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Role of Kisspeptin in livestock reproduction

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Abstract
The discovery of "Kisspeptin" has opened new vista to understand the regulatory mechanisms of ovarian steroids on control of GnRH secretion. Kisspeptin (Kp) appears to be involved in most (if not all transitional steps) of reproductive life, such as the onset of puberty, initiation of the breeding season and the dynamic changes of gonadotropin secretion throughout the oestrous cycle. Exogenous administration of Kp induces the secretion of gonadotropin (LH) in many species, mainly through stimulation of GnRH secretion including mares, pigs, bovines, ewes, canines, women and ultimately responsible for oocyte maturation and ovulation. Kp stimulates gonadotropin release most potently during the preovulatory phase of the menstrual cycle in women. Infusion of Kp caused synchronization of LH surge and ovulation in progesterone primed cyclic ewes and anoestrus ewes, respectively by activating hypothalamo-pituitary-gonadal axis. In this context, it has been suggested that Kp may be used as new tool to design new protocols for reproductive technologies in mammals.

Keywords: kisspeptin, livestock, reproduction, ovulation

Introduction
The recent advent of a small molecule "Kisspeptin" has opened new vista to understand the regulatory mechanisms of ovarian steroids on control of GnRH secretion (Caraty and Franceschini, 2008) [4]. Kisspeptin (Kp) appears to be involved in most (if not all transitional steps) of reproductive life, such as the onset of puberty, initiation of the breeding season and the dynamic changes of gonadotropin secretion throughout the oestrous cycle (Clarke *et al.*, 2015) [10].

Exogenous administration of Kp induces the secretion of gonadotropin (LH) in many species, mainly through stimulation of GnRH secretion including mares (Wilborn, 2008) [48], pigs (Lents *et al.*, 2008) [21, 22], bovines (Whitlock *et al.*, 2011; Naniwa *et al.*, 2013) [45, 28], ewes (Wang *et al.*, 2012) [43, 44], canines (Albers-Wolthers *et al.*, 2014) [1], women (Jayasena *et al.*, 2014) [17] and ultimately responsible for oocyte maturation and ovulation. It has been observed that, Kp stimulates gonadotropin release most potently during the preovulatory phase of the menstrual cycle in women (Dhillo *et al.*, 2007) [13]. Infusion of Kp caused synchronization of LH surge and ovulation in progesterone primed cyclic ewes and anoestrus ewes, respectively by activating hypothalamo-pituitary-gonadal axis (Caraty *et al.*, 2007) [5, 6]. In this context, it has been suggested that Kp may be used as new tool to design new protocols for reproductive technologies in mammals (Caraty and Franceschini, 2008) [4].

Genes encoding Kp and its receptors (KISS1 and KISS1R) have been documented in the ovaries of rat (Terao *et al.*, 2004) [42], hamsters (Shahed and Young, 2009) [37, 38], pigs and goats (Inoue *et al.*, 2009) [16], primate and human ovaries (Gaytan *et al.*, 2009; Cejudo Roman *et al.*, 2012) [15, 8], this indicate that Kp may also have direct gonadal effects and interact with metabolic pathways (Clarke *et al.*, 2015) [10]. Presence of Kp at high concentrations in porcine follicular fluid than serum revealed the involvement of Kp during follicular development and suggests an intrafollicular or systemic origin of action (Saadeldin *et al.*, 2012) [35]. However, the local role of Kp in controlling the ovulation process has not yet fully understood. Very few *in vitro* studies have been conducted to see the effect of Kp on IVM and fertilization of oocytes in farm animals. The expression of genes encoding Kp and its receptors were detected during IVM period in both oocytes and cumulus cells of pig (Saadeldin *et al.*, 2012) [35] and bovine (Ming *et al.*, 2015) [26] and also suggested that supplementation of Kp in IVM media improved the maturation efficiency of oocytes in pig and bovines. It has been suggested that, Kp has continuous and direct action on oocytes and cumulus cells in an autocrine-paracrine fashion.

