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ABSTRACT

It is already known that the discovery of kisspeptin was a revolutionary step in the understanding of regulation of neuroendocrine in reproduction. Kisspeptin is one of the main moderators of the gonadotropic axis, but the kisspeptin gene is known to be expressed in various regions of the central nervous system. The activity of kisspeptin is not limited to hypothalamic pituitary gonadal (HPG) axis; it participates in the regulation of multiple neuronal circuits in the limbic system. The limbic system is a part of the brain involved in behavioral and emotional reactions, and disturbances in its functioning may be a source of
some psychiatric as well as degenerative disorders. In the present review, we summarize the current state of knowledge concerning the role of kisspeptin in the limbic system and a new hope for the treatment of disturbances in its functioning.

**Key words: kisspeptin, hypothalamus, limbic system, neurodegenerative disease**

**INTRODUCTION**

Kisspeptin (KP), a protein named after the famous chocolates 'Kisses' has revolutionized both our knowledge of hypothalamic pituitary gonadal axis (HPG) and the understanding of neuroendocrine regulation of reproduction. Kisspeptin bases on the principle of feedback which allows for the maintaining of homeostasis in various physiological states of the body. The first information about the kisspeptin protein and its influence on the function of HPG axis appeared at the end of the 20th century during the studies on the function of dynorphin A and neurokinin B. The HPG works mainly due to the interaction and integration of brain and gonadal signals. In the rat, the estrogen’s receptor is not present on gonadotropin-releasing hormone (GnRH) neurons; consequently, gonadal feedback must be realized by the intermediate signaling pathway. The protagonist of this route is kisspeptin. Kisspeptin plays a decisive role in the control of fertility by initiating and regulating the process of puberty and pituitary secretion. Since 2005, it has been known to be the strongest activator of the HPG axis. Depriving kisspeptin or its receptor weakens fertility and reproductive physiology, while enhancement of the mutation function in the KISS1R gene results in premature maturation. In immature rats, administration of kisspeptin induced the onset of maturation, while administration of its antagonist delayed it.

Kisspeptin is encoded by the kisspeptin gene (KISS1). This neuropeptide performs different roles in brain functions. It is dynamically regulated by neuronal activity and increases synaptic transmission for a long time. The kisspeptin gene is expressed in the central nervous system as well as in many other organs. G-protein coupled receptor (GPR54) (receptor for KP13, coupled with G-54 protein) is fully activated by all products of the KISS1 gene and is essential for stimulation of GnRH secretion and induction of puberty. This receptor is highly expressed in the brain areas related to memory and emotions, including the hippocampus and amygdala. The wide distribution of kisspeptin fibers, as well as the kisspeptin receptor in central and peripheral nervous system,
is a reason for these proteins being involved in the regulation of multiple neuronal circuits and have been reported in a large number of physiological, as well as pathophysiological conditions of the reproductive system [19,96,108], diabetes [49,50,96], adiposity [41,45] and suppression of metastasis in various neoplasm [18,62], locomotor activity [101], and anxiety [101].

In all examined mammalian species, the localization of hypothalamic kisspeptin neurons is mostly similar. They are generally placed in the anteroventral periventricular nucleus (AVPV) and the preoptic periventricular nucleus (PeN), dorsomedial nucleus (DMN), and arcuate nucleus (ARN) [1,20,28,67,83]. A studied species contains at least two types of kisspeptin neurons in the hypothalamus [67], and another one in the medial amygdala of rodents [92]. The kisspeptin neurons are observed mainly in the preoptic/rostral hypothalamus in various mammalian species, including rodents [20,38,55,97], sheep [46,83], pigs [53], nonhuman primates [56,104,109] as well as human [88]. Due to different role of kisspeptin neurons, they additionally contain various neurotransmitters/neuromodulators or their precursors like galanin [47,81], enkephalin [81], dopamine [51] or GABA and glutamine [84]. Additionally, in the human, kisspeptin neurons, the co-expression of neuropeptides including neurokinin B [44], substance P [31] and cocaine- and amphetamine-regulated transcript CART were observed. The different co-transmitters present in the kisspeptin neurons suggest its multimodal functions and involvement in various behavioral activities in the brain structures.

