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Review

Peripheral action of kisspeptin at reproductive tissues—role in ovarian function and embryo implantation and relevance to assisted reproductive technology in livestock: a review

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Abstract

Kisspeptin (KISS1) is encoded by the *KISS1* gene and was initially found to be a repressor of metastasis. Natural mutations in the KISS1 receptor gene (*KISS1R*) were subsequently shown to be associated with idiopathic hypothalamic hypogonadism and impaired puberty. This led to interest in the role of KISS1 in reproduction. It was established that KISS1 had a fundamental role in the control of gonadotropin releasing hormone (GnRH) secretion. KISS1 neurons have receptors for leptin and estrogen receptor α (ERα), which places KISS1 at the gateway of metabolic (leptin) and gonadal (ERα) regulation of GnRH secretion. More recently, KISS1 has been shown to act at peripheral reproductive tissues. *KISS1* and *KISS1R* genes are expressed in follicles (granulosa, theca, oocyte), trophoblast, and uterus. KISS1 and KISS1R proteins are found in the same tissues. KISS1 appears to have autocrine and paracrine actions in follicle and oocyte maturation, trophoblast development, and implantation and placentation. In some studies, KISS1 was beneficial to in vitro oocyte maturation and blastocyst development. The next phase of KISS1 research will explore potential benefits on embryo survival and pregnancy. This will likely involve longer-term KISS1 treatments during proestrus, early embryo development, trophoblast attachment, and implantation and pregnancy. A deeper understanding of the direct action of KISS1 at reproductive tissues could help to achieve the next step change in embryo survival and improvement in the efficiency of assisted reproductive technology.

Summary Sentence

Kisspeptin acts within the brain to influence GnRH secretion, and there is now strong evidence that it also acts at peripheral reproductive tissues to directly influence ovarian function, embryo development, implantation and pregnancy.

Key words: kisspeptin, GnRH secretion, ovary, embryo, implantation, pregnancy.

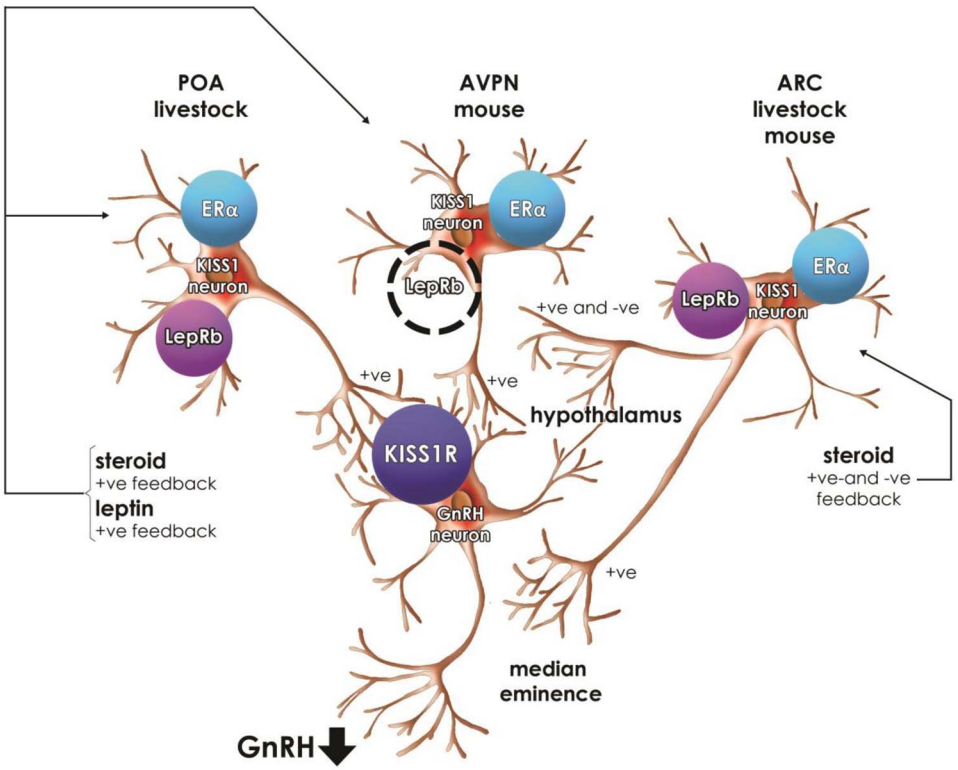

Figure 1. Diagrammatic representation of kisspeptin (KISS1) and GnRH neurons in the brain. KISS1 neurons have leptin (LepRb) receptors and ERα, which places KISS1 neurons at the gateway of metabolic (leptin) and gonadal (ERα) regulation of GnRH secretion. KISS1 neurons have axon projections to GnRH neuron cell bodies in the hypothalamus and GnRH neuron axons in the vicinity of the median eminence. In the mouse, KISS neurons are localized at the ARC and AVPV. In livestock, KISS1 neurons are localized to the ARC and POA. Estrogen-positive feedback operates at KISS1 neurons in the AVPV (mouse [220]), POA (primates [120]), and ARC and POA (sheep [40, 115]). Steroid positive and negative feedback acts at KISS1 neurons in the ARC across species. KISS1 appears to influence GnRH release within the median eminence by the interaction of KISS1 neuron synaptic terminals with GnRH neuron axons in sheep [116]. The LepRb receptor on KISS1 neurons in the AVPV is shown as a broken circle as there remains a lack of consensus with reports of the presence (e.g. [51]) and the absence (e.g. [47]).

