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# Variety of functions and effects of kisspeptin

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*A brief review of the literature on the properties and efficacy of kisspeptin, in particular, for the regulation of endocrine functions. The results of numerous experiments with kisspeptin in molecular biology, reproductive medicine and endocrinology, as well as the development of vaccines against malignant tumors, are analyzed. Kisspeptin is known to initiate a cascade of changes leading to the puberty. According to the reports, this peptide modifies the activity of glands that produce sex hormones, so it can be used in the treatment of diseases associated with the violation of puberty, especially amenorrhea in adolescent girls. The effect of this peptide is related to the activation of hypothalamic cells that produce GnRH, which regulates a level of gonadotropin-releasing hormone. Thus, kisspeptin can activate the reproductive system without violating the protective mechanisms of organism. The in-depth research of kisspeptin effects on all parts of the hypothalamic-pituitary-gonadal axis is promising, as well as the investigation of neuron-glial interactions in the central nervous system under the influence of this peptide.*

*Keywords: kisspeptin, gonadotropin-releasing hormone, hypothalamic-pituitary-gonadal axis.*

Kisspeptin (KP), a peptide product of the *Kiss1* gene, was identified in 2001 by three independent scientific groups as an endogenous ligand of the orphan G-protein coupled receptor (GPR54) [1–3]. The term *Kiss1* gene stems from the name of the place of its discovery, Hershey, Pensilvania, where the chocolate factory Hershey's Kiss was located.

However, the name is also based on a scientific argument as the «ss» indicates that the gene is a suppressor sequence, i. e. it prevents some biological processes, in particular, cancer dispersion. The peptide ligand was originally called metastin due to its ability to inhibit metastasis [4, 5], but later other effects of KP were discovered. Today KP is recognized as an intensive stimulator of the hypothalamic-pituitary-gonadal axis. It plays a key role in the regulation of sexual function [6]. This peptide is primarily considered for the treatment of various kinds of cancer [7], and is also used against infertility and other reproductive disorders [8–11]. During the investigations new properties of this peptide and prospects of its practical use have been discovered.



**Suppression of cancer metastasis**. KP was discovered during the study of antimetastatic effect of chromosome 6 in human melanoma cell lines [12, 13]. Using subtractive hybridization it was shown that specifically one gene was unregulated in the cells transfected with chromosome 6, a product of which appeared to be a metastasis suppressor [14]. However, this gene was found to be actually located on chromosome 1q32, but not on 6 [15]. Further research revealed the presence of *Kiss1* gene on chromosome 6 [16]. The metastatic suppression activity of the KP system was first detected in melanoma [3, 17], however, further studies revealed this effect in breast cancer as well [5, 18–21]. Most of the reports link the loss mutation of *Kiss1* to cancer progression and metastasis dissemination, although there are contradictions in this issue. Today the ability of KP system to metastasis suppression was found in the samples of thyroid cancer [22, 23], ovaries [24, 25], bladder [26], stomach [4, 27, 28, 29], esophagus [30], hepatocellular cancer [31, 32], pancreatic cancer [33, 34],

prostate [35, 36] and lung cancer [37]. Current research in this area is still in progress.

**Control of the epiphyseal synthetic activity**. The experiments on rats have shown that melatonin provides the activating effect on the gonads of young and mature rats, which can be enhanced by administration of KP [38, 39]. In contrast, the inactivation of the reproductive system was observed in old rats after the administration of melatonin, which was partially abolished after KP injections. This phenomenon may be a manifestation of a negative feedback between melatonin and KP in old animals [40]. Thus, KP is assumed to activate the epiphyseal synthesis of melatonin in young and mature animals, and this peptide is possibly inhibited in old rats.

**Neural transmission in hippocampus**. The *Kiss1* gene and mRNA of the Kiss1 receptor (Kiss1r) were found in the rat hippocampus [41], and they showed the influence on neural transmission in this area [42]. The KP system might be involved in neurogenesis and pathogenesis of epilepsy.

**Interaction with the adrenergic system of the brain**. The hypothalamus has many adrenergic fibers of both hypothalamic and extrahypothalamic origin constituting the adrenergic system of the brain. This system is essential in maturation of the hypothalamic-pituitary-gonadal complex [43]. Recently additional interaction mechanisms of the kisspeptinergic and alpha-adrenergic activation of the gonads have been discovered. The stimulation of alpha-adrenergic system of 1- and 3-month old rats by mezaton was found to activate the gonadal function, while the blockade of this system respectively inhibits the testicular activity [39]. The influence of kisspeptinergic system on gonads of young and mature animals during combined administration of KP and its antagonist is stronger than that of alpha-adrenergic system [38]. The similar effect is not observed in old rats [44]. At the same time, the introduction of prazosin does not inhibit the gonadal activity, and the blockade of KP receptors abolishes the powerful gonadal stimulating effect of mezaton in old animals. Another experiment has also shown that prazosin does not alter the effects of KP [5].