Leptin, discovered in 1994, is known to be produced by white fatty tissue (WAT) [112] and to have a major indirect effect on excitation of HPG axis. This stimulatory effect on the HPG axis is performed through the kisspeptin interneurons located in the anterior part of the hypothalamus which also possess the receptors for leptin [13,14,45]. Additionally, many regulatory factors influence the hypothalamic kisspeptin neurons and consequently, the release of kisspeptin. Energy reserves are essential for reproductive success. As a result, metabolic factors tightly control the synthesis and release of kisspeptin [107].

LIMBIC SYSTEM

In 2011 scientists began to examine kisspeptin and its effects outside the hypothalamus more closely. The expression of kisspeptin was also found in other components of the limbic brain structures, like amygdala [2,23,58,61,80,99], hippocampus [6–8,63] and olfactory...
system [80]. There are very few records regarding the expression of KISS1 in the striatum [63,68].

The limbic system is a set of structures in the brain that are involved in memory and emotions as well as in reproductive behaviors [82]. However, the precise link connecting those functions is still elusive and undefined. Defects in the functioning of the limbic system can be a source of many diseases. In the past years, kisspeptins emerged as physiological regulator of GnRH neurons and, hence, of the HPG axis. Some reviews summarized this function of kisspeptin; however, they focused mainly on the presence and role of kisspeptin in the hypothalamus [35,45,48,57,86]. There are some reports presenting other functions of kisspeptin such as decreasing food intake, as well as being one of the new hypothalamic anorexigenic factors [98].

Emotion and sexual responses are fundamental in human behavior. Researchers have shown kisspeptin as a link between the brain and the reproductive axis [23]. Kisspeptin administration enhances limbic and paralimbic system activity [23]. What is more, kisspeptin reduces sexual aversion and noticeably increases brain activity [23]. The author emphasizes kisspeptin participation in limbic system activity, behavior, and modulation of sex hormones [23]. On top of it, kisspeptin administration decrease negative mood [23]. The results indicate that kisspeptin also shows antidepressant-like effects [23]. Kisspeptin administration activates components of the reward system such as the hippocampus, amygdala and the cingulate and enhances the activity of this system [23]. Additional research shows; that kisspeptin increases emotional and sexual processing and decreases sexual aversion. This gives green light to the kisspeptin-based therapies for emotional and psychosexual disorders [22].

The reaction of other species is also interesting. Kisspeptin, via activation of the HPG axis, as well as modulation of releasing testosterone, has indirect effects on aggressive and territorial behavior in male lizards [71].

**BEHAVIORAL AND NEURAL REACTIONS TO EMOTIONS**

The amygdala, emotional center of the brain, is a part of the limbic system. It is closely related to anxiety, fear, reward, stress, and social behavior [82]. The medial nucleus of amygdala (MeA) is a most important brain region in sexual and emotional reaction [82] in which Kiss1 neurons were first described in male mice in 2004 [70]. Neurons of MeA contain
a lot of steroid hormone receptors which interact with the sex hormones and transfers olfactory information to areas closely related to kisspeptin like hypothalamic nuclei engaged in reproduction and defense [58]. Many studies on the amygdala indicate involvement of this structure in the regulation of females reproductive cycles and sexual behavior [61]. It is known that the kisspeptin neurons present in MeA are the third largest population of these neurons in the brain [70,92]. Today we know that MeA kisspeptin neurons are regulated by sex steroids (E2 via receptor) [92,99] and GABA (via receptor) [72]. MeA kisspeptin neurons send efferent projections to the hypothalamus [80,95] and are also interconnected with the accessory olfactory bulb (AOB) [58,78]. Additionally, they receive projections from vasopressin and TH neurons [80]. All this suggests that kisspeptin plays a much larger role in the regulation and functioning of the nervous system.