Introduction

The peptide kisspeptin (KISS1) is encoded by the *KISS1* gene and is a major regulator of reproductive function. The role of KISS1 within the brain to regulate gonadotropin releasing hormone (GnRH) secretion has been well characterized [1–13] (Figure 1). KISS1 also acts outside the brain at peripheral reproductive tissues (e.g. ovary, uterus) [14–16]. The aim of the present review was to bring together information on the emerging roles of KISS1 beyond the brain. A number of previous reviews have looked at different stages in the history of KISS1. It was considered important in the present review to first consolidate, into a single source, work that led to the discovery and characterization of KISS1. This approach will provide readers with the background of how discovery of the *KISS1* gene and KISS1 protein quickly led to an understanding of the fundamental role of KISS1 in GnRH release [3, 17].

In 1996, the expression of the *KISS1* gene was demonstrated in human nonmetastatic melanoma cells [18] (Table 1). This finding led to the suggestion that the expression of *KISS1* conferred the nonmalignant phenotype in melanoma cells [18]. Within 1 year, it was reported that the expression of *KISS1* did indeed suppress metastasis in human breast carcinoma cells [19]. The peptide encoded by *KISS1* was first isolated in 2001 from human placenta. It was named metastin by one research group to reflect its metastasis-suppressing properties [20]. A second research group named the peptide KISS1 as it belonged to the kisspeptins [21]. G protein-coupled receptor 54 (GPR54; renamed KISS1 receptor, KISS1R) had been discovered in 1999 as an orphan receptor in the rat brain [22]. In 2001, KISS1 was shown to bind to KISS1R (Table 1). Two years later in 2003, natural mutations in the *KISS1R* gene were found to be associated with idiopathic hypothalamic hypogonadism and impaired puberty in humans (Table 1). At the same time, targeted mutations of the *KISS1R* gene disrupted puberty in mice [23, 24]. The findings for KISS1R in humans and mice focused attention on the role of KISS1 in reproduction. Within a short period, it was established for rodents, ruminants, and primates that KISS1 induced the secretion of GnRH [25] and it had been shown that GnRH neurons expressed KISS1R [11, 26, 27] (Figure 1). It was also shown that KISS1 neurons in the brain expressed the receptor for leptin in mice [28] and sheep [29]. The latter led to the concept that KISS1 acts as a mediator in brain pathways that link metabolic status to reproductive function [29–39]. KISS1 neurons also express estrogen receptor α, further linking KISS1 to the reproductive neuroendocrine axis [40, 41] (Figure 1).

There is evidence that leptin can influence KISS1 neurons by indirect pathways that do not involve classical binding to the KISS1R. For example, selective deletion of KISS1R from hypothalamic KISS1 neurons had no apparent deleterious effect on puberty or fertility in female mice [42]. Also, intracellular signal transduction from the KISS1R typically involves the transcription factor, signal transducer and activator of transcription 3 (STAT3) [43], and STAT3 was shown

Table 1. Chronology of the discovery of kisspeptin (KISS1) and G protein-coupled receptor 54 (GPR54, renamed KISS1R).

Year	Event	Reference
1996	*KISS1* gene expression demonstrated in human nonmetastatic melanoma cells, suggesting that *KISS1* expression conferred the nonmalignant phenotype in melanoma cells	[18]
1997	*KISS1* expression shown to suppress metastasis in human breast carcinoma cells	[19]
1999	Discovery of orphan receptor GPR54 in rat brain	[22]
2001	Metastin/KISS1 isolated from human placenta as products of the *KISS1* gene	[20, 21]
2001	KISS1 shown to bind to orphan receptor GPR54	[20, 21, 210–212]
2003	Natural mutations in GPR54 shown to be associated with idiopathic hypothalamic hypogonadism and impaired puberty in humans	[213–217]
2003	Targeted mutation of *GPR54* gene disrupted puberty in mice	[23, 24]
2004	*KISS1R* expression demonstrated on GnRH neurons	[11, 26, 27]
2004	*KISS1* expression demonstrated in trophoblast giant cells in rats	[157]
2004	KISS1 shown to act as trophoblast repressor in women	[147]
2005	KISS1 shown to stimulate GnRH release through GPR54	[218]
2005	KISS1 shown to have a fundamental role in the onset of puberty in mice, subsequently shown in other species	[14, 27, 219]

to be absent from KISS1 neurons in mice [44, 45], rats [46], and sheep [47]. However, it was reported for mice that while STAT3 is required for the action of leptin in metabolic homeostasis and energy expenditure, STAT3 may not be obligatory for the effects of leptin on reproduction [48–50]. The above reports for rodents indicate that leptin can act at multiple sites, and through different pathways, within the brain to influence metabolism and reproduction [42, 44, 51, 52]. A further level of complexity in leptin action within the brain is the colocalization and interaction with neurokinin B (NKB) and dynorphin (Dyn) neurons, collectively termed KNDy neurons [7, 53–56]. The latter has been demonstrated particularly in the arcuate nucleus (ARC) in rodents [57, 58], sheep [59, 60], and cattle [61]. Interaction between KISS1, NKB, and Dyn in the ARC is associated with the regulation of both metabolic and reproductive functions [12, 62]. The metabolic actions of KISS1 within the brain also involve interaction with agouti-related peptide (AgRP)/neuropeptide Y neurons and proopiomelanocortin neurons of the ARC [63].