**Vasoconstrictive effect in the cardiovascular system**. In the human cardiovascular system both the peptide and receptor expressions were identified in the coronary artery, aorta, umbilical vein, moreover KP caused a strong vasoconstictive effect on two latter [45]. In addition, the peptide acts as a positive inotropic agent in the human and mouse heart, it increases the concentration of intracellular $Ca^{2+}$ [46]. We can assume that KP can operate as a cardiovascular transmitter.

**Effect of insulin secretion in pancreas**. In the pancreas high expression of the peptide and receptor has been identified in the human and mouse islet endocrine cells, where they can enhance the insulin secretion [47]. Further study showed that intravenous injection of KP-10 increases the insulin level in rats [48], though other investigators have found that injections of Kp-13 decrease glucose-induced insulin secretion in the perfusion model of the pancreas [49]. The difference may be due to the usage of diverse peptides in those experiments.

**Role in pregnancy and lactation**. The first reports on KP expression informed about high level of this peptide in the human placenta [2, 3, 50]. Now the presence of KP and its receptor expression is proved in the human trophoblast [51, 52], with higher expression in the first trimester of pregnancy than in the third, which correlates with invasiveness decreasing. Radioimmunoassay tests showed that KP circulates in very low concentrations in plasma of men and non-pregnant women [53]. During pregnancy the KP concentration in plasma increases dramatically, 1000-fold in the first trimester and 10000-fold in the third [54, 55]. KP prevents the trophoblast migration, at least *in vitro* [52], possibly due to the inhibitory regulation of matrix metalloprotease-2. The mRNA expression of *Kiss1* and Kiss1r was also detected in giant trophoblast cells of rat placenta [56], although the relevance of KP in physiology of pregnancy of nonhuman species has not been fully investigated. In addition to the function of KP in adults, it is also the master regulator of the gonadotropic axis activation in the fetus [55].

In accordance with a convincing role of KP system during pregnancy there are new, though conflicting data on the changes in KP expression during preeclampsia (an increase of pressure during pregnancy) [57–59]. In addition, an increase in KP-54 level is observed in the patients with normal weight and syndrome of polycystic ovaries, that is in accordance with the association of the protein with leptin and obesity. However, this result should be interpreted with caution because

of the usage of various tests. The expression of KP and Kiss1r was also found in human atherosclerotic plaques [45].

Lactation is an important physiological model of integration of energy balance and reproduction, as this phenomenon involves the activation of neuropeptide systems of appetite excitation, due to strong inhibition of pulsatile secretion of GnRH/LH (gonadotropic releasing hormone/luteinizing hormone). There are several systems which promote chronic hyperphagia of lactation. One of them inhibits the effects of metabolic hormones leptin and insulin resulting in adequate usage of the energy to satisfy metabolic needs of milk production. There is considerable overlap of all systems that regulate food intake and the GnRH secretion. This leads to increasing inhibitory regulation of *Kiss1*-neurons and possible violations of pulsatile output of GnRH. While low levels of leptin and insulin contribute to inhibition of *Kiss1*, that in turn can be a key factor in the suppression of GnRH during lactation, although the mechanisms responsible for this are unknown [60].

**Value for metabolism**. Scientific facts argue that reproduction mainly depends on energy resources and metabolic status of the organism, which is essential to good fertility. Malnutrition is associated with infertility in humans and animals. The biological mechanism based on the fact that the body is not getting enough food, turns off the mechanism of reproduction. Because of significant energy requirements of reproduction, the brain must inhibit fertility in compliance with the accessibility of food [61]. Energy reserves and metabolic status of the organism belong to the appropriate «modifiers» of early puberty and fertility. The different forms of metabolic stress from permanent lack of food for morbid obesity are often associated with reproductive disorders. The mechanisms of close connection between the energy balance and reproduction have been a subject of attention for a long time, but the understanding of neurobiological bases of this phenomenon is yet to be completed. In recent years there has been discussion about a role of various «metabolic hormones» that control the body's energy balance and reproduction [62].

The recent data have proved that the Kiss1r system can integrate both metabolic signals, such as nutrition and metabolism [63], and environmental signals such as photoperiod [64–66], that affects the reproductive system. Metabolic status is a key regulatory factor of the hypothalamic *Kiss1*-system [62]. *Kiss1*-neurons in the hypothalamus act as sensitive sensors of the energy balance. As a result of communication of these neurons with GnRH-neurons, the effect of metabolic products («metabolic hormones») on the first of them changes the activity of second ones and, respectively, of all gonadotropic axis. *Kiss1*-neurons act as factors for metabolic starting of reproduction, where leptin acts as a regulator of the hypothalamic *Kiss1* expression [67]. KPs cause the change in gonadotrophin secretion and the ovarian function accordingly. This influence can be realised via the KP–GPR54 system and the changes in hormonal status, as well as through the direct effect of active substances coming from the blood flow to the ovaries. KPs are the channels for metabolic regulation of reproduction and the effectors of leptin action on GnRH-neurons. KP serve as the mediators for the regulation of *Kiss1* expression by leptin, and also for revealing other potential metabolic modulators of KP-signaling, such as insulin, ghrelin, neuropeptide Y and melanin-concentrating hormone (MCH) [61, 68]. MCH is responsible for deactivation of the reproductive system when the body is under stress. More often this peptide is released during permanent malnutrition or excessive physical exertion. MCH partially blocks kisspeptin in metabolism, therefore prevents sexual maturation of the organism and implementation of reproduction [69].