Kim and his colleagues [61] were first to test the effect of sex steroids on rodent's MeA KISS1 neurons. In the MeA, as in the AVPV/PeN, KISS1 levels are highly regulated and dependent on the level of sex steroids [61]. According to Stephens and coworkers [99], KISS1 expression in MeA neurons rises at puberty, and it is compatible with developmental level of sex steroids. The author’s showed that Kiss-1 expression in the amygdaloid body is present only in pubertal period and is not expressed in MeA in the neonate or in the prepubertal period [99]. There is a relationship and dependence between amygdala kisspeptin signaling and the HPG axis. This is evidenced by observations on the direct kisspeptin administration into the medial amygdala which stimulate a luteinizing hormone (LH) secretion [21]. In turn, kisspeptin antagonist decreases in LH secretion.

Activation of kisspeptin neurons localized in the posterodorsal part of the medial amygdala (MePD) affects both social interaction and sexual partner preference in males’ mice [2]. Research on the activation of medial amygdala kisspeptin neurons shows increases of time spent by male mice investigating females [2]. It indicates a key role played by MePD kisspeptin in sexual and motivation behavior.

THE MISSING LINK: WHEN THE SMELL MEETS EMOTION

Olfactory bulbs are an important part of the sexual behavioral system due to the presence of direct olfactory pathways to the corticomedial nuclei of the amygdala [59]. Within the olfactory system, two distinct sensory systems can be distinguished; the main olfactory
system and accessory olfactory system [80]. The accessory olfactory bulb projects to MeA kisspeptin neurons [80] which are usually called “vomeronasal” amygdala [59]. This indicates the role of kisspeptin neurons in the processing of and responding to fragrance and pheromone information. Pheromones are detected and processed by accessory olfactory system which has been functionally linked to reproductive behavior [11]. Next, signals triggered by pheromones in the accessory olfactory system are transmitted to hypothalamus [42]. The connection between the olfactory signals and the reproductive neuroendocrine axis is indicated by the latest results obtained by Aggarwal's team [3]. Hellier [42] indicates that a reproductive success is an effect of close relationship of pheromones stimulation. Interestingly, the exact anatomical location of the kisspeptin receptor has not been described in the olfactory system so far.

Results obtained by Yang [111] confirm the effect of kisspeptin on the structures of the limbic system. It is known that kisspeptin receptors are present in brain structures involved in emotions. The administration of kisspeptin significantly affects the reception of aromatic stimuli. The activity of the main olfactory network as well as structures such as the hippocampus and amygdala increase due to the nice smell [111]. In various neurodegenerative diseases, the impairment of olfactory functions is observed [4,29]. In the Alzheimer’s or Parkinson's disease, the loss of olfaction may precede memory or motor disturbances [30]. To administer proper neuroprotective therapies, an early recognition of degenerative symptoms of the nervous system is necessary [91]. According to the role of kisspeptin in the olfactory and limbic structure, we might suspect that kisspeptins are a novel therapeutic potential in neurodegenerative diseases as well as reproductive disturbances.

**FUNCTION OF KISSPEPTIN IN HIPPOCAMPUS**

The functional role of kisspeptin in the hippocampus is still unknown. Many studies prove that kisspeptin works in the hippocampus as a neuropeptide neuromodulator [6,54,70,102]. GPR54 is strongly expressed in the granular cell of hippocampal dentate gyrus [6–8], which is the first step of the hippocampal trisynaptic circuit. Lee et al. [63] showed that GPR54 density in the hippocampus is very high in the granule cell of the dentate gyrus, whereas it is barely detectable in the pyramidal cells of CA1 and CA3. KISS1 and KISS1R are detected at high density in the hippocampus [6–8,63]. Kisspeptin in the hippocampus rises the synaptic transmission via the activation of a mitogen-activated protein kinases (MAPK)-
related signaling pathway in granular cell of the dentate gyrus [8]. According to some authors, this regulatory system can play a role in the pathogenesis of epilepsy [6,7]. Arai et al. [6–8] indicate that the neuronal activity strongly affects the expression of kisspeptin. They observed the greatest changes in kisspeptin expression after kainate injection [7], which is often used to obtain the model of temporal lobe epilepsy. Arai et al. [7] suggest the existence of positive feedback loop in the hippocampal formation. The excitability of granular cells is increased by the release of kisspeptin, which in turn has the effect of increasing the expression of kisspeptin [7]. The peptide system can play a role in epilepsy.