KISS1 belongs to the Arg-Phe-NH_2 (RF-amide) peptide superfamily [64, 65]. The kisspeptin group includes kisspeptin-54 (KISS1), kisspeptin-14, kisspeptin-13, and kisspeptin-10 [21, 10, 66] (Figure 2). KISS1 has an RF-amide motif (humans, nonhuman primates) or RY-amine motif (livestock, rodents) at the C-terminal, which is required for binding to KISS1R [67–69]. Natural sequence KISS1 undergoes rapid proteolytic degradation [70], and agonists have been developed, which have an extended half-life in circulation and high biological potency [71–74]. KISS1 antagonists have also been developed to study the effect of blocking KISS1 action [71, 72, 76–78]. KISS1 agonists and antagonists have been used primarily to study the role of KISS1 within the brain to regulate GnRH secretion [72, 73, 79–82]. The potential to use KISS1 analogs to study the action of KISS1 at other reproductive tissues (e.g. ovary, trophoblast, uterus) is discussed below.

The action of KISS1 at peripheral reproductive tissues (ovary, trophoblast, uterus) has emerged as an important component of the cellular and molecular processes associated with embryo survival, implantation, and the establishment of a pregnancy. The period leading to a pregnancy is a critical time for embryos, and recent reviews have highlighted how failure of the embryo to achieve attachment and implantation is a major cause of reproductive loss in ruminant livestock [39, 83–85]. Despite these reviews, more remains to be discovered about mechanisms associated with the interaction of the embryonic trophoblast with the uterine endometrial epithelium during attachment and implantation. In support of this conclusion, there have been many advances in the in vivo and in vitro production of embryos; yet, the capacity of embryos to survive, implant, and establish a pregnancy has remained essentially unchanged at around 30–50% for ruminant livestock [39, 83, 84, 86] and 20–30% for human in vitro fertilization (IVF) embryos [87]. Undoubtedly, there are maternal factors involved in pregnancy establishment [88–90]. However, embryo signaling is fundamental to the initiation of events that lead to implantation and pregnancy. This review looks at how the action of KISS1 at peripheral reproductive tissues contributes to the processes that support embryonic development and implantation. The review first describes the distribution of KISS1 in peripheral tissues, and it then considers local actions (autocrine, paracrine) of KISS1 in reproductive processes. The information is used to support the argument that the local action of KISS1 at peripheral reproductive tissues needs to be considered when KISS1 is utilized in assisted reproduction. The present review builds on articles that have looked at the broader role of KISS1 in reproduction beyond the brain [80, 91–94]. While the review is directed at the action of KISS1 at peripheral reproductive tissues, it would be incomplete if it did not include some seminal papers on the discovery of KISS1 and the classical role of KISS1 in the regulation of GnRH secretion. This is why a consolidated history of KISS1 is provided at the beginning of the review and the action of KISS1 at the brain is also presented. The review brings together in one article the biology of KISS1 and the current and potential future applications of KISS1 in assisted reproduction.

Distribution and function of KISS1 and KISS1R in the brain and reproductive tissues

Studies on the localization of KISS1 and KISS1R protein using immunohistochemistry, and *KISS1*and *KISS1R* mRNA using in situ hybridization, have predominantly utilized antibodies and PCR primers, respectively, generated against human, mouse, and rat proteins and DNA sequences. The reader should consult specific articles for details on the methodology employed in studies where antibodies and PCR primers have been used for comparative studies in species other than humans and rodents. This level of detail is outside the scope of the review, but it may explain some of the apparent discrepancies across studies on KISS1 and KISS1R localization [95].

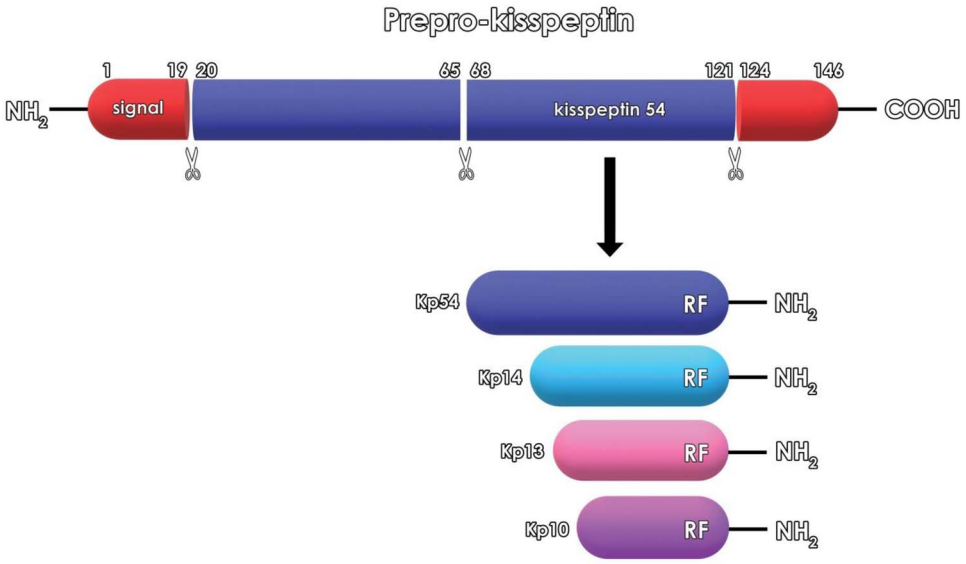

Figure 2. Diagrammatic representation of prepro-kisspeptin, which is the precursor for kisspeptins, KISS-54 (Kp54, KISS1), KISS-14 (Kp14), KISS-13 (Kp13), and KISS-10 (Kp10) [15]. The kisspeptins belong to the Arg-Phe-NH_2 (RF-amide) peptide superfamily and have the RF-amide or RY-amide motif at the C-terminal, which is required for binding to KISS1R (GPR54) [64]. Figure adapted from the literature including Pinilla et al. [9]