In the mid-1990s, it was proved that leptin, the hormone of adipose tissue, is an important signal for transmission information to the metabolic center of sexual maturation and reproduction, but the mechanism of leptin action on GnRH-neurons has been controversial for many years [70]. The basic functions of leptin were taken into account, which are to decrease the energy loss by reducing the synthesis of thyroid hormones and thermogenesis, mobilization of energy resources due to increased production of glucocorticoids [71] and inhibition of the reproductive function [72]. In starving mice the leptin injection promotes correction of neuroendocrine disorders associated with decreased level of endogenous leptin, that reduces the activity of the thyroid and gonads in the background of adrenals stimulation [73]. This low level of leptin is the basis of metabolic and neuroendocrine shifts typical for anorexia

nervosa and starvation. The concentration of leptin is a physiological signal of energy sufficiency for reproductive function and affects the production of steroid hormones in the ovaries [74]. During puberty the leptin concentration in blood increases [75]. Negative energy balance and insufficient energy reserves reduce leptin production, thus decreasing the leptin-mediated secretion of hypothalamic GnRH and the reproductive function [76].

Recent studies have shown that leptin acts via its receptor (LepRb), affecting the reproductive and neuroendocrine axis, but the nature and location of relevant LepRb-neurons are under investigation. Leptin probably affects directly or indirectly the hypothalamic GnRH-neurons or KP-neurons, which are the main regulators of GnRH-neurons. The Immunohistochemical analysis of mice and sheep female brain has been used to evaluate the potential mechanisms. The analysis did not reveal any LepRb in GnRH-neurons, *Kiss1*-neurons of anteroventral periventricular nucleus (PVN) and in *Kiss1*-cells of the arcuate nucleus. It allows us to suggest that leptin does not modulate the reproduction directly on any of these neuronal populations. LepRb-neurons, primarily in the ventral premammilary hypothalamic nucleus and in the subregion of the preoptic area, are in close contact with GnRH-neurons. In addition, an unknown population of LepRb-neurons is in close contact with the arcuate nucleus and *Kiss1*-neurons of PVN. Taken together, these results demonstrate that leptin interacts with the neuroendocrine reproductive axis via some populations of LepRb-neurons, located afferently to both *Kiss1*-, and GnRH-neurons [77].

The discovery of leptin clearly demonstrates the relationship between the adipose tissue and the neuroendocrine axis since leptin affects the appetite and the reproductive system. The adipose tissue is a main source of leptin, it is no longer seen simply as a depot for fat storage. The recent studies have shown that many genes of neuropeptides, interleukins and biologically active substances, such as leptin and insulin-like growth factors I and II, are also produced in the adipose tissue, which can affect the appetite and the reproductive system. The targets of leptin in the hypothalamus include the neuropeptides Y, proopiomelanokortin and KP. The nutritional signals are detected by the CNS and transmitted by the neuroendocrine system into signals regulating LH secretion. Leptin also directly affects the GnRH release from the hypothalamus, LH – from the pituitary and the ovarian follicular steroidogenesis [76, 78].

**Neuroendocrine regulation of puberty and reproduction**. There are many evidences that Kiss1r signaling is required for the puberty beginning. People and mice with violation of the receptor Kiss1r or the *Kiss* gene are unable to undergo puberty [79–81]. Injection of KP induced the premature puberty, while central injection of the KP antagonist delayed puberty in prepubertal rats [11, 82]. During puberty the communication between KP and GnRH-neurons increases, resulting in enhanced hypothalamic expression of *Kiss1* mRNA and Kiss1r in rats and monkeys [83], in the increase of appositions between kisspeptin fibers and GnRH-neurons [84], frequency of KP pulsation, and sensitivity of GnRH-neurons to KP higher level [85]. GnRH-neurons exhibit great plasticity at the cellular and molecular levels, and subpopulations of GnRH1-neurons in the preoptic area are highly responsive to specific environmental and hormonal conditions [86]. KP can also act on the pituitary [87, 88].

The crucial role of KP and its receptor in regulation of the reproductive function was originally described in the observations of Kiss1r with the mutations leading to a loss of function in some patients with idiopathic hypogonadotropic hypogonadism, and it was discovered on the model of transgenic mice [80, 82, 89]. KP has been recognized as a major regulator of the hypothalamic-pituitary-gonadal axis, which controls puberty, in larger number of species. KP can stimulate the release of gonadotropin in human [9], mouse [90, 91], rat [92–95], monkey [96, 97], sheep [91, 98]. GnRH is shown to be a direct mediator of this effect in monkey, sheep, pig [99], goat [100]. GnRH antagonists block KP-induced gonadotropin release [10, 36]. Further experiments showed that GnRH-neurons express the Kiss1r [101, 102]. And key researches on Kiss1r- and *Kiss1*-knockout mice showed that functional Kiss1r is required for GnRH secretion and release of LH and follicle-stimulating hormone (FSH) [11, 103, 104].