Effect of Kisspeptin on reproduction

Kisspeptins (Kp) are peptide products of the KISS1 gene, which was discovered by Lee *et al.*, in 1996 [20] as a metastasis-suppressing gene in malignant melanoma cells (Lee *et al.* 1996) [20]. Kp is now best known as a multifunctional peptide because of its role in cancer, the cardiovascular system and reproduction (Mead *et al.*, 2007) [24]. The reproductive dimension of the KISS1/KISS1R system was discovered in late 2003, when KISS1R (previously known as GPR54) gene mutations were first reported in humans and mice suffering hypogonadotropic hypogonadism (De Roux *et al.*, 2003 and Seminara *et al.*, 2003) [11, 36]. From that moment onwards, Kp became known as a master regulator of the reproductive axis in a hierarchical manner (Tena-Sempere, 2006) [41] and among the most potent elicitors of GnRH-gonadotrophin secretion in a variety of mammalian species, including humans (Roseweir and Millar, 2009 and Pineda *et al.*, 2010) [33, 34, 25]. It works primarily on the hypothalamus to activate GnRH neurons; in addition, neuroanatomical studies have allowed identification of a discrete population of Kp neurons in different hypothalamic areas (Smith *et al.*, 2005; Kauffman *et al.*, 2007) [39, 40]. Kp acts primarily at central levels to regulate ovarian function is well defined, the possibility of additional effects at other sites of the hypothalamic–pituitary– ovarian axis cannot be ruled out (Roa and Tena-Sempere, 2007) [32]. Bilban *et al.* (2004) [2] identified Kp as an endocrine– paracrine regulator of trophoblast invasion.

Expression of Kisspeptin on genes

In rodents, the expression of KISS1 and KISS1R genes were detected in the ovary (Terao *et al.*, 2004) [42]. In addition, Kp and KISS1R immunoreactivity were recently demonstrated in ovarian tissue sections from cyclic rats, where KISS1, but not KISS1R, gene expression was shown to fluctuate in a cycle dependent manner under the regulation of pituitary LH (Castellano *et al.*, 2006) [7]. Moreover, ovarian expression of KISS1 and KISS1R genes was recently documented in fish (Nocillado *et al.*, 2007) [29], hamsters (Shahed and Young, 2009) [37, 38], pigs and goats (Inoue *et al.*, 2009) [16] and primates (Gaytan *et al.*, 2009) [15].

Role of Kisspeptin on ovulation

Kp stimulates ovulation in rats (Matsui *et al.*, 2004), ewes (Caraty *et al.*, 2007) [5, 6] and mares (Briant *et al.*, 2006). Furthermore, inhibitors of cyclooxygenase-2 known to disturb follicular rupture, ovulation and inhibited KISS1 gene expression selectively in the rat ovary (Gaytan *et al.*, 2009) [15]. Together, these reports suggest a local role of Kp is directly controlling the ovulation process, but a clear picture of its local function has not yet fully emerged. Roseweir *et al.* (2009) [33, 34] discovered a potent Kp antagonist (p234) that revealed the critical roles of Kp in both female puberty and the preovulatory gonadotrophin surge (Pineda *et al.*, 2010 and Millar *et al.*, 2010) [30, 25]. Kp enhanced the sensitivity of reproductive steroids to somatotropic axis and it acts as integrator of LH and Growth Hormone (GH) release (Whitlock *et al.*, 2015) [47]. Kp caused increased LH secretion in bovines (Naniwa *et al.*, 2013; Whitlock *et al.*, 2008) [28, 46], prepubertal heifers (Kadokawa *et al.*, 2008) [18], ewes (Redmond *et al.*, 2011 and Wang *et al.*, 2012) [31, 43, 44], acyclic mares (Wilborn, 2008) [48], swine (Lents *et al.*, 2008) [21, 22] and dogs (Cheng *et al.*, 2011; Elderen, 2014) [9]. Single injection of Kp-54 can induce egg maturation in women with sub fertility in dose dependent manner (Jayasena *et al.*, 2014) [17].

***In vivo* effects of Kisspeptin in different livestock species**

Bovines

Kadokawa *et al.* (2008) [18] observed that, Kp 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. Whitlock *et al.* (2011) [45] reported that, lactation status and stage of lactation did not change the sensitivity of the GH system to Kp. However, an effect of stage of lactation on Kp stimulated LH secretion was detected in the dairy cows. Reproductive steroids enhance the sensitivity of the somatotropic axis to physiologically relevant doses of Kp and it is an integrator of LH and GH release in bovines (Whitlock *et al.*, 2008) [46]. Administration of full-length Kp causes LH secretion, which is sustained for a few hours, and it is capable of stimulating follicular development and/or ovulation (Naniwa *et al.*, 2013) [28].

Sheep

Kp 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 (Caraty *et al.* (2007) [5, 6]. Kp stimulates pulse-like release of LH within 15 min following intra venous injections, and increases the frequency and amplitude of LH pulses and estradiol in prepubertal ewe lambs (Redmond *et al.*, 2011 and Wang *et al.*, 2012) [31, 43, 44]. Whitlock *et al.* (2015) [47] reported that, Kp stimulates the gonadotropic axis of ruminants *in vivo*.