Brain

The localization of KISS1 neurons within the brain has been extensively reviewed for rodents, primates, and production animals [25, 96, 97] (Figure 1). KISS1 neurons are concentrated in the ARC, anteroventral periventricular nucleus (AVPV), and preoptic area (POA) [98–103] (Figure 1). There are species differences in where KISS1 neuron cell bodies are concentrated [25]. In mice, KISS1 neuron cell bodies are located primarily in the ARC and AVPV [104–107]. In cattle [82, 108], buffalo [109–112], sheep [7, 25, 99, 100, 113–118], and primates [119], KISS1 cell bodies are found in the ARC and POA (Figure 1). In a recent report, *KISS1* mRNA expression was found in the amygdala in female rats and was shown to be associated with puberty [78, see also 120]. Axonal projections of KISS1 neurons have synaptic terminals in the vicinity of GnRH neuron cell bodies in the hypothalamus [73, 108, 121] and GnRH neuron axons in the vicinity of the median eminence [115, 122, 123] (Figure 1). KISS1 is released at synaptic terminals and binds to KISSR on GnRH neurons [121] (Figure 1).

Ovaries

The expression of *KISS1* and *KISS1R* genes, and the presence of KISS1 and KISS1R protein, has been demonstrated in follicles, oocytes, and corpora lutea in the rat [124–126], mouse [127], Siberian hamster [128], rabbit [16], cat [129], dog [130], goat [131], sow [132, 133], and human and nonhuman primates [134, 135]. In rats, *KISS1* and *KISS1R* expression was low in prepubertal animals and expression increased in the theca cells of follicles and luteal tissue in response to treatment with gonadotropin [124, 125]. In dogs, KISS1R protein, but not KISS1 protein, was present in ovaries of prepubertal animals [130]. In rats, ovarian *KISS1* and *KISS1R* showed constant expression, whereas KISS1 protein increased during the preovulatory period, suggesting a role for KISS1 in ovulation [124]. Similarly, in the Siberian hamster, KISS1 and KISS1R protein levels were highest at proestrus and estrus [128]. The Siberian hamster is a photoperiodic long-day breeder, and ovarian KISS1 and KISS1R levels were higher during long days than in short days [128]. Follicular *KISS1* and *KISS1R* mRNA have been localized in both granulosa cells (dog [130]; cat [129]; human [135]) and theca cells (rat [124]; human and marmoset [134]; cat [129]). The expression of *KISS1* and *KISS1R* in follicles (granulosa, theca, oocyte) and corpora lutea, together with the presence of KISS1 and KISS1R proteins, provides strong evidence that local KISS1 has important autocrine and paracrine actions in ovarian function [138] (Figure 3). In support of this, *KISS1* mRNA increased around 80-fold during the attainment of meiotic competence in mouse oocytes [137]. Also, oocyte-specific *KISS1R* knockout mice failed to ovulate, suggesting an important role for KISS1 action on oocytes in ovulation [138]. Furthermore, $KISS1R^{-/-}$ mutant mice showed arrested follicular development, even with normal gonadotrophin secretion [139]. In addition, KISS1 increased both the basal and human chorionic gonadotropin-induced progesterone production when added to cultured rat luteal cells [125]. It is feasible that ovarian KISS1 may have an endocrine action, particularly at the ipsilateral uterus through counter current transfer in the ovarian–uterine vasculature. The latter could potentially complement trophoblastic KISS1 in preparing the uterine endometrial epithelium for trophoblast attachment and implantation.

There is evidence that the receptor, neurotrophic receptor tyrosine kinase 2 (NTRK2), and its ligand, brain-derived neurotrophic factor (BDNF), are expressed in rodent follicles and interact with KISS1R to influence follicular development [140–143] (Figure 3). Oocyte-specific deletion of NTRK2 was associated with disorganized follicles and oocyte death in mice [142]. *BDNF* mRNA and BDNF protein were also reported in buffalo follicles and influenced both oocyte maturation and early embryonic development [144]. The putative interaction between NTRK2 and KISS1R in follicular function and embryo development provides yet another example of the emerging complexity in molecular mechanisms associated with embryo survival, implantation, and pregnancy. As argued earlier in this review, this complexity requires a deeper understanding before the next step change can be achieved in embryo survival and the efficiency of assisted reproductive technology.