Investigation on the mechanism of communication between KP and GnRH-neurons revealed that the activity of GnRH-neurons is increased by KP [105], as shown by the method of c-Fos imunoreactivity, KP de-

*Different effects of kisspeptin*

| Area of influence | Effect | Species | References |
|---|---|---|---|
| Hypothalamus | Gonadotropin releasing (GnRH) | Human, rat, mouse, monkey, sheep, goat, pig, European sea bass | [9, 90, 94, 95, 98, 100–103] |
| GnRH-neurons | Depolarization, increasing pulsation | Human, rat, mouse | [107, 108, 111] |
| Pituitary | FSH and LH releasing | Human, rat, mouse | [83, 90] |
| Epiphysis | Stimulation of melatonin synthesis in young and mature animals, depression – in the old ones | Rat | [38, 40, 41] |
| Hippocampus | Neural transmission | Rat | [42, 43] |
| Alpha-adrenergic system | Strong activation in young and mature organism and neutral effect in old one | Rat | [39, 44, 46] |
| Placenta | Prevents the trophoblast migration, regulates the gonadotropic axis activation in the fetus | Human | [54, 57] |
| Heart | Positive inotropic effect | Human, mouse | [48] |
| Aorta, umbilical vein | Strong vasoconstriction | Human | [47] |
| Pancreas | Affects the insulin secretion | Human, rat, mouse | [49, 50] |
| Testes | Enhances the secretory activity, pancreases testosterone production | Rat | [107, 120, 121] |
| Ovaries | Activating of estrogen releasing | Human, rat | [115] |
| Skin, thyroid, ovaries, bladder, breast, stomach, esophagus, liver, pancreas, lung, prostate | Metastasis supression | Human, rat, mouse | [3, 4, 5, 10, 24, 26, 32, 34, 37] |

polarizes GnRH-neurons [85, 106] and raises their pulsation [107–110].

The regulation of the *Kiss1* expression and, to a lesser degree, of mRNA of the receptor Kiss1r by sex steroids was registered in the hypothalamus of a number of species. Gonadoectomized mice, sheep and rhesus- macaques showed an increase in the expression of *Kiss1* mRNA in the arcuate nucleus or in the infundibular region [101, 111, 112]. Replacement of sex steroids reduces the expression of *Kiss1* mRNA in relation to the target levels [83]. This scheme is believed to be the negative feedback control of gonadotropin secretion. And, conversely, the preovulatory level of LH includes the positive feedback in mice and rats, probably it is regulated by neurons in the anteroventral PVN [113]. The expression of the *Kiss1* mRNA decreased in anteroventral PVN in ovariectomized rats and increased with recovery of the estrogen levels. This is mediated by estrogen receptors ERa [114]. However, this control mechanism varies in different species: in sheep and primates the KP-neurons are located in the arcuate nucleus and in the preoptic area, and the regulation of both positive and negative feedback gonadotropin secretion probably occurs in the arcuate nucleus [115–117].

Kisspeptin affects both the female and male reproductive systems, influencing the same neuroendocrine centers. KP stimulates the hypothalamic-pituitary-gonadal axis by changing the activity of gonads through the activation of release of relevant hormones, including hypothalamic gonadoliberin [82]. GnRH, in turn, activates the release of FSH and LH [118]. FSH activates spermatogenesis, affecting the Sertoli cells. LH influences the Leydig cells, which produce testosterone. Thus, the normal course of spermatogenesis depends mainly on these two hormones [105]. The research results showed that the male rats had the significant increase of gonadal functional activity after KP injections. Moreover, intense activating by KP was observed even after combined injections of prazosin, which has an inhibitory effect on the synthetic activity of testicles [119].

Thus, by changing metabolic state of the body the endogenous production of additional quantity of hormones can be enhanced or reduced and thereby the sexual function can be stimulated or inhibited. These findings provide scientific justification for strong interest in exploring the possibility of stimulation of the reproductive system by changing the diet, primarily by increasing its energy value. The time of puberty is sensitive to both overeating and malnutrition at the early postnatal stage and the changes in hypothalamic expression of KP are assumed to be based partly on this phenomenon. The details are not numerous and discoveries in this area are waiting for their researchers. Based on these scientific investigations the practical methods have been developing to regulate the reproduction. They include both pharmacological and organizational means. The table summarizes briefly the global researches related to the KP effects, known today.

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Різноманіття функцій та ефектів кіспептину

Резюме

*Представлено короткий огляд літературних даних з дослідження властивостей та ефективності застосування кіспептину, зокрема, для регуляції ендокринних функцій організму. Проаналізовано численні результати експериментів з використанням кіспептину в молекулярній біології, репродуктивної медицині, ендокринології, а також при розробці вакцин проти злоякісних утворень. Згаданий пептид ініціює каскад змін, які призводять до пубертату. За наявними даними, кіспептин змінює активність залоз, які продукують статеві гормони, внаслідок чого він може знайти застосування у лікуванні захворювань, пов'язаних з порушенням пубертату, зокрема, аменореї у дівчат-підлітків. Дія цього пептиду обумовлена активацією клітин гіпоталамуса, що виділяють гонадоліберин, який регулює рівень гонадотропних гормонів. У той же час кіспептин активує репродуктивну систему, не порушуючи при цьому захисних механізмів організму. Видається перспективним більш поглиблене вивчення ефекту кіспептину на всі ланки гіпоталамо-гіпофізарно-гонадальної осі, а також дослідження нейроно-гліальних взаємодій у центральній нервовій системі під впливом даного пептиду.*

