Kisspeptin in the Limbic System: New Insights Into Its Neuromodulatory Roles

Wilfredo López-Ojeda, M.S., Ph.D., and Robin A. Hurley, M.D.

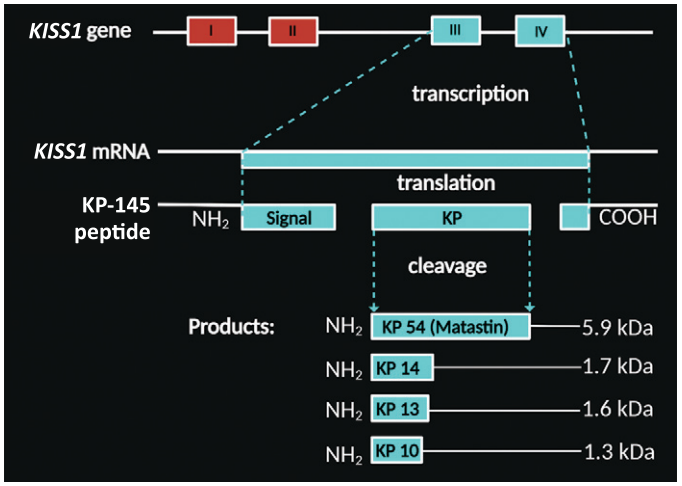

FIGURE 1. Kisspeptin (KP) isoforms in humans based on prior reports and UniProtKB data (1–4). KP accounts for a member of the neuropeptide family originating from the cleavage of a 145-amino acid precursor peptide encoded by the *KISS1* gene, originally identified as a metastasis suppressor gene (5). This gene produces the 54-amino acid peptide (metastin or KP-54), which can be cleaved into shorter forms or functional fragments (i.e., KPs 14, 13, and 10) with comparable potencies (6). COOH=carboxy terminal; kDa=protein product size; NH_2=amino terminal. All images created under the terms of the Creative Commons Attribution License and created with BioRender.com.