The dentate gyrus of the hippocampus is one of main neurogenic niches in the adult brain. Neural stem cells are located in this place and produce progenitors that travel near their final location like granular cell layer of the dentate gyrus [15]. The continuous addition of new granule cell population in the dentate gyrus has the potential to make a preferential participation to neural circuit transformation. There is possibility that kisspeptin and GPR54 are recruited to regulate neurogenesis in combination with other neurotrophic factors [64,65]. This is supported by the antimetastatic actions of kisspeptin [64,65]. The observations carried out by Arai et al. [8] show that activation of GPR54 by metastin reversibly increases excitatory synaptic transmission in the granule cells of dentate gyrus.

NEW THERAPEUTIC APPROACH TO THE TREATMENT OF RECOGNITION MEMORY DISORDERS

The Alzheimer's disease (AD) is associated with a loss of cognitive function due to the progressive loss of neurons and their synapses. Given the increasing incidence of AD, finding new effective therapeutic strategies is now of the utmost importance. The GPR54 mRNA is highly expressed in the hippocampus [6], what may indicate that kisspeptin might be engaged in learning and memory processes. Hippocampus has a critical role in control of learning and memory, and its damage causes dysfunction in the processing of memory, memory consolidation and recognition [79]. As the role of kisspeptin and GPR54 in recognition processes was unclear, Jiang and his colleagues [54] were the first to undertake research into the relationship of the kisspeptin/GPR54 system in memory recognition. His research was inspired by a Gyula Telegdy report [102] in which he pointed that kisspeptin makes learning and memory consolidation in mice easier.
In 2012 Milton [69] underlines that Alzheimer's disease involves changes in the functioning of the hypothalamic-pituitary-gonadal (HPG) axis. He shows that kisspeptin might be a factor preventing neurotoxicity of amyloid-β peptide in vitro. Additionally, Milton [17] was the first to show in vitro interaction of kisspeptin with amyloid-β peptide that suggests a potential role of kisspeptin in Alzheimer's disease pathology. Milton [69] is a mastermind of the idea of using kisspeptin peptides in preventing, detecting and treating of diseases including Alzheimer’s, Creutzfeldt-Jakob disease and Type 2 diabetes. Three years later, Jiang [54] shows that injection kisspeptin-13 into the lateral ventricle and hippocampus activates receptors GPR54, prolongs the memory retention, makes easier the creation of object recognition memory, and improves memory deficit.

The pyramidal neurons of the CA1 sector of the hippocampus are particularly damaged during Alzheimer's disease [100]. After the injection of beta amyloid into the hippocampus, kisspeptin-13 shows neuroprotective effects, alleviates disorders, effects positively on improving spatial memory, and significantly prevents neuronal loss [60]. Further research is needed to determine whether the neuroprotective effects of kisspeptin against amyloid-β peptide toxicity are via direct binding to amyloid-β peptide or via the receptor.

The wide expression of kisspeptin in structures involved in memory mechanisms and learning processes suggests interactions with cholinergic systems. Babaei [9] indicates therapeutic function of kisspeptin. The injection of KP-13 into lateral cerebral ventricle had a positive effect on memory and facilitated spatial learning in induced Alzheimer's disease. This endogenous peptide has an important role in alleviating the cognitive deficit by increasing the cholinergic response. As kisspeptin interacts with many neuropeptides involved in learning and memory, its action may be mediated through these receptor systems, which should be further investigated. Gamma-aminobutyric acid (GABA) is an example here. This is a key neurotransmitter and is closely related to behavioral disorders. Studies have shown that administration of kisspeptin highly reduces the level of GABA in the limbic system in humans [24]. Kissorphin, a peptide derived from kisspeptin-10, prevents acute impairment of memory, cognitive functions, and short-term spatial learning due to ethanol administration [36].