*Ключові слова: кіспептин, гонадотропний рилізинг-гормон, гіпоталамо-гіпофізарно-гонадальна вісь.*

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Разнообразие функций и эффектов кисспептина

Резюме

*Представлен краткий обзор литературных данных по исследованию свойств и эффективности применения кисспептина, в частности, для регуляции эндокринных функций организма. Проанализированы многочисленные результаты экспериментов с использованием кисспептина в молекулярной биологии, репродуктивной медицине, эндокринологии, а также при разработке вакцин против злокачественных образований. Указанный пептид инициирует каскад изменений, ведущих к пубертату. По имеющимся дан- ным, кисспептин изменяет активность желез, продуцирующих половые гормоны, вследствие чего он может найти применение в лечении заболеваний, связанных с нарушением пубертата, в част- ности, аменореи у девочек-подростков. Действие данного пептида связано с активацией клеток гипоталамуса, выделяющих гонадолиберин, регулирующий уровень гонадотропных гормонов. В то же время кисспептин активирует репродуктивную систему, не нарушая при этом защитных механизмов организма. Представляется перспективным более углубленное изучение эффекта кисспептина на все звенья гипоталамо-гипофизарно-гонадальной оси, а также исследование нейроно-глиальных взаимодействий в центральной нервной системе под влиянием данного пептида.*

*Ключевые слова: кисспептин, гонадотропный рилизинг-гормон, гипоталамо-гипофизарно-гонадальная ось.*

REFERENCES

1. *Kotani M., Detheux M., Vandenbogaerde A., Communi D., Vanderwinden J. M., Le Poul E., Brezillon S., Tyldesley R., Suarez-Huerta N., Vandeput F., Blanpain C., Schiffmann S. N., Vassart G., Parmentier M.* The metastasis suppressor gene KiSS-1 encodes kisspeptins, the natural ligands of the orphan G protein-coupled receptor GPR54 // J. Biol. Chem.–2001.–**276**, N 37.–P. 34631–34636.
2. *Muir A. I., Chamberlain L., Elshourbagy N. A., Michalovich D., Moore D. J., Calamari A., Szekeres P. G., Sarau H. M., Chambers J. K., Murdock P., Steplewski K., Shabon U., Miller J. E., Middleton S. E., Darker J. G., Larminie C. G., Wilson S., Bergsma D. J., Emson P., Faull R., Philpott K. L., Harrison D. C.* AXOR12, a novel human G protein-coupled receptor, activated by the peptide KISS-1 // J. Biol. Chem.–2001.–**276**, N 31.–P. 28969–28975.
3. *Ohtaki T., Shintani Y., Honda S., Matsumoto H., Hori A., Kanehashi K., Terao Y., Kumano S., Takatsu Y., Masuda Y., Ishibashi Y., Watanabe T., Asada M., Yamada T., Suenaga M., Kitada C., Usuki S., Kurokawa T., Onda H., Nishimura O., Fujino M.* Metastasis suppressor gene KiSS-1 encodes peptide ligand of a G-protein-coupled receptor // Nature.–2001.–**441**, N 6837.–P. 613–617.
4. *Ergen A., Canbay E., Bugra D., Zeybek U., Yamaner S., Bulut T.* Plasma Kisspeptin-54 levels in gastric cancer patients // Int. J. Surg.–2012.–**10**, N 5.–P. 551–554.
5. *Tanaka M., Csabafi K., Telegdy G.* Neurotransmissions of antidepressant-like effects of kisspeptin-13 // Regul. Pept.–2012.–[Epub ahead of print] 10.1016/j.regpep.2012.08.017.
6. *Navarro V. M.,. Castellano J. M, Fernandez-Fernandez R., Barreiro M. L., Roa J., Sanchez-Criado J. E., Aguilar E., Dieguez C., Pinilla L., Tena-Sempere M.* Developmental and hormonally regulated messenger ribonucleic acid expression of KiSS-1 and its putative receptor, GPR54, in rat hypothalamus and potent luteinizing hormone-releasing activity of KiSS-1 peptide // Endocrinology.–2004.–**145**, N 10.–P. 4565–4574.
7. *Lee J. H., Welch D. R.* Identification of highly expressed genes in metastasis-suppressed chromosome 6/human malignant melanoma hybrid cells using subtractive hybridization and differential display // Int. J. Cancer.–1997.–**71**, N 6.–P. 1035–1044.
8. *Dhillo W. S., Chaudhri O. B., Patterson M., Thompson E. L., Murphy K. G., Badman M. K., McGowan B. M., Amber V., Patel S., Ghatei M. A., Bloom S. R.* Kisspeptin-54 stimulates the hypo-

thalamic-pituitary gonadal axis in human males // J. Clin. Endocrinol. Metab.–2005.–**90**, N 12.–P. 6609–6615.