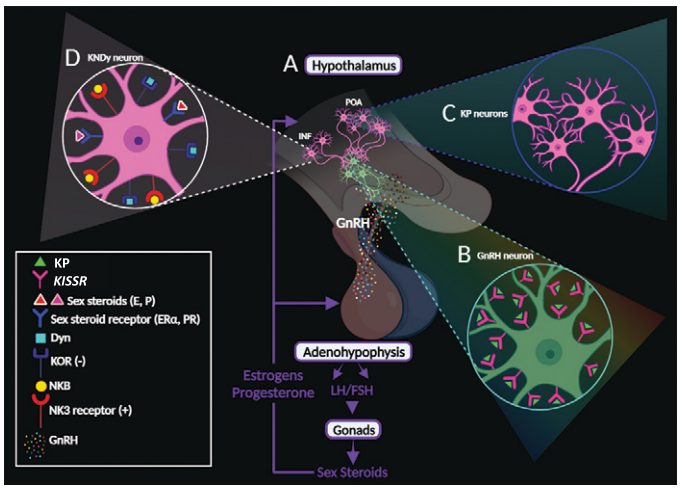

FIGURE 2. The empirical neuroanatomy and the kisspeptin (KP) gonadotrophin-releasing hormone (GnRH) pathway and the relationship between KP, neurokinin B (NKB), dynorphin (Dyn), and GnRH-secreting neurons in humans. In humans (A and B), KP neurons are concentrated in the hypothalamus within the preoptic area (POA) and the infundibular (INF) nuclei (analogous to the rostral periventricular region of the third ventricle and arcuate nucleus in rodents), which are rich in GnRH cells expressing the G-protein-coupled receptor-54 protein (GPR54, *KISS1R*) (7, 8). When GnRH neurons are activated by KP, they secrete GnRH, which triggers the release of gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) from the adenohypophysis. In turn, this cascades the release of the gonadal sex steroids (i.e., estrogens, progesterone, and testosterone), forming feedback loops to regulate GnRH secretion from the hypothalamus, as well as LH, and FSH release from the adenohypophysis (9, 10). In the POA (C), the KP neurons are more numerous in females and provide input to a higher percentage of GnRH neurons (11, 12). In the INF nucleus (D), the KP cells also synthesize Dyn and NKB, thus named KP/NKB/Dyn (KNDy) neurons (13, 14). Dyn is an opioid, functioning at the kappa opioid receptor (KOR) system (15). NKB is an endogenous peptide that belongs to the family of tachykinins (12). Theoretically, NKB starts and/or accelerates synchronized KNDy neuronal responses via the neurokinin-3 (NK3) receptors (stimulatory [+]) to release KP, resulting in GnRH release via the stimulation of *KISSR* expressed by the GnRH neurons. Lastly, Dyn released from KNDy neurons halts KNDy stimulation via KOR (inhibitory [–]) (16, 17). E=estrogen; ERα=estrogen receptor α; P=progesterone; PR=progesterone receptor.

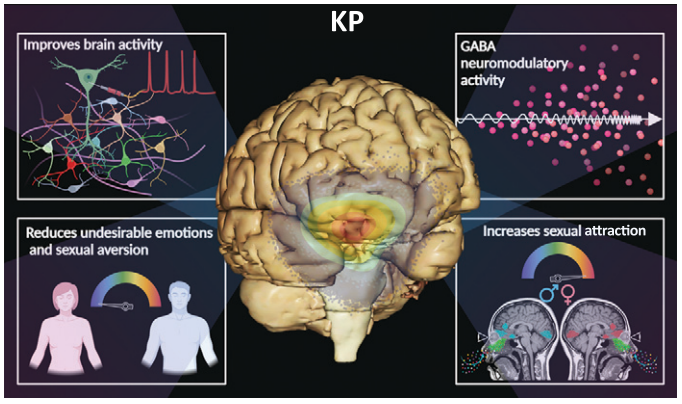

FIGURE 3. Effects of kisspeptin (KP). KP is a multifunctional neuropeptide present in the highlighted areas of the midbrain and other brain regions (spectrum of colors: yellow, green, and orange). KP has been demonstrated to improve brain activity, modulating the levels of gamma-aminobutyric acid (GABA) in the brain and decreasing undesirable emotional responses (negative mood) and sexual aversion (18–20). In addition, it improves neural processing by increasing sexual attraction (perception of beauty) on the basis of olfactory (odor stimuli) and visual cues (21).

COVER. A three-dimensional virtual dissection of the human brain, emphasizing the location of the midbrain structures. Created under the terms of the Creative Commons Attribution License. Created with VH Dissector and BioRender.com.

Information regarding the functions of kisspeptin (KP) in the processing of emotions, cognition, and the links between reproduction and the limbic system is emerging. In fact, KP has been recently regarded as a behavioral hormone influencing multiple structures within the limbic neural network (19, 22–24), including the hypothalamic-pituitary-gonadal (HPG) and hypothalamic-pituitary-adrenal neuroendocrine axes. These neuroendocrine circuits dictate the regulatory mechanisms of important signaling neurotransmitters and hormones (i.e., gonadal steroids and stress hormones) (25, 26). In the central nervous system (CNS), KP functions as a central endocrinological regulator for sexual development and human reproductive functions (27, 28).

NEUROCHEMISTRY OF KP

KP is a member of the neuropeptide family originating from the cleavage of a 145-amino acid precursor peptide encoded by the *KISS1* gene, originally identified as a metastasis suppressor gene (5). This gene produces the 54-amino acid peptide (metastin or KP-54), which can be cleaved into shorter forms (i.e., KPs 14, 13, and 10) with comparable potencies (6) (Figure 1). Its function is contingent on binding to its cognate receptor (*KISS1R*), first known as the orphan G-protein-coupled receptor 54 (GPR54) protein (29). Herein, nomenclature regarding *KISS1* and *KISS1R* is used in reference to the human genes, proteins, and their various gene products collectively known as KPs, as established by the Human Genome Organization Gene Nomenclature Committee (30).