Swine

Lents *et al.* (2008) [21, 22] indicated that, peripheral administration of Kisspeptin increased serum concentrations of LH but not FSH or GH. Thus, Kp can activate gonadotropic hormones but not somatotropic hormone secretion in prepubertal gilts. But it plays a role in the mechanism involved in initiating puberty in swine.

Dogs

Cheng *et al.* (2011) [9] conducted a study in dogs and observed that, Kp induces LH secretion effectively and also an elevation in blood LH concentrations in neutered dogs. Canine Kp elicits robust gonadotrophin and oestradiol responses in anoestrous bitches, suggesting that canine KISS1/KISS1R are cogent targets for modulating reproduction in dogs (Albers-Wolthers *et al.*, 2014) [1].

Conclusions

The discovery of "Kisspeptin" has opened new vista to understand the regulatory mechanisms of ovarian steroids on control of GnRH secretion. Kisspeptin (Kp) appears to be involved in most (if not all transitional steps) of reproductive life, such as the onset of puberty, initiation of the breeding season and the dynamic changes of gonadotropin secretion throughout the oestrous cycle. Exogenous administration of Kp induces the secretion of gonadotropin (LH) in many species, mainly through stimulation of GnRH secretion including mares, pigs, bovines, ewes, canines, women and ultimately responsible for oocyte maturation and ovulation. Kp stimulates gonadotropin release most potently during the preovulatory phase of the menstrual cycle in women. Infusion

of Kp caused synchronization of LH surge and ovulation in progesterone primed cyclic ewes and anoestrus ewes, respectively by activating hypothalamo-pituitary-gonadal axis. In this context, it has been suggested that Kp may be used as new tool to design new protocols for reproductive technologies in mammals.