9. *Dhillo W. S., Chaudhri O. B., Thompson E. L., Murphy K. G., Patterson M., Ramachandran R., Nijher G. K., Amber V., Kokkinos A., Donaldson M., Ghatei M. A., Bloom S. R.* Kisspeptin-54 stimulates gonadotropin release most potently during the preovulatory phase of the menstrual cycle in women // J. Clin. Endocrinol. Metab.–2007.–**92**, N 10.–P. 3958–3966.
10. *Matsui H., Tanaka A., Yokoyama K., Takatsu Y., Ishikawa K., Asami T., Nishizawa N., Suzuki A., Kumano S., Terada M., Kusaka M., Kitada C., Ohtaki T.* Chronic administration of the metastin/kisspeptin analog KISS1-305 or the investigational agent TAK-448 suppresses hypothalamic pituitary gonadal function and depletes plasma testosterone in adult male rats // Endocrinology.–2012.–**153**, N 11.–P. 5297–5308.
11. *Sonigo C., Binart N.* Overview of the impact of kisspeptin on reproductive function // Ann. Endocrinol. (Paris).–2012.–**73**, N 5.–P. 448–458.
12. *Welch D. R., Chen P., Miele M. E., McGary C. T., Bower J. M., Stanbridge E. J., Weissman B. E.* Microcell-mediated transfer of chromosome 6 into metastatic human C8161 melanoma cells suppresses metastasis but does not inhibit tumorigenicity // Oncogene.–1994.–**9**, N 1.–P. 255–262.
13. *Miele M. E., Robertson G., Lee J. H., Coleman A., McGary C. T., Fisher P. B., Lugo T. G., Welch D. R.* Metastasis suppressed, but tumorigenicity and local invasiveness unaffected, in the human melanoma cell line MelJuSo after introduction of human chromosomes 1 or 6 // Mol. Carcinog.–1996.–**15**, N 4.–P. 284–299.
14. *Miele M. E., Jewett M. D., Goldberg S. F., Hyatt D. L., Morelli C., Gualandi F., Rimessi P., Hicks D. J., Weissman B. E., Barbanti-Brodano G., Welch D. R.* A human melanoma metastasis-suppressor locus maps to 6q16.3-q23 // Int. J. Cancer.–2000.–**86**, N 4.–P. 524–528.
15. *Lee J .H., Miele M. E., Hicks D. J., Phillips K. K., Trent J. M., Weissman B. E., Welch D. R.* Kiss-1, a novel human malignant melanoma metastasis-supressor gene // J. Natl Cancer Inst.–1996.–**88**, N 23.–P. 1731–1737.
16. *West A., Vojta P. J., Welch D. R., Weissman B. E.* Chromosome localization and genomic structure of the KiSS-1 metastasis suppressor gene (KISS1) // Genomics.–1998.–**54**, N 1.–P. 145–148.
17. *Shirasaki F., Takata M., Hatta N., Takehara K.* Loss of expression of the metastasis suppressor gene KiSS1 during melanoma progression and its association with LOH of chromosome 6q16.3-q23 // Cancer Res.–2001.–**61**, N 20.–P. 7422–7425.
18. *Stark A. M., Tongers K., Maass N., Mehdorn H. M., Held-Feindt J.* Reduced metastasis-suppressor gene mRNA-expression in breast cancer brain metastases // J. Cancer Res. Clin. Oncol.–2005.–**131**, N 3.–P. 191–198.
19. *Kostadima L., Pentheroudakis G., Pavlidis N.* The missing kiss of life: transcriptional activity of the metastasis suppressor gene KiSS1 in early breast cancer // Anticancer Res.–2007.–**27**, N 4B.–P. 2499–2504.
20. *Marot D., Bieche I., Aumas C., Esselin S., Bouquet C., Vacher S., Lazennec G., Perricaudet M., Kuttenn F., Lidereau R., de Roux N.* High tumoral levels of Kiss1 and G-protein-coupled receptor 54 expression are correlated with poor prognosis of estrogen receptor-positive breast tumors // Endocr. Relat. Cancer.–2007.–**14**, N 3.–P. 691–702.
21. *Mitchell D. C., Stafford L. J., Li D., Bar-Eli M., Liu M.* Transcriptional regulation of KiSS-1 gene expression in metastatic melanoma by specificity protein-1 and its coactivator DRIP-130 // Oncogene.–2007.–**26**, N 12.–P. 1739–1747.