An essential component of reproduction, KP plays a fundamental role in the initiation of puberty and sexual maturation via the regulation of the HPG axis (29, 31–34). In humans, KP neurons are concentrated in the hypothalamus within the preoptic area and the infundibular nucleus (analogous to the rostral periventricular region of the third ventricle and arcuate nucleus in rodents), which are rich in gonadotrophin-releasing hormone (GnRH) cells expressing *KISS1R* (7, 8) (Figure 2A). Essentially, when GnRH neurons are activated by KP, they secrete GnRH, which triggers the release of gonadotropins, luteinizing hormone, and follicle-stimulating hormone from the adenohypophysis. This, in turn, triggers the release of the gonadal sex steroids (e.g., estrogens and progesterone) (9, 10) (Figure 2A).

Studies of both animals and humans indicate that the central and peripheral administration of exogenous KP leads to the hormonal stimulation of this reproductive cascade (35, 36). KP and GnRH neurons are positioned at the upper tier of the HPG neuroendocrine axis (Figure 2B and 2C). The administration of GnRH antagonists halts the stimulatory effect of KP (37). Similar to luteinizing hormone, KP exhibits synchronized pulsatile secretions within the hypothalamus, confirming its role as a GnRH pulse generator in mammalian species, including humans (36, 38–41). However, while KP is an essential element for GnRH and luteinizing hormone rhythm control, its pulsatility per se is not required for the generation of these pulses (40). Given these characteristics and influences on neuroendocrine function, KP and its signaling pathways are potential therapeutic targets for sex hormone disorders and other endocrinologic conditions (40, 42).

SEXUAL DIMORPHISM

The KP neurons of the preoptic area and infundibular regions exhibit conspicuous anatomical variations in humans, with sexual dimorphisms being some of the most thought provoking. These sexual dimorphisms are responsible for differential behaviors, as regulated by the HPG axis between genders (3). In the preoptic area, the KP neurons are more numerous in females and provide input to a higher percentage of GnRH neurons (11, 12) (Figure 2C). In the infundibular nucleus, the KP cells also synthesize dynorphin (Dyn) and neurokinin B (NKB), and thus they are named KP/NKB/Dyn (KNDy) neurons (13, 14). Dyn is an opioid functioning in the kappa opioid receptor system (15). NKB is an endogenous peptide that belongs to the family of tachykinins (12). Tachykinins are encoded by the tachykinin-3 (*TAC3*) gene and act at the neurokinin-3 receptor, which is also encoded by the *TAC3* gene (14, 43). To date, both NKB and Dyn peptides are regarded as cotransmitters of the KP signaling pathways (i.e., human reproduction) (3) (Figure 2D). In addition, human KP neurons coexpress other peptides, such as substance P and cocaine- and amphetamine-regulated transcripts (44, 45). The coexistence of these neurotransmitters indicates a multimodal role, with KP modulating various behavioral processes (2).

In adults, the infundibular nucleus KP neurons also exhibit a female-dominant sex difference among heterosexuals, as well as male-to-female transexuals (12, 46, 47). Results from animal and human studies indicate that KNDy neurons exert an important function in the regulation of the negative feedback effects of sex steroid hormones on GnRH neurons, regulating luteinizing hormone pulsatility and gonadotropins release (14, 48). Taken altogether, KP sex differences add to a comprehensive body of evidence on the sexual dimorphism of the HPG axis in humans (3).

