

The Roles of the Amygdala Kisspeptin System

Edouard G. A. Mills, MRCP¹ Kevin T. O'Byrne, PhD² Alexander N. Comninou, MRCP, PhD^{1,3}

¹Section of Endocrinology and Investigative Medicine, Imperial College London, Hammersmith Hospital, London, United Kingdom

²Department of Anatomy, Department of Women and Children's Health, Faculty of Life Sciences and Medicine, King's College London, London, United Kingdom

³Department of Endocrinology, Imperial College Healthcare NHS Trust, Hammersmith Hospital, London, United Kingdom

Address for correspondence Alexander N. Comninou, MRCP, PhD, Section of Endocrinology and Investigative Medicine, Imperial College London, Hammersmith Hospital, 6th floor Commonwealth Building, Du Cane Road, London, W12 0NN, United Kingdom (e-mail: a.comninou@imperial.ac.uk).

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Abstract

The hypothalamic hormone kisspeptin (encoded by the *KISS1/kiss1* gene) is the master regulator of the reproductive axis with its role in controlling gonadotrophin hormone secretion now well characterized. However, identification of kisspeptin and its cognate receptor expression within the amygdala, a key limbic brain region whose functions contribute to a broad range of physiological and behavioral processes, has heightened interest concerning kisspeptins' role in the broader aspects of reproductive physiology. In this review, we detail the important developments and key studies examining the emerging functions of this kisspeptin population. These studies provide novel advances in our understanding of the mechanisms controlling reproductive neuroendocrinology by defining the crucial role of the amygdala kisspeptin system in modulating pubertal timing, reproductive hormone secretion, and pulsatility, as well as its influence in governing-related behaviors. To this end, the role of the amygdala kisspeptin system in integrating reproductive hormone secretion with behavior sheds new light onto the potential use of kisspeptin-based therapeutics for reproductive and related psychosexual disorders.

Keywords

- ▶ kisspeptin
- ▶ amygdala
- ▶ pubertal timing
- ▶ pulsatility
- ▶ reproductive behavior

The kisspeptin family of neuropeptides (encoded by the *KISS1/kiss1* gene) is now a well-established orchestrator of the hypothalamic–pituitary–gonadal (HPG) reproductive axis. In humans and mice, inactivating mutations of the genes encoding kisspeptin or its cognate receptor result in failed puberty and infertility,^{1–3} whereas conversely activating mutations of the kisspeptin receptor cause central precocious puberty.⁴ Together, these seminal findings testify to the functional significance of kisspeptin-mediated pathways in regulating normal reproductive function.

The majority of kisspeptin neurons reside in two major hypothalamic populations: the anteroventral periventricular nucleus (AVPV) and the arcuate nucleus (ARC, equivalent to the human infundibular nucleus).^{5–9} Given this, hypothalamic kisspeptin signaling has received considerable research attention with its role in modulating gonadotrophin-releasing

hormone (GnRH) secretion now well characterized. However, smaller extra-hypothalamic kisspeptin and kisspeptin receptor populations also exist in key limbic and paralimbic brain regions, including the amygdala. *Kiss1* mRNA has been detected in the mouse amygdala,^{6,10,11} *kiss1r* mRNA in the rat amygdala,^{8,12} and *KISS1* and *KISS1R* mRNA in the human amygdala.^{13,14}

The amygdala is a paired almond-shaped group of nuclei located deep within each temporal lobe of the brain. The nuclei of the amygdaloid complex can be subdivided into three groups: the basolateral, the cortical, and the centromedial (composed of the medial amygdala [MeA] and central nuclei).¹⁵ Evidence from animal and human research points to the amygdala playing a fundamental role in regulating an array of physiological and behavioral processes, including arousal, reward, fear, anxiety, and social behavior.^{16–20}

However, the underlying neural mechanisms which govern many of these processes—especially related to kisspeptin signaling—were largely elusive until recently.