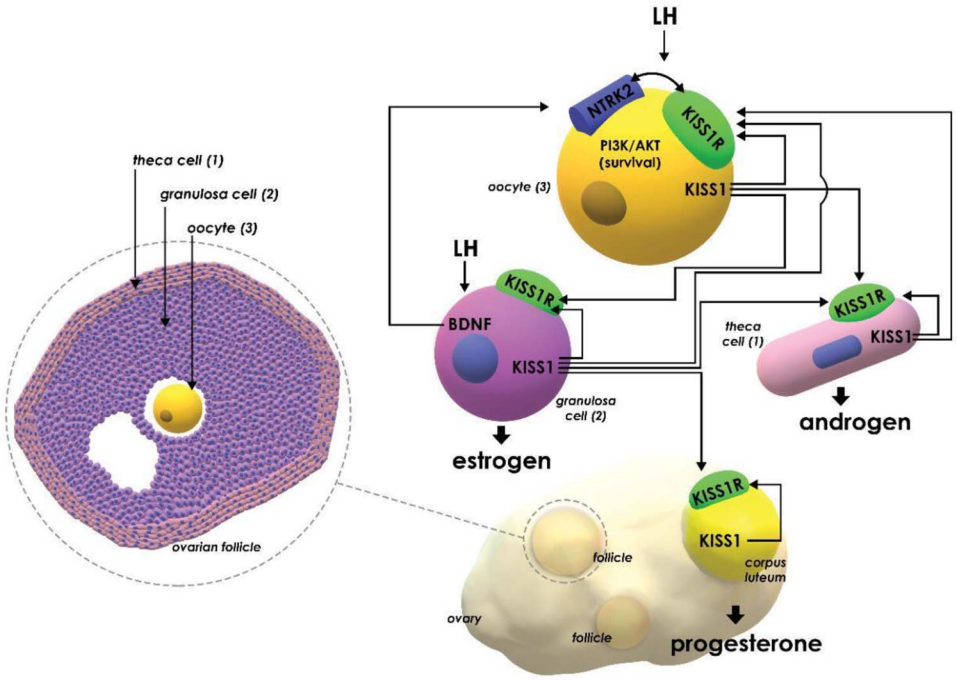

Figure 3. Diagrammatic representation of the putative autocrine and paracrine actions of kisspeptin (KISS1) in ovarian follicles and corpus luteum. KISS1 and KISS1 receptor (KISS1R) proteins are found in granulosa cells, theca cells, oocytes, and corpus luteum. Granulosa KISS1 is thought to influence thecal cells, the oocyte, and corpus luteum, while theca KISS1 is thought to influence the oocyte. Oocytes also have NTRK2 receptors that appear to act cooperatively with KISS1R. In response to luteinizing hormone (LH), granulosa cells produce BDNF, which stimulates receptor NTRK2 on oocytes, and BDNF may be a mechanism associated with puberty. Oocytes that lack NTRK2 do not respond to gonadotropin to activate PI3K/AKT, which is required for oocyte survival and the acquisition of oocyte developmental competency and the ability to form a blastocyst [141, 142, 220]. These putative actions of KISS1 may not be universal and species differences are likely to exist.

Trophoblast and placenta

As noted above, *KISS1* gene expression and KISS1 protein were first demonstrated in human placenta [18]. It was subsequently shown that the expression of *KISS1* and *KISS1R* was highest early in placentation in women, and this led to the suggestion that KISS1 was involved in early trophoblast implantation [145]. It was also shown that *KISS1* expression was localized to villous trophoblast tissue while *KISS1R* expression occurred in both villous trophoblast and extravillous trophoblast [145–147]. The latter finding led to the suggestion that trophoblast-derived KISS1 may have both autocrine and paracrine actions during early implantation [146–148] (Figure 4). There is now strong evidence in women that KISS1 produced by the trophoblast regulates the infiltration of the uterine epithelium by the syncytiotrophoblast early in implantation [91, 94, 148–153] (Figure 4). Systemic levels of KISS1 were related to the likelihood of implantation in women undergoing assisted reproduction and embryo transfer [154]. In a seminal paper on KISS1 [20], it was proposed that KISS1 influences trophoblast implantation through interaction with cell–cell adhesion molecules and extracellular matrix proteins (see also 155). The fundamental importance of adhesion molecules in trophoblast attachment to the uterine epithelium was reviewed recently [84]. *KISS1R* expression by the uterus in pregnant rats and mice coincided with the period of implantation, suggesting a role for trophoblast KISS1 in rodents that is similar to the role in women [92, 147, 156–158]. A role for KISS10 and KISS1R in the interaction between the trophoblast and uterus has also been proposed in dogs [159]. The functional role of KISS1 during implantation is to regulate the rate of syncytiotrophoblast cell invasion and angiogenesis, which helps to ensure that early placentation is a sequential and controlled process [146, 147, 160]. KISS1, therefore, has an analogous role in the repression of cell migration both in early pregnancy and tumor metastasis [147]. In contrast to the information in humans, mice with mutant *KISS1* and *KISS1R* developed an apparently normal placenta and supported implantation and pregnancy [161]. Further studies are required to elucidate what would appear to be species differences in the absolute requirement for KISS1 signaling in reproductive tissues in females.

The role of the KISS1–KISS1R system during implantation has received less attention in livestock compared with rodents and humans. The interaction of the trophoblast with the uterine endometrial epithelium, implantation, and placentation is notably different events across species [162–165]. In rodents and humans, the trophoblast aggressively infiltrates [166] the endometrial epithelial cells to achieve implantation (hemochorial placentation), whereas, in livestock, implantation is a less invasive process (epitheliochorial placentation—pig; synepithelialchorial placentation—cow, goat, and sheep) [167–169] (Figure 4). Also, implantation appears to have a narrower window in rodents and humans compared with livestock [170]. These differences in type of placentation could mean that, while the KISS1-KISS1R system has an important role in implantation in rodents and humans, the same system may have a lesser role in livestock. Notwithstanding, cultures of bovine cotyledon epithelial cells derived from first-trimester pregnant cows expressed KISS1R [171]. The addition of KISS-10 to the cultures both stimulated and suppressed epithelial cell proliferation in two separate cell lines [171]. Stimulation of cell proliferation occurred in the cell line that