KISS1 GENE/*KISS1R* DISTRIBUTION IN THE CNS

While KP influences hypothalamic-mediated functions (e.g., reproduction, energy balance, food intake, and metabolism), the *KISS1* gene is expressed in other locations of the human brain (2, 3, 49, 50). *KISS1* has been identified in the amygdala, caudate, cingulate, globus pallidus, hippocampus, medial and superior frontal gyri, nucleus accumbens, parahippocampal gyrus, substantia nigra, putamen, thalamus, and spinal cord (2, 12, 22, 29, 34, 51). KP's influence on behavior extends from the hypothalamus to other limbic structures and beyond, mediating (in part) anxiety, fear (as well as other emotions), and olfaction (18, 19, 22, 51).

KP in the Limbic System

Habenula. The habenula is recognized as a phylogenetically preserved diencephalic-paired neuroanatomical structure that is present in virtually all vertebrates (52). The mammalian habenula comprises two important cellular groups or subnuclei: the medial habenula (MHb) and the lateral habenula (LHb). The medial component fibers (dopaminergic) connect with the interpeduncular nucleus, while the lateral cell group fibers (serotonergic) project to the ventral tegmental area (VTA) and raphe, respectively (52). In humans, the habenula has an approximate diameter of 5–9 mm and a total volume of 30–36 mm^3 (53).

The habenula is an important component of the emotion centers of the brain, contributing to the modulation of a wide repertoire of emotions, such as fear, reward, anxiety, and depression (54, 55). Its neuroanatomical circuits include inputs from the limbic system, including the basal ganglia, as well as outputs to the midbrain, releasing dopamine (from the pars compacta of the substantia nigra and VTA) and serotonin (from the median and dorsal raphe nuclei, respectively). Thus, the habenula is involved in two major neuromodulatory monoaminergic pathways of the midbrain: the dopaminergic and serotoninergic systems (54, 55). The habenula appears to function as a processing center for emotional and aversive responses, including aversively motivated learning and emotional decision making (55–58). In addition, it appears to have an important modulatory role in the perception of pain and certain mechanisms of analgesia (59).

Emotional decision-making processes are associated with important physiological elements of reproduction (i.e., sex steroids and stress hormones) (36, 40, 41). Habenular inputs from sex centers in the hypothalamic region potentiate key hormonal regulators via the HPG axis and KP circuitry (58). Sex-hormone alterations during menopausal and pre- to postpartum transitions may lead to symptoms of depression and altered emotional processing (60). Disturbances of the habenula may contribute (in part) to psychiatric conditions, such as addiction, attention-deficit hyperactivity disorder, major depression, and schizophrenia (55, 61–64). Moreover, results from a human brain study (postmortem histological tissues) revealed less neurons in the habenula and decreased volumes of both MHb and LHb in persons diagnosed with major depression or bipolar disorder (65).

There are no significant sex differences in the structural anatomy of the habenula in humans. However, there are some important sexually dimorphic traits documented in the literature. For example, animal studies have revealed molecular dimorphisms in the expression of neurotransmitters, neuropeptides, and other neuroactive substances (e.g., glutamate, vasopressin, and tachykinins) (58). Additionally, the habenula exhibits functional sexual dimorphisms in response to stress, including sex differences in metabolic processes and neural activity (66–68). In humans, the sex differences in habenular stress responses are connected with increased susceptibility to stress-related disorders (i.e., anxiety and depression), as well as fluctuating sex steroids (69–71). Predictably, the habenula and KP have been implicated in the modulatory mechanisms of anxiety, fear, reward, and mood regulation (18, 19, 22, 51, 58, 72).

The LHb has a strategic anatomical location in the CNS, with pathways joining the forebrain to the ventral midbrain and hindbrain regions (73). Some investigators have described the LHb as the "antireward center" of the brain (74). Animal studies have revealed that it prevents behaviors leading to negative reward (i.e., punishment); however, it reinforces behaviors associated with positive reward (75, 76). Therefore, the LHb regulates the mechanisms of motivated behaviors and decision making (55). Social behaviors (e.g., avoidance, fighting, mating, and parenting) are important elements for communication in social animals (humans included), thereby critical for survival. These behaviors are regulated by neural circuits involving neuroanatomical structures (e.g., the habenula, amygdala, and prefrontal cortex), collectively referred to as the social behavior network (SBN), further integrating social decision making (77). The cellular components of the SBN are significantly influenced by sex steroids (estrogens, progesterone, and testosterone) and certain neuropeptides (i.e., KP, GnRH, and Neuropeptide Y) required for the regulation of social behaviors (77–82).

