadotrophin is modulated by the kisspeptin [5].

Kisspeptins are a number of structurally related amidated peptides, which are derived from the differential proteolytic processing of a common precursor of 145 amino acids encoded by the *KISS1* gene [6]. Kisspeptin (Kp) is synthesized in the arcuate nucleus (ARC) and preoptic area (POA) of the hypothalamus and is a regulator of gonadotropin releasing hormone in the hypothalamus [7]. In vertebrates, 3 different genes encoding for kisspeptins and 4 genes encoding for its receptor have been identified. Both kisspeptin (Kiss) and its receptor (KissR) were demonstrated as crucial players of the reproductive function in mammals [8]. They act upstream in the gonadotropic axis by activating gonadotropin-releasing hormone (GnRH) neurons and are considered as major puberty gatekeepers and reproduction regulators [9]. Mutations or targeted deletions of *Kiss* or *KissR* resulted in hypogonadotropic hypogonadism in human and rodents [10]. This pathology is characterised by the failure of the reproductive function due to low circulating levels of gonadotropin hormones (LH and FSH), inducing low plasmatic levels of sex steroids including oestradiol, testosterone and progesterone [11].

Effects of Kisspeptin on Animal Reproductive Traits

Kisspeptin and Puberty

Puberty is initiated through strengthening of excitatory cues and diminishing of inhibitory signs over GnRH neurons, creating a constant increase in pulsatile release of GnRH from hypothalamus. Increased GnRH pulsing activates the downstream elements causing a rise in gonadotropins and sex hormones, gametogenesis, secondary sex characteristics, and rapid growth that led to the achievement of fertility [12]. Timing of puberty onset is determined by genetic and environmental factors as well as gene-environment interactions and is effectively different between males and females. It has been shown that puberty will not occur without proper interaction of Kisspeptins and their corresponding receptor, *e.g.*, inactivating mutations of *GPR54 gene* in hypogonadotropic hypogonadism subjects [13].

Kisspeptin and Pituitary

In vitro studies of rat pituitary cells and of primary cell cultures derived from ovine, bovine, and porcine pituitaries, have described minor stimulatory effects of Kisspeptin on LH. For example, it was shown that *KISS1* and *GPR54* were expressed in rat gonadotrophs, which was differentially regulated by steroids. In females, *KISS1* expression was upregulated by E2, while *GPR54* expression was upregulated by GnRH and down-regulated by chronic exposure to E2. In accordance with this study, molecular analysis of Kisspeptin signalling in mice showed that Kisspeptin induces *LHβ* and *FSHβ* gene expression, and this induction is protein kinase C dependent and mediated by the immediate early genes [14]. In addition, modest stimulatory effects of Kisspeptin on LH and GH secretion were reported in gonadotrophs and somatotrophs of peripubertal male and female rats [15]. Evidence against this argument was documented by other reports. On the other hand, although intravenous (IV) administration of kisspeptin-10 activated LH release, pre-treatment with a GnRH-R antagonist blocked this effect [16]. Similarly, in sheep, in which the hypothalamus and pituitary were surgically disconnected, IV administration of Kisspeptin failed to induce LH secretion [17]. These may suggest that gonadotrophs are not direct targets of Kisspeptin *in vivo*. Compelling evidence showed that co-administration of Kisspeptin and GnRH increased LH release [18]. It should be noted that the direct stimulatory effects of Kisspeptin on pituitary and gonadotropin release are below that of GnRH, and the main stimulatory effect of Kisspeptin on gonadotrophin release is mediated via the hypothalamus.