References

1. Albers-Wolthers KH, De Gier J, Kooistra HS, Rutten VP. Identification of a novel kisspeptin with high gonadotrophin stimulatory activity in the dog. Neuroendocrinology. 2014; 99(3-4):178-189.
2. Bilban M, Ghaffari-Tabrizi N, Hintermann E, Bauer S, Molzer S, Zoratti C *et al.* Kisspeptin-10, a KiSS-1/metastin-derived decapeptide, is a physiological invasion inhibitor of primary human trophoblasts. Journal of cell science. 2004; 117(8):1319-1328.
3. Briant C, Schneider J, Guillaume D, Ottogalli M, Duchamp G, Bruneau B *et al.* Kisspeptin induces ovulation in cycling Welsh pony mares. Animal Reproduction Science. 2006; 94(1-4):217-219
4. Caraty A, Franceschini I. Basic aspects of the control of GnRH and LH secretions by kisspeptin: potential applications for better control of fertility in females. Reproduction in Domestic Animals. 2008; 43(s2):172-178.
5. Caraty A, Smith JT, Lomet D, Ben Said S, Morrissey A. Kisspeptin synchronizes preovulatory surges in cyclical ewes and causes ovulation in seasonally acyclic ewes. Endocrinology. 2007; 148(11):5258-5267.
6. Caraty A, Smith JT, Lomet D, Ben Said S, Morrissey A. Kisspeptin synchronizes preovulatory surges in cyclical ewes and causes ovulation in seasonally acyclic ewes. Endocrinology. 2007; 148(11):5258-5267.
7. Castellano JM, Navarro VM, Fernandez-Fernandez R. Ontogeny and mechanisms of50 action for the stimulatory effect of kisspeptin on gonadotropin-releasing hormone system of the rat. Molecular and cellular endocrinology. 2006; 257:75-83.
8. Cejudo Roman A, Pinto FM, Dorta I, Almeida TA, Hernandez M. Analysis of the expression of neurokinin B, kisspeptin, and their cognate receptors NK3R and KISS1R in the human female genital tract. Fertility and Sterility. 2012; 97:1213-1219.
9. Cheng CH, Chou CH, Hsu MC, Chen BH, Fan YC, Chiu CH. The Effect of IV injected Kisspeptin on Blood Concentrations of LH in Neutered Dogs. Taiwan Veterinary Journal. 2011; 37(2):136-142. (In Chinese)
10. Clarke H, Dhillo WS, Jayasena CN. Comprehensive review on kisspeptin and its role in reproductive disorders. Endocrinology and Metabolism. 2015; 30(2):124-141
11. De Roux N, Genin E, Carel JC, Matsuda F, Chaussain JL, Milgrom E. Hypogonadotropic hypogonadism due to loss of function of the KiSS1-derived peptide receptor GPR54. Proceedings of the National Academy of Sciences. 2003; 100(19):10972-10976.
12. Decourt C, Robert V, Anger K, Galibert M, Madinier JB. A synthetic kisspeptin analog that triggers ovulation and advances puberty. Scientific reports. 2016; 6:26908.
13. Dhillo WS, Chaudhri OB, Thompson EL, Murphy KG. Kisspeptin-54 stimulates gonadotropin release most potently during the preovulatory phase of the menstrual cycle in women. The Journal of Clinical Endocrinology & Metabolism. 2007; 92(10):3958-3966.
14. Elderen MV. Dose-response study with canine kisspeptin-10 *in vivo* and *in vitro*. Thesis submitted to Faculty of Veterinary Medicine, Utrecht University, Utrecht, The Netherlands, 2014
15. Gaytan F, Gaytan M, Castellano JM, Romero M, Roa J. KiSS-1 in the mammalian ovary: distribution of kisspeptin in human and marmoset and alterations in KiSS-1 mRNA levels in a rat model of ovulatory dysfunction. American Journal of Physiology-Endocrinology and Metabolism. 2009; 296(3):E520-E531
16. Inoue N, Hirano T, Uenoyama Y, Tsukamura X, Okamura H, Maeda K. Localization of kisspeptin and gonadotrophin releasing hormone (GnRH) in developing ovarian follicles of pigs and goats. Biology of Reproduction. 2009; 81:551.
17. Jayasena CN, Abbara A, Comninos AN, Nijher GM, Christopoulos G *et al.* Kisspeptin-54 triggers egg maturation in women undergoing *in vitro* fertilization. The Journal of clinical investigation. 2014; 124(8):3667-3677.
18. Kadokawa H, Matsui M, Hayashi K, Matsunaga N, Kawashima C, Shimizu T *et al.* Peripheral administration of kisspeptin-10 increases plasma concentrations of GH as well as LH in prepubertal Holstein heifers. Journal of Endocrinology. 2008; 196(2):331-334.
19. Kauffman AS, Gottsch ML, Roa J, Byquist AC, Crown A, Clifton DK *et al.* Sexual differentiation of Kiss1 gene expression in the brain of the rat. Endocrinology. 2007; 148(4):1774-1783
20. Lee JH, Miele ME, Hicks DJ, Phillips KK, Trent JM, Weissman BE *et al.* KiSS-1, a novel human malignant melanoma metastasis-suppressor gene. Journal of the National Cancer Institute. 1996; 88(23):1731-1737
21. Lents CA, Heidorn NL, Barb CR Ford JJ. Central and peripheral administration of kisspeptin activates gonadotropin but not somatotropin secretion in prepubertal gilts. Reproduction. 2008; 135(6):879-887
22. Lents CA, Heidorn NL, Barb CR, Ford JJ. Central and peripheral administration of kisspeptin activates gonadotropin but not somatotropin secretion in prepubertal gilts. Reproduction. 2008; 135(6):879-887.
23. McGrath BM, Scott CJ, Wynn PC, Loy J, Norman ST. Kisspeptin stimulates LH secretion but not ovulation in mares during vernal transition. Theriogenology. 2016
24. Mead EJ, Maguire JJ, Kuc RE, Davenport AP. Kisspeptins: a multifunctional peptide system with a role in reproduction, cancer and the cardiovascular system. British journal of pharmacology. 2007; 151(8):1143-1153
25. Millar RP, Roseweir AK, Tello JA, Anderson RA, George JT, Morgan K *et al.* Kisspeptin antagonists: unraveling the role of kisspeptin in reproductive physiology. Brain research. 2010; 1364:81-89.
26. Ming HE, Wang Jun, Yang Yu-Jiang, Liu Zi-Wei, Liu Xun, Lv Wen-Fa. Expression and Function of Kisspeptin during Bovine Oocyte Maturation *in vitro*. Chinese Journal of Animal Science. 2015; 51(11)
27. Naniwa Y, Nakatsukasa K, Setsuda S, Oishi S, Fujii N. Effects of full-length kisspeptin administration on follicular development in Japanese Black beef cows. The Journal of reproduction and development. 2001; 59(6):588.
28. Naniwa Y, Nakatsukasa K, Setsuda S, Oishi S, Fujii N, Matsuda F *et al.* Effects of full-length kisspeptin