However, KISS1 expression is inhibited during metabolic stress [85,90]. It is suggested that an attenuation of kisspeptin signaling reduces metabolism as kisspeptin levels are inversely proportional to insulin secretion [5]. A decrease in KP signaling causes a decrease in brain metabolism [5].
BEHAVIORAL THEORY OF DEPRESSION AND KISSPEPTIN

The limbic system seems to be involved in severe mental illnesses such as schizophrenia and depression. Base for depression is still incompletely understood and little is known about its pathogenesis [75]. One of the reasons is the lack of consensus on the pathology and etiology of depression. Some symptoms characteristics for depression are impossible to be modeled on laboratory animals. As of today, the criteria for identifying animal models of depression are based on actions of antidepressant drugs and responses to stress [110]. Animal models played big roles in the development of antidepressant drugs. Two of the most frequently used examinations are an open field test and forced swimming test. The open field is a very popular animal model of anxiety-like behavior. The forced swim test is a behavioral test for rodents and is one of the most frequently used tests for evaluation of antidepressant drugs [76]. Telegdy [101,102] shows that kisspeptin-13 has strongly influence activity, climbing and swimming times. In this study, kisspeptin-13 displays antidepressant-like effects in a forced swimming test [101]. In open field test, the injection of kisspeptin-13 into lateral cerebral ventricles stimulates the HPA axis which is the most important adaptive neuroendocrine system [37]. Kisspeptin-13 in the open field test has a big impact on behavior in rats. In addition, kisspeptin-13 induces hyperthermia [25]. This suggests a potential role for kisspeptin in thermogenesis.

The observations carried out by Adekunbi et al. [2] focused on kisspeptin neuronal population in MeA which is involved in anxiety response. Adekunbi et al. [2], in contrast to Teledgy’s results [25], showed that the selective activation of MeA kisspeptin neurons reduces anxiety in mice. Injection of kisspeptin-13 in rats reduced time spent in the open arms of the elevated-plus maze. Adekunbi’s mice were less anxious which was evidenced by longer exploratory time in the open arms of the elevated plus maze [2]. Similar results were obtained in another experiment regarding the effect of kisspeptin on anxiety behavior in male mice. Delmas and colleagues [27] focused on the role of KISS1R signaling in anxiety behavior. Research shows a tendency for decreased anxiety behavior in rapport to the elevated plus maze. Such differences in specificity likely result from differences between the two species. Further work is necessary to answer the questions about the role of signaling kisspeptin in anxiety in various species, as kisspeptin has an antidepressant role not only in rodents. Ogawa [73] indicates that interaction between kisspeptin and the serotonergic system plays an
important role in the modulation of fear in zebrafish. Later studies by his team showed that the blockade of serotonin receptors abolished the effect of kisspeptin, which modulated the serotonergic system through glutamatergic neurotransmission [32,33,74]. The role of kisspeptin-based therapy requires further study and explanation as there are clear links between kisspeptin and anxiety.

**CONCLUSIONS**

Today, kisspeptin is undoubtedly one of the basic proteins regulating not only the mechanisms underlying reproductive functions, but also the neuronal networks that integrate sexual and emotional behavior with reproductive functions. To date, most of the data concentrate on the sexual role of kisspeptin in the central nervous system, so it will be of great interest in the coming years to investigate its role in emotion and memory function in healthy condition as well as in the diseases. The results indicating the therapeutic role of kisspeptin in neuropsychiatric and neurodegenerative diseases represent a promising path for the development of research into this problem. Future studies will, undoubtfully, investigate the influence of kisspeptin on behaviors in various species including humans and attempt to delineate the precise neuronal pathways involved. Furthermore, with a better understanding of these processes, there may emerge potential therapeutic applications to aid patients with various neurodegenerative, emotional or psychosexual diseases.