22. *Ringel M. D., Hardy E., Bernet V. J., Burch H. B., Schuppert F., Burman K. D., Saji M.* Metastin receptor is overexpressed in pa pillary thyroid cancer and activates MAP kinase in thyroid cancer cells // J. Clin. Endocrinol. Metab.–2002.–**87**, N 5.–P. 2399.
23. *Stathatos N., Bourdeau I., Espinosa A. V., Saji M., Vasko V. V., Burman K. D., Stratakis C. A., Ringel M. D.* KiSS-1/G protein-coupled receptor 54 metastasis suppressor pathway increases myocyte-enriched calcineurin interacting protein 1 expression and chronically inhibits calcineurin activity // J. Clin. Endocrinol. Metab.–2005.–**90**, N 9.–P. 5432–5440.
24. *Zhang S. L., Yu Y., Jiang T., Lin B., Gao H.* Expression and significance of KiSS-1 and its receptor GPR54 mRNA in epithelial ovarian cancer // Zhonghua Fu Chan Ke Za Zhi.–2005.–**40**, N 10.–P. 689–692.
25. *Hata K., Dhar D. K., Watanabe Y., Nakai H., Hoshiai H.* Expression of metastin and a G-protein-coupled receptor (AXOR12) in epithelial ovarian cancer // Eur. J. Cancer.–2007.–**43**, N 9.–P. 1452–1459.
26. *Sanchez-Carbayo M., Belbin T. J., Scotlandi K., Prystowsky M., Baldini N., Childs G., Cordon-Cardo C.* Expression profiling of osteosarcoma cells transfected with MDR1 and NEO genes: regulation of cell adhesion, apoptosis, and tumor suppression-related genes // Lab. Invest.–2003.–**83**, N 4.–P. 507–517.
27. *Dhar D. K., Naora H., Kubota H., Maruyama R., Yoshimura H., Tonomoto Y., Tachibana M., Ono T., Otani H., Nagasue N.* Down-regulation of KiSS-1 expression is responsible for tumor invasion and worse prognosis in gastric carcinoma // Int. J. Cancer.–2004.–**111**, N 6.–P. 868–872.
28. *Guan-Zhen Y., Ying C., Can-Rong N., Guo-Dong W., Jian-Xin Q., Jie-Jun W.* Reduced protein expression of metastasis-related genes (nm23, KISS1, KAI1 and p53) in lymph node and liver metastases of gastric cancer // Int. J. Exp. Pathol.–2007.–**88**, N 3.–P. 175–183.
29. *Yao H. L., Yang Z. L., Li Y. G., Liu G. W. In situ* hybridization study on the expression of Kiss-1 and KAI-1 metastasis suppressor genes in gastric cancer // Zhonghua Wei Chang Wai Ke Za Zhi.–2007.–**10**, N 3.–P. 274–277.
30. *Ikeguchi M., Yamaguchi K., Kaibara N.* Clinical significance of the loss of KISS-1 and orphan G-protein-coupled receptor (hOT7T175) gene expression in esophageal squamous cell carcinoma // Clin. Cancer Res.–2004.–**10**, N 4.–P. 1379–1383.
31. *Ikeguchi M., Hirooka Y., Kaibara N.* Quantitative reverse transcriptase polymerase chain reaction analysis for KISS-1 and orphan G-protein-coupled receptor (hOT7T175) gene expression in hepatocellular carcinoma // J. Cancer Res. Clin. Oncol.–2003.–**129**, N 9.–P. 531–535.
32. *Hou Y. K., Wang Y., Cong W. M., Wu M. C.* Expression of tumor metastasis-suppressor gene KiSS-1 and matrix metalloproteinase-9 in portal vein tumor thrombus of hepatocellular carcinoma // Ai Zheng.–2007.–**26**, N 6.–P. 591–595.
33. *Masui T., Doi R., Mori T., Toyoda E., Koizumi M., Kami K., Ito D., Peiper S. C., Broach J. R., Oishi S., Niida A., Fujii N., Imamura M.* Metastin and its variant forms suppress migration of pancreatic cancer cells // Biochem. Biophys. Res. Commun.–2004.–**315**, N 1.–P. 85–92.
34. *Liang S., Yang Z. L.* Expression of KiSS-1 mRNA in pancreatic ductal adenocarcinoma and non-cancerous pancreatic tissues in SD rats // Zhong Nan Da Xue Xue Bao Yi Xue Ban.–2007.–**32**, N 1.–P. 109–113.
35. *Roseweir A. K., Kauffman A. S., Smith J. T., Guerriero K. A., Morgan K., Pielecka-Fortuna J., Pineda R., Gottsch M. L., Tena-Sempere M., Moenter S. M., Terasawa E., Clarke I. J., Steiner R. A., Millar R. P.* Discovery of potent kisspeptin antagonists delineate physiological mechanisms of gonadotropin regulation // J. Neurosci.–2009.–**29**, N 12.–P. 3920–3929.