A plethora of studies have demonstrated that manipulation of kisspeptin-mediated pathways may deliver potential therapeutic strategies for individuals suffering from reproductive disorders, including hypothalamic amenorrhea,²¹ hyperprolactinemia,²² and hypogonadism in men²³ and as a trigger for oocyte maturation in an in vitro fertilization setting.²⁴ In addition, there are emerging roles for the influence of kisspeptin in sexual and emotional behavior.^{25–27} It is curious to note that many of the processes regulated by the amygdala are also under the control of kisspeptin signaling, suggesting that some of these processes are indeed governed by the amygdala kisspeptin system.

In this review, we detail the current literature regarding the role of the amygdala kisspeptin system. English published articles indexed in PubMed were retrieved by means of a series of manual literature searches including the following keywords: kisspeptin, KISS1/kiss1, KISS1R/kiss1r, amygdala, distribution, puberty, pulsatility, and reproductive/sexual behavior. Reference lists of selected studies and hand searches were also performed. Searches were conducted till June 1, 2019, to ensure inclusion of the most current data.

Neuroanatomical Connections

Understanding the neuronal inputs and where amygdala kisspeptin neurons project fibers to provides valuable mechanistic insight to their functional significance. In male rats, amygdala kisspeptin neurons maintain reciprocal connections with the accessory olfactory bulb,¹² which has an established role in conveying pheromonal cues,²⁸ with evidence demonstrating these kisspeptin neurons are targeted directly by pheromonal pathways.²⁹ In addition, approximately 15% of GnRH neurons in the hypothalamic preoptic area receive inputs from amygdala kisspeptin neurons,¹² suggesting they act as a plausible relay between pheromonal inputs and the HPG axis. It is interesting to note that these findings in rats are in close agreement with a neuroanatomical study in Kiss1-CRE transgenic mice which revealed fibers projecting from amygdala kisspeptin neurons through the medial forebrain bundle to the preoptic area, as well as extending further into the accessory olfactory bulb.³⁰ Taken together, these findings from male rats and transgenic mice provide an anatomical framework for amygdala kisspeptin neurons to transmit sexually relevant olfactory cues to modulate the HPG axis.

Additionally, in male rats amygdala kisspeptin neurons are located in close apposition and receive innervation from vasopressinergic and dopaminergic neurons,¹² with these neurotransmitter systems recognized to play a key role in the control of social behavior.^{31,32} This implies functional interplay between the amygdala kisspeptin system and other neurotransmitter systems to modulate the necessary behaviors required to optimize reproductive success.

A further physiologically relevant communication has been mapped in rodents demonstrating that kisspeptin neurons in the MeA form projections directly onto kisspeptin neurons

in the ARC.³³ These data match the results of a previous study in ovariectomized goats where an anterograde tracer was injected into the MeA, revealing direct efferent projections into a subset of ARC kisspeptin/neurokinin B (NKB) neurons.³⁴ Given that the MeA contributes to regulating a broad range of physiological and behavioral responses, these data signify that some aspects of these responses are likely processed via the MeA to ARC kisspeptin neurons to modulate reproductive function. Along these lines, it is notable that the median eminence lacks direct projections from the MeA in male rodents.²⁹ This raises the possibility that in male rodents, rather than direct GnRH release at GnRH nerve terminals, the amygdala kisspeptin system influences the HPG axis through complex interplay with other neurotransmitter systems (such as GABA¹²) or via interneuronal pathways.²⁹ However, this remains to be fully explored and studied in female rodents.

Collectively, through a combination of neuronal tracing and immunohistochemical techniques, these studies demonstrate important neuroanatomical populations and connections involving amygdala kisspeptin neurons and receptors (summarized in ►Table 1). Hence, these findings have generated interest concerning the role of the amygdala kisspeptin system as a pivotal candidate in the control of the HPG axis and reproductive behavior.

Kisspeptin and Kisspeptin Receptor Expression within the Amygdala

The amygdala has received substantial recent attention for its role in regulating social and reproductive behaviors in a sexually dimorphic manner to influence reproductive function.^{35,36} Therefore, understanding patterns of amygdala kisspeptin system expression may provide valuable mechanistic insight to explain changes in sexually differentiated behaviors observed across the lifespan.