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**Abbreviations**

AD - Alzheimer's disease

AOB - accessory olfactory bulb

AVPV - anteroventral periventricular nucleus
ARC - arcuate nucleus
DMN - dorsomedial nucleus
E2 - estradiol
FSH - follicle-stimulating hormone
GPR54 - G-protein coupled receptor
GABA - gamma-aminobutyric acid
GnRH - gonadotropin-releasing hormone
HPG - hypothalamic pituitary gonadal axis
KISS1 - kisspeptin gene
KISS1R - kisspeptin receptor
KP - kisspeptin
LH - luteinizing hormone
MAPK - mitogen-activated protein kinases
MeA - medial nucleus of amygdala
MePD - posterodorsal part of medial amygdala
PeN - rostral periventricular nucleus
POA - preoptic area
T - testosterone
WAT - white fatty tissue
Figure 1. Diagram summarizing the integrated function of the major populations of kisspeptin neurons.

1) The primary functions of hypothalamic kisspeptin are its roles in stimulating reproduction and mediating sex steroid feedback signaling. Kisspeptin neurons are situated in the anterior ventral periventricular nucleus (AVPV), periventricular nucleus (PeN) and arcuate nucleus (ARC) of the hypothalamus. The diagram shows the effect of kisspeptin neurons on GnRH neurons depending on the place of occurrence. In the case of AVPV / PeN, it is a body cell, while for ARC, it is a median eminence. Sex steroid hormones inhibit the expression of KiSS-1 mRNA in the ARC and induce expression in the AVPV/ PeN. When sex steroids are low, KiSS1 expression increases in ARC and decreases in AVPV / PeN. Major elements having reproductive control are hypothalamic GnRH neurons that release GnRH into the bloodstream system. GnRH influences FSH and LH gonadotropins, which in turn regulate gonadal function [12,57,96,105];
2) Pituitary: synthesize and secrete gonadotropin hormones [luteinizing hormone (LH) and follicle-stimulating hormone (FSH)];

3) Gonads: gamete generation and the production of sex hormones such as estrogen and testosterone;

4) The third big population of kisspeptin neurons (in addition to those present in the hypothalamus) is present in the medial nucleus of amygdala (medial amygdala, MeA) [70];

4a) Kisspeptin neurons from MeA send axons to the preoptic area of hypothalamus (POA) where many GnRH neurons are present [80];

4b) Estradiol (E2) acts on MeA kisspeptin neurons via estrogen receptor α (Erα) [92,99];

4c) Kisspeptin neurons in MeA are reciprocally linked to the accessory olfactory bulb (AOB) [58,80];

4d) Kisspeptin neurons in MeA are downregulated by GABA signaling via gamma-aminobutyric acid B (GABAB) receptor [72];

4e) Kisspeptin neurons in MeA get projections from vasopressin and tyrosine hydroxylase (TH) neurons [80];

5) Leptin, produced by white adipose tissue (WAT), has a stimulating effect on the activity of GnRH hypothalamic neurons. Kisspeptin neurons are present in the group of intermediate neurons that have leptin receptors [90];

6) Effect of external factors on kisspeptin neurons in hypothalamus, like stress, age, nutrition, and pheromones [89,93].
Figure 2. Kisspeptins are a family of small but important peptides that play a key role in the regulation of neuroendocrine reproductive function through the nervous pathways. The diagram demonstrates products of the KISS1 gene. Presented are the precursor kisspeptin-145 and the functional kisspeptin fragments: kisspeptin-54 and shorter peptides such as kisspeptin-14, kisspeptin-13, kisspeptin-10 (suffix showing the number of amino acids).
Figure 3. Summary of therapeutic roles of kisspeptin.

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