Amygdala. KP and its cognate *KISS1R* gene are expressed in other key emotional structures of the limbic system, including the amygdala, in varied animal species (i.e., rodents) and humans (20). The sex differences in the amygdalar size appear to be ambiguous, with some studies indicating larger volumes in females and others reporting larger volumes in males (83–86). Despite these inconsistencies, the average volumetric size of the human amygdala ranges between 1.24 cm^3 and 1.63 cm^3 (87).

In addition to its roles in fear and anxiety, the amygdala also has an important role in reproduction, intervening over the release of gonadotrophic hormone, thus regulating essential mechanisms of reproductive physiology (88). Aside from its canonical involvement in fear, the regulation of reproductive and social behaviors in a sexually dimorphic manner has become a new center of attention in neurophysiology (24, 89). In humans, the peripheral administration of KP enhances functional MRI (fMRI) amygdalar activity in response to sexual and nonsexual contextual images among men (19). Similarly, men receiving peripheral intravenous KP injections exhibited higher fMRI-resting connectivity in the amygdala-cingulate circuit, indicating enhanced sexual and emotional processing (20).

Recently, the amygdala has been presented as an extrahypothalamic center, regulating body energy and metabolic homeostatic processes (90–92). There is an intimate connection between energy homeostasis and reproductive functions (90). Sex hormones are important metabolic modulators, capable of controlling foundational elements of energy homeostasis. Sex steroid dysregulation may lead

to mental illnesses and eating disorders, such as anorexia nervosa, bulimia nervosa, and binge eating disorder (93–96).

POTENTIAL THERAPEUTIC IMPLICATIONS

Evidence from human studies indicates that KP has possible clinical applications and therapeutic uses for psychiatric and sexual dysfunctions. For example, KP has been shown to improve brain activity, modulating the levels of gamma-aminobutyric acid in the brain and decreasing undesirable emotional responses (negative mood) and sexual aversion (18–20). Additionally, it improves neural processing by increasing attraction (perception of beauty) on the basis of olfactory (odor stimuli) and visual cues (21) (Figure 3). The role of KP in improving olfactory and limbic functions opens the possibility for its therapeutic potential in neurodegenerative conditions, such as Alzheimer's disease and Parkinson's disease, in which anosmia may precede the cognitive and motor dysfunctions (2, 97–99)

CONCLUSIONS

KP within the limbic system is a critical neuropeptide in the regulation of reproduction and emotional behaviors. Within the hypothalamus, KP (together with the tachykinins, NKB, and Dyn) promotes the physiologic activity (i.e., oscillatory) dictating the pulsatile secretion of GnRH and synchronizing luteinizing hormone pulses; therefore, it is considered the central component of the GnRH pulse generator. In this role, KP acts as the "master regulator" of reproductive neurophysiology, integrating the emotional components of certain limbic circuits via the regulation of GnRH neurons and release of sex steroids.

The emerging information on behavioral neuroscience suggests an intriguing relationship between KP and other fundamental monoaminergic systems (aside from dopaminergic and serotonergic), potentially modulating other behavioral responses. The newly identified role of KP in these systems has potential implications for clinical and research neuropsychiatry, particularly in relation to modulating sexual and emotional behaviors in humans and its implications for psychiatric disorders associated with reproductive biological imbalances. Current innovations in neuroimaging technology and molecular biology present opportunities to advance our understanding of the multiple roles of KP in reproductive, neurodegenerative, emotional, and other neuropsychiatric disorders.

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