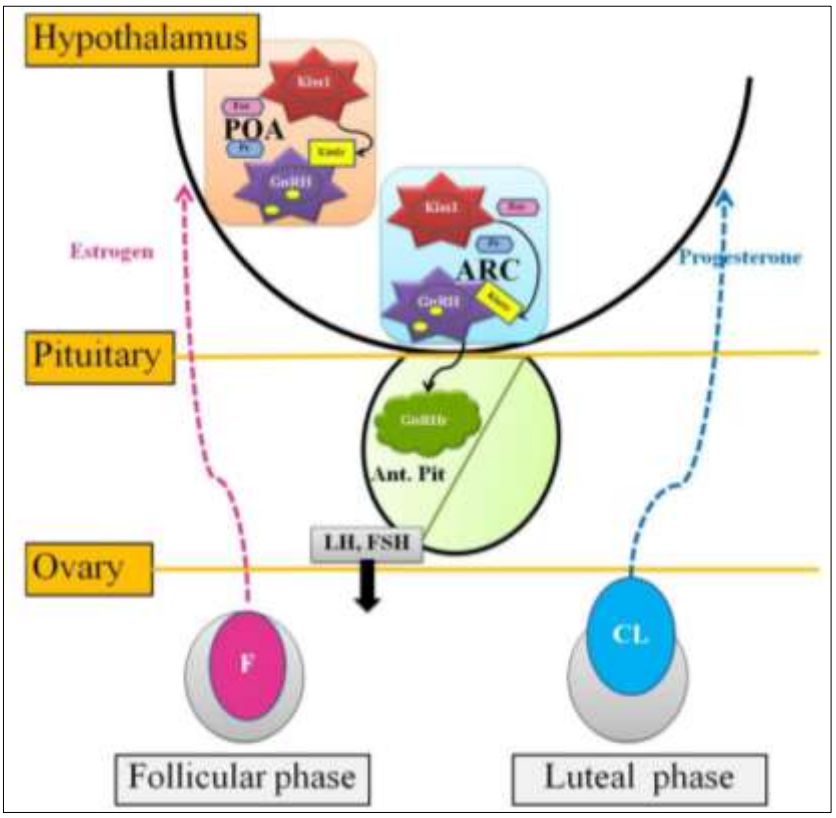

Fig 1: Mode of action of kisspeptin

Kisspeptin and Ovary

The GnRH plays a central role in the reproductive system via stimulating the production of both LH and FSH, with slow GnRH plasticity (< 1 pulse per 2 to 3 hours) favouring FSH secretion and fast pulse frequencies (> 1 pulse per hour) supporting LH secretion. Frequency of GnRH pulses varies throughout the menstrual cycle, thereby controlling the differential production of pituitary gonadotropins [2]. The GnRH secretion is directly or indirectly modulated by many cues. Gonadal steroid feedback generally reduces GnRH, except at the time of the pre-ovulatory LH surge. Increased oestrogen levels at the end of the follicular phase, besides activated progesterone receptors, activate KISS1 neurons in the AVPV thereby increasing GnRH pulse frequency and amplitude, leading to the LH surge and ovulation [19]. Following ovulation, with rise in progesterone levels, GnRH pulse frequency slows, increasing FSH production.

Kisspeptin and Pregnancy

Dramatic increase in Kisspeptin concentration was also seen

in human plasma during pregnancy, which was mainly produced in the placenta. On the other hand, histochemical analysis showed that Kiss1 mRNA is localized in syncytiotrophoblast; both these data together suggest the possible role of Kisspeptin in the regulation of trophoblast invasion. The highest expression levels of Kiss1 and Kiss1R mRNAs in trophoblast cells correspond with the maximum trophoblast invasion, when the aggressive process should be effectively regulated. Furthermore, in rodents the highest expression of both Kiss1 and Kiss1R was seen in the placenta. Studies have shown that Kisspeptin appears to control trophoblast migration via down-regulating the activity of some many matrix metalloproteinases (MMPs) [20].

Kisspeptin and Lactation

There is a temporal increase in plasma oxytocin levels following IV administration of Kisspeptin 10 in female rats; nevertheless intra-cerebroventricular (icv) injection of Kisspeptin 10 did not affect circulating oxytocin levels. On the other hand, the disintegration of vagal afferent input blunted the release of oxytocin; all this evidence together was the basis of the hypothesis that Kisspeptin 10 acts as a hormone (rather than a neuropeptide) on peripheral targets and indirectly activates oxytocin neurons. Recently, it has been shown that central Kisspeptin 10 administration excited oxytocin neurons at the end of pregnancy and during lactation, indicating the required Kisspeptin-induced secretion of oxytocin for parturition and lactation. Increased plasma Kisspeptin during pregnancy might hence accelerate oxytocin release, yet oxytocin receptor expression and oxytocin sensitivity remain low prior to childbirth [21].

Dosage of Kisspeptin

Dose for five species *viz*. cattle, sheep, goat, pig and horse are suggested as 0.1 nmol/kg, 15.6 nmol/head, 0.77 nmol/head, 780 nmol/head and 390nmol/head, respectively [22].

Studies on Animals

Bovine

Kisspeptin stimulates the secretion of LH and GH in prepubertal heifers and there is a possibility for important links among Kisspeptin, the reproductive axis, and also the somatotropic axis [23]. Reproductive steroids enhance the sensitivity of the somatotropic axis to physiologically relevant doses of kisspeptin and it is an integrator of LH and GH release in bovines. Administration of full-length kisspeptin causes LH secretion, which is sustained for a few hours, and it can stimulate follicular development and/or ovulation [24].

Ovine

Kisspeptin is a potent stimulator of gonadotropin secretion in sheep. Continuous infusion of Kp can synchronize LH surges in progesterone-primed cyclical ewes and cause ovulation in seasonally acyclic ewes. stimulates pulse-like release of LH within 15 min following intra-venous injections, and increases the frequency and amplitude of LH pulses and oestradiol in prepubertal ewe [25]. There is evidence that *in vivo* administration kisspeptin increases GnRH secretion in ruminants [26].

Porcine

Peripheral administration of kisspeptin increased gonadotropic hormones in the gilts without affecting somatotropic functions but it is acts on onset of puberty in the animals [4].

Canine

Administration of kisspeptin in dogs induces secretion of the LH and the blood concentration of LH improved even in the neutered dogs. Canine kisspeptin elicited robust gonadotrophin and oestradiol responses in anoestrous in female dogs, suggesting that canine KISS1/KISS1R are cogent targets for modulating reproduction in dogs [27].

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