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Perspective

Kisspeptin: A Game Changer in Reproduction?

Velmurugan S*
National Institute of Animal Biotechnology, India

***Corresponding author:** Velmurugan S, National Institute of Animal Biotechnology, Miyapur, Hyderabad, India

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Perspective

Kisspeptin has recently been identified as the master controller of reproductive axis upstream to GnRH. Neuroendocrine control of GnRH neurons by kisspeptin orchestrates the sequences that take place during the oestrous cycle [1]. In the hypothalamus, kisspeptin is expressed in arcuate nucleus and rostral periventricular region in rats and in arcuate nucleus and preoptic area in sheep [2,3]. Apart from hypothalamus, Kiss1 gene expression and kisspeptin/GPR54 immunoreactivity have been reported in extra-hypothalamic tissues, such as ovaries [4].

In the cyclic rat ovary, the distribution pattern of kisspeptin varies depending on the stage of oestrous cycle. Strong kisspeptin immune reactivity was detected in growing and preovulatory follicles and in corpus luteum. Kisspeptin gene expression increases in ovary at the time of ovulation and the increase in expression is prevented by blocking the preovulatory surge of gonadotropins in rats [4]. Hence, kisspeptin has been proposed to be a regulator of ovulation at the ovarian level. However, the key function of kisspeptin at the ovarian level and the effect of kisspeptin on the follicular dynamics as a whole is poorly understood. Moreover, tissue expression pattern of kisspeptin have not been studied in domestic animal species.

Administration of kisspeptin elevated plasma levels of FSH and LH in ewes: In ovariectomized oestradiol treated ewes, upon peripheral administration of kisspeptin, there is an immediate release of FSH and LH; decline in LH level ensues after the initial rise, while FSH level remains high for several hours [5]. Induction of LH by kisspeptin administration has been reported in steer, pre-pubertal calves and ovariectomized cows [6]. While a single dose of kisspeptin induced only a short-lived stimulation of LH release, repeated intravenous administration induced a sustained train of FSH and LH pulses in sheep [5]. A slow constant infusion of kisspeptin resulted in continuous increase in plasma gonadotropin levels over several hours in ewes and cows [5,7]. Pulsatile administration of kisspeptin once every hour for 24 hours enhanced gonadotropin secretion, ovarial steroidogenesis, stimulation of LH surge and ovulation in ewes [8].

The stage of reproductive cycle also influences the magnitude of response to kisspeptin administration. The response to kisspeptin has been found to be the most effective during late follicular phase. In addition, response to kisspeptin as a single bolus dose has been found to be larger in anoestrus period compared to luteal phase of breeding season in ewes [9]. Kisspeptin treatment also resulted in ovulation in more than 80% of kisspeptin-treated anoestrus ewes, whereas less than 20% of untreated controls ovulated [5].

In women, administration of kisspeptin induced oocyte maturation [10]. Interestingly, plasma levels of kisspeptin increases tremendously in pregnant women due to placental synthesis and lower plasma kisspeptin level could even predict mis-carriage in women [11]. The levels of kisspeptin during pregnancy and correlation, if any, with gestational and post-partum disorders are yet to be studied in animals.

Major causes of infertility in cattle and buffaloes are delayed puberty, anoestrus and repeat breeding. These problems are prevalent even in well-organized farms that meet the recommended level of nutrition, micronutrient supplementation, routine vaccination and deworming practices and hygiene. Hence, hormonal based treatments are usually sought. The existing hormonal therapies that manipulate HPG axis act at the level of GnRH or below. Currently, GnRH analogues or LH is being used to induce ovulation after an oestrus synchronization protocol using progesterone and/or PGF2α. Although effective compared to no treatment at all, there is a considerable failure rate associated with these treatments. E.g. the conception rate is only 50-55% in a synchronization protocol that uses GnRH and PGF2α [12]. Hence, new therapeutic strategies aiming at increased conception rate and reduced fertility disorders are warranted. Upstream to GnRH, kisspeptin might stimulate a more natural pattern of hormonal release than existing strategies. The potential application of kisspeptin to manage reproduction in farm animals has been thoroughly reviewed by Caraty et al [13].

Studies on ovarian physiology may enable us to come up kisspeptin based supplements for *in vitro* biotechniques. Optimization of the effective dose and studies on folliculogenesis will help us to formulate an oestrus synchronization regimen, which can be used as a treatment strategy for repeat breeders and also a management strategy for embryo collection and transfer in embryo biotechnology, and to standardize a protocol to induce oestrus and ovulation in pre-pubertal and anoestrus animals. Studies on expression pattern of kisspeptin and its receptor in domestic animal species will further the knowledge in regulation of reproduction. Plasma levels of kisspeptin may predict fertility level in non-pregnant animals and gestation period and periparturient status in pregnant animals. Kisspeptin may even be a biomarker for predicting reproductive disorders associated with gestation, parturition and postpartum period. Studies testing these hypothetical statements in domestic animal species, so as to understand kisspeptin regulation of reproductive axis and to optimize the dosing regimen, might potentially revolutionize therapeutic strategies for infertility disorders.

This area of reproduction research on kisspeptin is novel and exciting but warrants thorough exploration. Several questions remain to be answered in kisspeptin physiology: How kisspeptin modulates reproductive axis in cyclical and non-cyclical animals? At what dose, route, mode and frequency of administration is kisspeptin effective as a therapeutic molecule? How to avoid receptor desensitization? What is the role of increasing level of kisspeptin during pregnancy? When these questions are answered, the kisspeptin research can be taken to

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the next level: Computing kisspeptin based treatment strategies for fertility disorders.

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