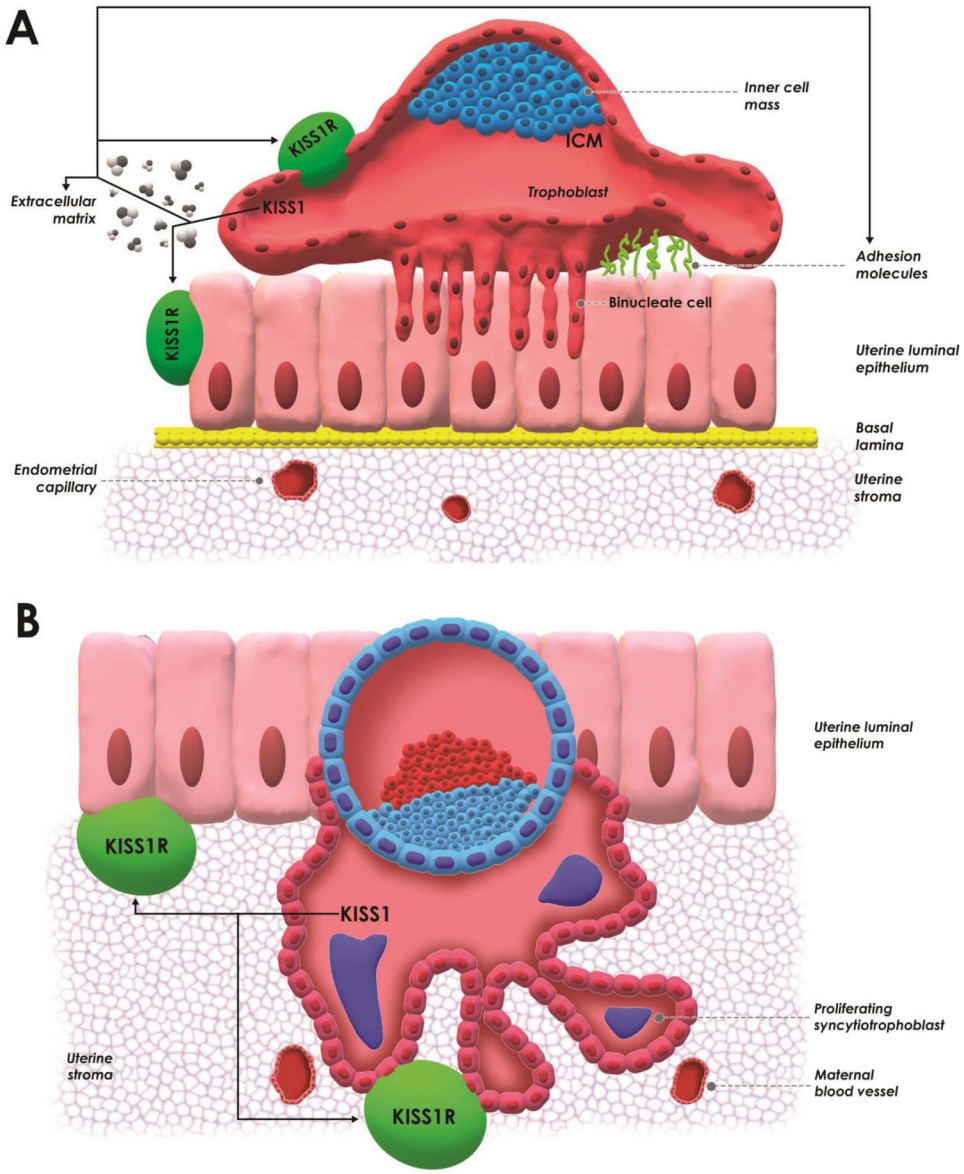

Figure 4. Diagrammatic representation of trophoblast attachment and implantation. In synepithelialchorial placentation in ruminants, (A) the trophoblast does not penetrate the basal lamina and uterine stroma but forms villi-like projections into the uterine endometrial epithelium that include binucleate cells [167–169]. In hemochorial placentation in rodents and humans, (B) the syncytiotrophoblast infiltrates the uterine endometrial stroma [166; see also 163]. Illustrated are proposed autocrine and paracrine actions of trophoblast KISS 1 at the trophoblast and uterus, respectively. The different types of placentation could be associated with different actions for trophoblast-derived KISS1 at the uterine KISS1R. Trophoblast KISS1 may influence the initial attachment of the trophoblast to the uterine endometrial epithelium (A and B) by interaction with cell–cell adhesion molecules and extracellular matrix proteins [20, 155].

showed upregulation of *KISS1R* mRNA [171]. A strong case can be made that the KISS1–KISS1R system should be further investigated in livestock, given that the failure of embryo implantation remains the major cause of reproductive wastage, particularly in ruminants [39, 83, 84].

Application of KISS1 in assisted reproduction in livestock

Control of GnRH secretion

The most common use of KISS1 in assisted reproduction is to control GnRH and gonadotropin secretion in order to influence gonadal function, particularly in livestock [13, 73, 81, 172–183]. Treatment with either human or mouse KISS-10 was associated with LH secretion and better synchronization of ovulation compared with GnRH in crossbred dairy heifers [175] and crossbred Hereford beef heifers and cows [82]. Bovine KISS-53 likewise induced LH section and growth of the dominant follicle in Japanese Black beef cows [184]. KISS1 administered by osmotic minipump for 48 h during proestrus improved follicle growth and ovulation rate in anestrous Nelore (*Bos indicus*) cows [179]. However, single treatment with mouse KISS1 (3 mg, i.m.) at the time of fixed-time artificial insemination (AI) did not improve the fertility outcome in prepubertal Nelore heifers [185].