Kisspeptin expression in the rodent amygdala is restricted to the MeA and prominently the posterodorsal subnucleus of the MeA (MePD; but not observed in other amygdaloid regions),¹¹ an area whose functions contribute to a wide range of social, emotional, and sexual behaviors.^{37,38} In gonad-intact rodents, this expression is sexually dimorphic with higher levels in males than in diestrus females.¹¹ In addition, MeA kisspeptin expression is positively modulated by circulating gonadal sex steroids,¹¹ supported by findings that kisspeptin expression is absent in the neonatal and early prepubertal amygdala of rodents.³⁹ Consistent with this, although MeA kisspeptin expression is undetectable in juvenile male rats, it significantly increases during late puberty mirroring the pubertal increase in circulating gonadal sex steroids.⁴⁰

Further evidence for the influence of circulating gonadal sex steroids on the amygdala kisspeptin system comes from data demonstrating that MeA kisspeptin expression is robustly reduced in gonadectomized rodents of both sexes, but becomes significantly upregulated by estradiol or testosterone supplementation.¹¹ It is also interesting to note that dihydrotestosterone (a nonaromatizable androgen) treatment does not affect MeA kisspeptin levels, highlighting that in this region kisspeptin

Table 1 Summary of the influence of the amygdala kisspeptin (KP) system on reproductive function in goats (G), humans (H), and rodents (R)

Reproductive function	Influence of kisspeptin
Reproductive hormone secretion	<ul style="list-style-type: none">• Intra-MeA KP administration dose dependently ↑ LH in female R⁴⁶• Intra-MeA KP receptor antagonist administration ↓ LH in female R⁴⁶• Intra-MeA KP administration ↑ LH in male R⁴⁷
Reproductive hormone pulsatility	<ul style="list-style-type: none">• Intra-MeA KP receptor antagonist administration ↓ LH pulsatility in female R⁴⁶• Continuous optogenetic stimulation of MePD KP neurons ↑ LH pulse frequency in female R⁴⁸
Pubertal timing	<ul style="list-style-type: none">• Intra-MePD KP receptor antagonist administration delays puberty, disrupts estrous cyclicity, and ↓ preovulatory LH surge in female R⁵²
Olfaction	<ul style="list-style-type: none">• Exposure to female urine ↑ MeA KP neuronal activity and ↑ LH in male R²⁹• Reciprocal connections between AOB and amygdala KP neurons, with subset GnRH neurons in POA receiving input from amygdala in male R¹²• Kisspeptin olfactory anatomical framework in female G³⁴
Reproductive behavior	<ul style="list-style-type: none">• Intra-MeA KP administration dose dependently ↑ excopula erections and ↑ LH release in male R⁴⁷• DREADDs activation of MePD kisspeptin neurons augments sexual partner preference and attenuates anxiety in male R⁵⁶
Human brain processing	<ul style="list-style-type: none">• Peripheral KP administration enhances fMRI amygdala activity in response to sexual and nonsexual bonding images in male H⁵⁷• Peripheral KP administration enhances fMRI resting connectivity in the amygdala–cingulate network in male H⁶⁰

Abbreviations: AOB, accessory olfactory bulb; DREADDs, designer receptors exclusively activated by designer drugs; fMRI, functional magnetic resonance imaging; GnRH, gonadotrophin-releasing hormone; Kiss1r, kisspeptin receptor; LH, luteinizing hormone; MeA, medial nucleus of the amygdala; MePD, posterodorsal subnucleus of the medial amygdala.

expression is modulated via the estradiol-receptor(ER; rather than androgen receptor) pathway.¹¹ Specifically, this estradiol-induced upregulation has been shown to be modulated primarily via the ERα signaling pathway (rather than the ERβ)⁴⁰ with approximately half of MeA kisspeptin neurons expressing ERα in both gonadally intact male mice and female mice in diestrus.⁴¹