administration on follicular development in Japanese Black beef cows. The Journal of reproduction and development. 2013; 59(6):588.
29. Nocillado JN, Levavi-Sivan B, Carrick F, Elizur A. Temporal expression of G-proteincoupled receptor 54 (GPR54), gonadotropin-releasing hormones (GnRH), and dopamine receptor D2 (drd2) in pubertal female grey mullet, Mugil cephalus. General and comparative endocrinology. 2007; 150(2):278-287
30. Pineda R, Aguilar E, Pinilla L, Tena-Sempere M. Physiological roles of the kisspeptin/GPR54 system in the neuroendocrine control of reproduction. Progress in brain research. 2010; 181:55-77.
31. Redmond JS, Macedo GG, Velez IC, Caraty A, Williams GL, Amstalden M. Kisspeptin activates the hypothalamic–adenohypophyseal–gonadal axis in prepubertal ewe lambs. Reproduction. 2011; 141(4):541-548
32. Roa J, Tena-Sempere M. KiSS-1 system and reproduction: comparative aspects and roles in the control of female gonadotropic axis in mammals. General and comparative endocrinology. 2007; 153(1):132-140.
33. Roseweir AK, Millar RP. The role of kisspeptin in the control of gonadotrophin secretion. Human reproduction update. 2009; 15(2):203-212
34. Roseweir AK, Kauffman AS, Smith JT, Guerriero KA, Morgan K. Discovery of57 potent kisspeptin antagonists delineate physiological mechanisms of gonadotropin regulation. The Journal of Neuroscience. 2009; 29(12):3920-3929
35. Saadeldin IM, Koo OJ, Kang JT, Kwon DK, Park SJ, Kim S *et al.* Paradoxical effects of kisspeptin: it enhances oocyte *in vitro* maturation but has an adverse impact on hatched blastocysts during *in vitro* culture. Reproduction, Fertility and Development. 2012; 24(5):656-668.
36. Seminara SB, Messager S, Chatzidaki EE, Thresher RR. The GPR54 gene as a regulator of puberty. New England Journal of Medicine. 2003; 349(17):1614-1627.
37. Shahed A, Young KA. Differential ovarian expression of KiSS-1 and GPR-54 during the estrous cycle and photoperiod induced recrudescence in Siberian hamsters (Phodopus sungorus). Molecular Reproduction and Development. 2009; 76:444-452.
38. Shahed A, Young KA. Differential ovarian expression of KiSS-1 and GPR-54 during the estrous cycle and photoperiod induced recrudescence in Siberian hamsters (Phodopus sungorus). Molecular Reproduction and Development. 2009; 76:444-452.
39. Smith JT, Cunningham MJ, Rissman EF, Clifton DK, Steiner RA. Regulation of Kiss1 gene expression in the brain of the female mouse. Endocrinology. 2005a; 146:3686-3692.
40. Smith JT, Dungan HM, Stoll EA, Gottsch ML, Braun RE, Eacker SM *et al.* Differential regulation of KiSS-1 mRNA expression by sex steroids in the brain of the male mouse. Endocrinology. 2005b; 146:2976–2984
41. Tena-Sempere M. The roles of kisspeptins and G protein-coupled receptor-54 in pubertal development. Current opinion in pediatrics. 2006; 18(4):442-447.
42. Terao Y, Kumano S, Takatsu Y, Hattori M, Nishimura A, Ohtaki T *et al.* Expression of KiSS-1, a metastasis suppressor gene, in trophoblast giant cells of the rat placenta. Biochimica et Biophysica Acta. 2004; 1678:102-110.
43. Wang J, Sun L, Zhang T, Zhou H, Lou Y. Effect of peripheral administration of kisspeptin-10 on dynamic LH secretion in prepubertal ewes. Asian-Australasian journal of animal sciences. 2012; 25(6):785.
44. Wang J, Sun L, Zhang T, Zhou H, Lou Y. Effect of peripheral administration of kisspeptin-10 on dynamic LH secretion in prepubertal ewes. Asian-Australasian journal of animal sciences. 2012; 25(6):785.
45. Whitlock BK, Daniel JA, Wilborn RR, Maxwell HS, Steele BP, Sartin JL. Effect of kisspeptin on regulation of growth hormone and luteinizing hormone in lactating dairy cows. Journal of Animal Science and Biotechnology. 2011; 2:131-40
46. Whitlock BK, Daniel JA, Wilborn RR, Rodning SP, Maxwell HS, Steele BP *et al.* Interaction of estrogen and progesterone on kisspeptin-10-stimulated luteinizing hormone and growth hormone in ovariectomized cows. Neuroendocrinology. 2008; 88(3):212-215
47. Whitlock, Brian K, Joseph A Daniel, Lisa L Amelse, Valeria M Tanco, Kelly A Chameroy *et al.* Kisspeptin receptor agonist (FTM080) increased plasma concentrations of luteinizing hormone in anestrous ewes. PeerJ3. 2015; e1382.
48. Wilborn R. Effect of Kisspeptin on the Hypothalamic-Pituitary-Gonadal Axis of the Mare (Doctoral dissertation), 2008.