The KISS-10 agonist C6 induced fertile ovulations in ewes that had been pretreated with progesterone [79]. The same agonist advanced puberty in female mice when administered daily for

5 days [73, see also 27]. The latter finding led to the suggestion that KISS1 agonists may have potential in the management of puberty in livestock. In this regard, KISS-10 induced gonadotropin secretion and influenced ovarian function in prepubertal buffalo [183], cattle [180], sheep [186, 187], and pigs [177, 188]. KISS-10 also induced gonadotropin secretion and ovulation in seasonally anestrous ewes [189, 190] and synchronized ovulation in goats [79]. KISS-10 (10 µg/kg live weight) additionally stimulated LH secretion in both the breeding and nonbreeding seasons in buffalo cows [181] and ewes [117]. Hence, treatment with KISS1 can stimulate quiescent GnRH neurons in both prepubertal and seasonally anestrous females. While KISS1 has mainly been used in vivo to influence hypothalamic GnRH neurons, human KISS-10 was reported to stimulate LH secretion in cultured anterior pituitary cells derived from prepubertal male Holstein calves [191]. The action of KISS1 at the pituitary is outside the scope of this review but needs to be considered within the broader biology of KISS1 in reproduction in rodents, primates, and livestock [192–196].

Control of ovarian function

The local role of KISS1 in ovarian function is less well researched compared with the effects on GnRH secretion. As noted above, KISS1 and KISS1R have been localized in granulosa, theca, and oocytes, and KISS1 is present in follicular fluid. These findings have led to the suggestion that follicular KISS1 has autocrine and paracrine actions within follicles, including the effects on the oocyte (Figure 3). KISS1 is expressed by the cumulus–oocyte complex (COC) in mice [127] and was reported to be necessary for ovulation in this species [138].

A role for KISS1 in oocyte maturation has been informed by IVF studies. In sheep, the proportion of oocytes that showed cumulus expansion and extrusion of the first polar body at the end of in vitro culture (IVC) was highest when KISS1 was included in the culture media [197]. In cattle, the addition of KISS1 during IVC and IVF increased the proportion of blastocysts relative to gonadotropins [198]. Similar beneficial effects of KISS1 on IVF oocyte maturation and developmental competence have been reported in buffalo [199] and pigs [132, 200]. The addition of KISS1 to cultured pig COCs improved oocyte maturation and increased the blastocyst formation rate [132]. After hatching, however, blastocysts had reduced trophoblast outgrowths in the presence of KISS1 [132]. Also in the pig, KISS1 enhanced embryo development in parthenogenetically activated oocytes [200]. In women, systemic injection of KISS-54 induced oocyte maturation [201].

KISS1 and KISS1R single-nucleotide polymorphisms and fertility

Single-nucleotide polymorphisms (SNPs) occur in the *KISS1* and *KISS1R* genes, and in some studies, these SNPs have been linked with fertility in livestock. In goats, *KISS1* SNPs were associated with differences in prolificacy between Boer, Guanzhong, and Saanen breeds [202]. However, *KISS1* and *KISS1R* SNPs were not associated with prolificacy between prolific Jintang and nonprolific Tibetan goat breeds [131]. In the latter study, *KISS1* expression in the pituitary was greater for Jintang goats, and it was suggested that this could be linked with prolificacy. *KISS1* SNPs were associated with acrosome integrity and fertility in Holstein Friesian (*Bos taurus*) and Khillari (*B. indicus*) bulls [203]. Given the peripheral action of KISS1 at reproductive tissues, the discovery and validation of *KISS1* and *KISS1R* SNPs have potential for their inclusion in genomic selection indices for fertility in livestock. Other SNPs have been associated with the function of the endometrium and capacity to support embryo development and pregnancy in crossbred beef cows [89], and future studies may discover relationships between these SNPs and KISS1 and KISS1R.

Integration of KISS1–KISS1R in follicular function and embryo development

The basic and applied literature reviewed above makes a strong case that KISS1 and KISS1R are fundamentally involved in the peripheral regulation of ovarian function, early embryo development, implantation, and placentation (Figure 5). The interaction of KISS1–KISS1R with NTRK2 [140–143] and cell–cell adhesion molecules [20] shows that KISS1 does not act in isolation at reproductive tissues. Rather, KISS1 is integrated with other molecular mechanisms that influence ovarian function and embryo development. The largest body of literature supporting peripheral KISS1–KISS1R action is for women and rodents. While not as voluminous, there is sufficient evidence to conclude that the local action of KISS1–KISS1R at reproductive tissues is also important in livestock [91, 93]. The failure of assisted reproductive technology to make any meaningful advance in the proportion of embryos that survive and establish a pregnancy has led to a renewed focus on the biology of early embryo development, implantation, and pregnancy establishment. Recent reviews have considered the role of the transforming growth factor-beta (TGFβ) superfamily and interferon tau [83], cell–cell adhesion molecules [84], and melatonin [204]. These and other recent reviews have highlighted the complexity of local molecular mechanisms [205–208]. The present review has sought to further embed KISS1–KISS1R in this area of biology. The argument is made that a deeper understanding of local mechanisms is needed in order to better inform the next phase of assisted reproductive technology, which seeks to improve embryo survival and pregnancy. Further research is required during the periods of proestrus/estrus, early embryo development, and trophoblast attachment and implantation (Figure 5).