In addition to modulation by oestradiol, kisspeptin expression in the MeA is also regulated by γ-aminobutyric acid (GABA), the principle inhibitory neurotransmitter in the central nervous system of adult mammals.⁴² Indeed, most MeA kisspeptin neurons coexpress the GABA_{B1} subunit.⁴³ Hence, in global GABA_BR knockout (KO) mice of both sexes, removal of GABA_BR signaling robustly upregulates MeA kisspeptin expression, suggesting that endogenous GABA normally acts via GABA_BR to downregulate MeA kisspeptin expression.⁴³ Notably, kisspeptin expression does not differ between wild-type and GABA_BR knockout mice in the AVPV and the ARC demonstrating that this GABA_BR regulation of kisspeptin expression is limited to extrahypothalamic kisspeptin populations.⁴³

A recent study explored the interaction between estradiol and GABA using GABA_BR KO mice revealing that although estradiol normally increases MeA kisspeptin levels, expression was further upregulated by estradiol treatment in GABA_BR KO mice.⁴⁴ This suggests that stimulatory estradiol and inhibitory GABA_BR signaling are able to independently regulate kisspeptin expression in the MeA. Furthermore, removal of circulating gonadal sex steroids by gonadectomy in these mice did not abolish kisspeptin expression signifying that it is not exclusively dependent on estradiol stimulation, but also on additional as yet unknown factors.⁴⁴

Collectively, these studies provide new advances in our understanding of the mechanisms which modulate the amygdala kisspeptin system. How changes in kisspeptin expression affect resultant sexually differentiated behaviors remains to be fully studied.

Reproductive Hormone Secretion and Pulsatility

Although the arcuate nucleus has emerged as the likely intrinsic source of the Kisspeptin-GnRH pulse generator in rodents,⁴⁵ there is increasing evidence that the amygdala kisspeptin system also exerts a pivotal influence over gonadotrophin hormone secretion and reproductive neuroendocrine physiology.

In a study employing manganese-enhanced magnetic resonance imaging (MRI) in adult male mice, peripheral administration of kisspeptin resulted in a marked decrease in neuronal activity in the MeA (indicative of an overall inhibitory effect) and was temporally associated with increased LH secretion.⁴⁶ Furthermore, direct injection of kisspeptin into the MeA of adult female rats also dose dependently increased circulating levels of LH, whereas blocking the endogenous amygdala kisspeptin system by intra-MeA administration of a kisspeptin receptor antagonist (peptide-234) decreased pulsatile and overall LH secretion.⁴⁶ A similar response has been observed by direct injection of kisspeptin into the MeA of male rats, resulting in increased plasma LH levels.⁴⁷ These findings support the notion that the amygdala kisspeptin system plays an important role in modulating gonadotrophin secretion and pulsatility.

To further examine the influence of the amygdala kisspeptin system on pulsatile LH secretion, a recent study used an optogenetic approach to selectively stimulate MePD kisspeptin neurons in fully conscious adult female mice.⁴⁸ Continuous stimulation using 5 Hz (but not lower frequencies of 0.5 and 2 Hz) resulted in an increased LH pulse frequency, suggesting that MePD kisspeptin neuronal activity can modulate the hypothalamic GnRH pulse generator once a minimal activation requirement has been reached.⁴⁸

Taken together, these data demonstrate that the amygdala kisspeptin system acts as an upstream regulator and interplays with the HPG axis to modulate reproductive hormone secretion and its pulsatility (summarized in ►Table 1). To date, most studies have been undertaken in female rodents; therefore, it will be of interest to examine the effect of the amygdala kisspeptin system on reproductive hormone pulsatility in male species.

Pubertal Timing

The MeA undoubtedly plays a key role in regulating pubertal timing as evidenced by advancing pubertal onset by amygdala lesioning in macaques⁴⁹ and rats,⁵⁰ whereas conversely stimulating the amygdala delays onset in rats.⁵¹ Given the importance of kisspeptin as the crucial regulator of pubertal timing,^{1,2,4} the influence of the amygdala kisspeptin system has been assessed. In post-weaning and young adult female rats, blocking the endogenous amygdala kisspeptin system by direct injection of a kisspeptin receptor antagonist (peptide-234) into the MePD has been observed to delay pubertal onset, disrupt estrous cyclicity, and reduce the occurrence of preovulatory LH surges.⁵² These findings lend support to the MePD playing a central role in pubertal timing and ovulation (summarized in ►Table 1).

Furthermore, given the association between maternal obesity and precocious puberty in girls⁵³ and boys,⁵⁴ a study has been undertaken to understand the mechanism by which intrauterine obesogenic environments disrupt reproductive function in offspring. Maternal obesity in rats (achieved following a 6-week energy-dense diet prior to mating and throughout pregnancy and lactation) resulted in upregulation of kisspeptin expression in the MePD of prepubertal male and female offspring, but unaffected expression in the ARC and AVPV.⁵² It is intriguing to note that at 3 months, female offspring demonstrated reduced kisspeptin expression in all three brain regions, whereas this was observed only in the MePD of males suggesting sexual dimorphism.⁵² Collectively, these data reveal that maternal obesity may act via the amygdala kisspeptin system to modulate the reproductive function of offspring.

Reproductive Behavior

Across an assortment of species, olfactory cues from species- and gender-specific pheromones are an important means of communicating information about the social and sexual status of an animal and act as key precursors to mediating reproductive behavior.²⁸ A recent study has provided evidence for the

importance of the amygdala kisspeptin system in olfactory-reproductive pathways. Male mice exposed to female urine demonstrated a twofold increase in MeA kisspeptin neuronal activity (determined by c-Fos) with a concomitant LH surge.²⁹ Interestingly, 71% of MeA kisspeptin neurons expressed the GABAergic marker Vgat and 29% expressed the glutamatergic marker Vglut2.²⁹ These findings highlight a crucial role for the amygdala kisspeptin system as a mediator which integrates opposite-sex olfactory stimuli to modulate the HPG axis, potentially through interplay with GABAergic and glutamatergic neurotransmitter systems which themselves have established effects on the HPG axis and related behaviors.⁵⁵

It is interesting to consider the mechanisms by which pheromonal cues are conveyed from the amygdala to modulate the HPG axis and whether species differences exist. As previously mentioned, in rodents reciprocal connections exist between the accessory olfactory bulb and amygdala kisspeptin neurons, and a subset of GnRH neurons in the hypothalamic preoptic area receive inputs from amygdala kisspeptin neurons.¹² This provides an anatomical framework for amygdala kisspeptin neurons to process olfactory cues to influence the HPG axis. Consistent with this, efferent projections from the MeA have been detected terminating in a subset of ARC kisspeptin/NKB neurons in ovariectomized goats.³⁴ In this study, a recording electrode was implanted and aimed at the ARC kisspeptin/NKB neuronal population. Notably, treatment with an NKB receptor antagonist completely suppressed multiple-unit activity (indicative of GnRH pulse generator activity) and LH responses to male pheromones.³⁴ This implies that in female goats, processing of male pheromones occurs via the MeA to ARC kisspeptin/NKB neurons to modulate the HPG axis.

For reproduction to fully function, the HPG axis must be accompanied by appropriate related behaviors, including the establishment of partner preference and sexual arousal. Studies in rodents provide evidence for the importance of the amygdala kisspeptin system in governing these sociosexual behaviors. In male rats, direct injection of kisspeptin into the MeA has been shown to dose dependently elicit multiple copulatory erections, an effect which was blocked by pretreatment with a kisspeptin receptor antagonist (peptide-234).⁴⁷ Direct injection of kisspeptin into the MeA also increased plasma LH levels, highlighting that MeA kisspeptin signaling modulates GnRH release and gonadotrophic hormone secretion while governing male sexual behavior. It is intriguing to note that when kisspeptin was infused into the lateral cerebroventricle, there were no observed erections (despite comparable rise in circulating LH levels), demonstrating LH independence and site specificity of the MePD for kisspeptin's role in regulating erections.⁴⁷

In addition, different experimental paradigms have been employed to assess reproductive behavior. In adult male mice, activation of MePD kisspeptin neurons using the pharmacosynthetic DREADDs (designer receptor exclusively activated by designer drugs) technology augmented sexual partner preference as indicated by double the amount of time spent by male mice investigating an estrous female.⁵⁶ Stimulating MePD kisspeptin neurons using this approach also resulted in increased social interaction and exploratory duration in the open arms of an elevated plus maze suggesting attenuated

anxiety behavior.⁵⁶ Collectively, these data support an essential role for the amygdala kisspeptin system in modulating sexual motivation and social behavior to facilitate maximal reproductive success (summarized in ►Table 1).