Conclusions

There is compelling evidence that the KISS1–KISS1R receptor system participates in the local regulation of ovarian function, early embryo development, implantation, and placentation. While the evidence is strongest for humans and rodents, there is sufficient information for livestock to conclude that the peripheral KISS1–KISS1R system is also important in production animals. Interesting features of KISS1 are as follows: (1) it acts within the brain and at the periphery and (2) it is associated with metastasis and reproduction. KISS1 shares these features with melatonin (brain and periphery [204]) and cell–cell adhesion molecules (metastasis and reproduction [84]). This review has made the case that both the brain and peripheral actions of KISS1 need to be considered when KISS1 is utilized in assisted reproduction. It is possible that when KISS1 is used to regulate GnRH and gonadotropin secretion to control follicular growth and ovulation, it may also impact oocyte maturation and early embryo development. The control of ovulation with KISS1 typically involves acute treatment to cause an immediate release of GnRH and LH. It is likely that chronic treatment with KISS1 will be required for beneficial effects on follicles and oocytes, and early embryo development and implantation. These processes occur over a longer time than the release of GnRH and LH. Longer-term

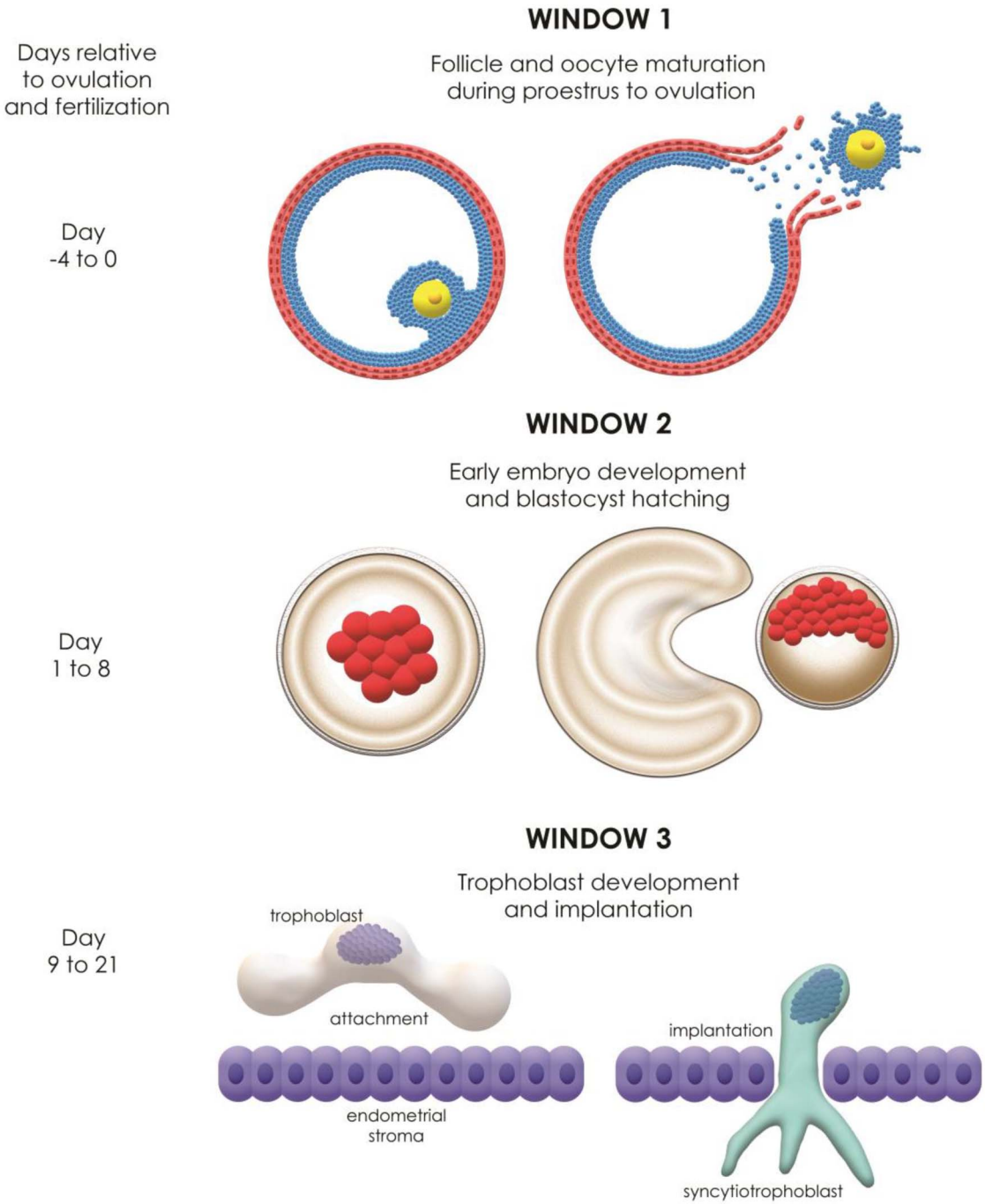

Figure 5. Diagrammatic representation of windows during which longer-term treatment with kisspeptin (KISS1) may be beneficial to follicle and oocyte maturation (Window 1), early embryo development (Window 2), and trophoblast development, attachment, and implantation (Window 3). *KISS1* and *KISS1* receptor (*KISS1R*) gene expression and KISS1 and KISS1R proteins occur in the respective reproductive tissues in each window. The days relative to ovulation and fertilization are for cattle.

treatments with KISS1 will utilize agonists that have an extended half-life in circulation and high biological potency. The potential to downregulate KISS1R with longer-term use of KISS1 agonists will need to be studied. As noted above, a deeper understanding of the biology of early embryo development and implantation is necessary for the next step change improvement in embryo survival and pregnancy in assisted reproduction. The interesting path taken by the field of KISS1 research is that it started with the placenta and cancer, it moved to the brain and reproduction, and then it returned to the placenta and reproduction.

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Conflict of interest

The authors have declared that no conflict of interest exists.

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