Human Brain Processing

Translating the behavioral findings from animals into human studies requires less invasive techniques. To this end, advances in neuroimaging offer a unique opportunity to explore the intricacies of kisspeptin and behavior in more detail.

In a functional MRI (fMRI) study of healthy heterosexual men, peripheral administration of kisspeptin enhanced neuronal activity in the amygdala in response to both sexual and nonsexual couple-bonding images.⁵⁷ It is intriguing to note that this enhancement of the amygdala to bonding images also correlated with improvements in positive mood. In addition, on viewing sexual images, kisspeptin activated the amygdala more in participants with lower baseline behavioral drive and reward traits. This may indicate that by modulating amygdala neuronal activity, kisspeptin is able to drive a desire for reproduction in people who are less responsive to reward.⁵⁷ These findings are also of potential therapeutic significance, given desire for sexual stimulation and desire to bond are key prerequisites for successful reproduction, and the amygdala has been implicated in both processes.^{58,59}

Given kisspeptin's important role in human sexual and emotional brain processing during stimulatory tasks, it is interesting to consider its effects on resting brain amygdala connectivity. In a second fMRI study of healthy heterosexual men, peripheral administration of kisspeptin enhanced resting global connectivity in the amygdala–cingulate network.⁶⁰ Crucially, this established network has important roles in controlling emotions and bonding.^{61–63}

It is salient to note that in both of these studies, kisspeptin administration had no effect on other relevant hormones (testosterone, oxytocin, and cortisol). This suggests that the observed fMRI effects were derived from kisspeptin and independent from the influence of these hormones that could affect amygdala neuronal activity. Collectively, these studies provide strong evidence for the amygdala as a central component in kisspeptin's role as a neuroendocrine modulator of human sexual and emotional brain activity. Future studies may seek to investigate women and patients with psychosexual disorders to examine the effect of kisspeptin administration further on sexual and emotional brain processing.

Conclusion and Future Directions

The relationship between hypothalamic kisspeptin signaling and its regulation of gonadotrophin hormone secretion has received considerable attention. However, the identification of amygdala kisspeptin and receptor expression, an important neural site implicated in regulating an array of physiological and behavioral processes, has heightened interest regarding their role in reproductive function. In this review, we have detailed the important developments and key

studies examining the functions of this elusive kisspeptin population. Through various experimental paradigms, the amygdala kisspeptin system has emerged as crucial for modulating pubertal timing, reproductive hormone secretion, and pulsatility. This indicates the importance of these kisspeptin neurons as essential gatekeepers and an upstream regulator of the central control mechanisms governing reproductive physiology. In addition, for successful reproduction, the HPG axis must usually be accompanied by appropriate related behaviors. Indeed, recent studies have begun to uncover the positive facilitatory role which the amygdala kisspeptin system plays in controlling sexual behavior, including processing pheromonal cues, determining partner preference, and mediating sexual arousal, as well as its pivotal role in human sexual and bonding brain processing. These novel findings underscore the emerging role of the amygdala in integrating reproductive behaviors to modulate the HPG axis. Importantly, these findings will help drive future studies examining for sexual dimorphisms and exploring other species to provide new advances in our understanding of the mechanisms controlling reproductive neuroendocrinology. To this end, the role of the amygdala kisspeptin system in governing pubertal timing, reproductive hormone secretion and pulsatility, and reproductive behavior sheds new light into the possibility of using kisspeptin-based therapeutics for reproductive and related psychosexual disorders.

Conflict of Interest

None declared.

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