36. *Matsui H., Takatsu Y., Kumano S., Matsumoto H., Ohtaki T.* Peripheral administration of metastin induces marked gonadotropin release and ovulation in the rat // Biochem. Biophys. Res. Commun.–2004.–**320**, N 2.–P. 383–388.
37. *Zohrabian V. M., Nandu H., Gulati N., Khitrov G., Zhao C., Mohan A., Demattia J., Braun A., Das K., Murali R., Jhanwar-Uniyal M.* Gene expression profiling of metastatic brain cancer // Oncol. Rep.–2007.–**18**, N 2.–P. 321–328.
38. *Matvienko M. G., Pustovalov A. S., Buzynska N. O., Dzerzhinsky M. E*. Morphofunctional changes in prepubertal rat testes under kisspeptin influence against blockade and activation of alpha-adrenergic receptors and melatonin administration // Bulletin of Luhansk National Taras Shevchenko University.–2012.–**1**, N 17.–P. 101–109.
39. *Matvienko M., Pustovalov A., Dzerzhinsky M*. Morphofunctional changes in rat testes under kisspeptin influence against blockade and activation of alpha-adrenergic receptors and melatonin administration // Bulletin of Kyiv Taras Shevchenko National University. Biology.–2012.–**1**, N 60.–P. 41–43.
40. *Matvienko M. G., Pustovalov A. S., Buzynska N. O., Dzerzhinsky M. E*. Morphofunctional changes in 24-month rat testes under kisspeptin influence against blockade and activation of alpha-adrenergic receptors and melatonin administration // Visnyk Problem Biologii i Meditsiny.–2012.–**2**, N 3.–P. 170–173.
41. *Arai A. C., Xia Y. F., Suzuki E., Kessler M., Civelli O.,Nothacker H. P.* Cancer metastasis-suppressing peptide metastin upregulates excitatory synaptic transmission in hippocampal dentate granule cells // J. Neurophysiol.–2005.–**94**, N 5.–P. 3648–3652.
42. *Arai A. C., Orwig N.* Factors that regulate KiSS1 gene expression in the hippocampus // Brain Res.–2008.–**1243**.–P. 10–18.
43. *Dzerzhinsky M., Matvienko M., Pustovalov A., Buzynska N*. Kisspeptin influence on rat testes after administration of melatonin, prazosin, mezaton // 26th Conf. of Eur. Comparative Endocrinologists CECE 2012 (Zurich, Switzerland, 21–25 August 2012): Programme and abstract book.–Zurich, 2012.–P. 106.
44. *Matvienko M. G., Pustovalov A. S., Buzynska N. O., Dzerzhinsky M. E*. Kisspeptin influence on rat testes after administration of prazosin, mezaton and melatonin: II Sci. Conf. of Young Physiologists «Physiology: from Molecules to the Body» (8–9 October, 2012).–Kyiv, 2012.–P. 47.
45. *Mead E. J., Maguire J. J., Kuc R. E., Davenport A. P.* Kisspeptins are novel potent vasoconstrictors in humans, with a discrete localization of their receptor, G protein-coupled receptor 54, to atherosclerosis-prone vessels // Endocrinology.–2007.–**148**, N 1.–P. 140–147.
46. *Kirby H., Mead E., Maguire J., Pitkin S., Colledge W. H., d'Anglemont de Tassigny X., Davenport A. P.* Kisspeptins as inotropic agents in human and mouse heart // Proc. Physiol. Soc.–2008.–**11**.–P. C152.
47. *Hauge-Evans A. C., Richardson C. C., Milne H. M., Christie M. R., Persaud S. J., Jones P. M.* A role for kisspeptin in islet function // Diabetologia.–2006.–**49**, N 9.–P. 2131–2135.
48. *Bowe J. E., King A. J., Kinsey-Jones J. S., Foot V. L., Li X. F., O'Byrne K. T., Persaud S. J., Jones P. M.* Kisspeptin stimulation of insulin secretion: mechanisms of action in mouse islets and rats // Diabetologia.–2009.–**52**, N 5.–P. 855–862.
49. *Silvestre R. A., Egido E. M., Hernandez R., Marco J.* Kisspeptin-13 inhibits insulin secretion without affecting glucagon or somatostatin release: study in the perfused rat pancreas // J. Endocrinol.–2008.–**196**, N 2.–P. 283–290.
50. *Lee J. H., Welch D. R.* Suppression of metastasis in human breast carcinoma MDA-MB-435 cells after transfection with the metastasis suppressor gene, KISS-1 // Cancer Res.–1997.–**57**, N 12.–P. 2384–2387.
51. *Janneau J. L., Maldonado-Estrada J., Tachdjian G., Miran I., Motte N., Saulnier P., Sabourin J. C., Cote J. F., Simon B., Frydman R., Chaouat G., Bellet D.* Transcriptional expression of genes involved in cell invasion and migration by normal and tumoral trophoblast cells // J. Clin. Endocrinol. Metab.–2002.–**87**, N 1.–P. 5336–5339.
52. *Bilban M., Ghaffari-Tabrizi N., Hintermann E., Bauer S., Molzer S., Zoratti C., Malli R., Sharabi A., Hiden U., Graier W., Knofler M., Andreae F., Wagner O., Quaranta V., Desoye G.* Kisspeptin-10, a KiSS-1/metastin-derived decapeptide, is a physiological invasion inhibitor of primary human trophoblasts // J. Cell Sci.–2004.–**117**, Pt 8.–P. 1319–1328.
53. *Dhillo W.S., Savage P., Murphy K. G., Chaudhri O. B., Patterson M., Nijher G. M., Foggo V. M., Dancey G. S., Mitchell H., Seckl M. J., Ghatei M. A., Bloom S. R.* Plasma kisspeptin is raised in patients with gestational trophoblastic neoplasia and falls during treatment // Am. J. Physiol. Endocrinol. Metab.–2006.–**291**, N 5.–E878–884.
54. *Horikoshi Y., Matsumoto H., Takatsu Y., Ohtaki T., Kitada C., Usuki S., Fujino M.* Dramatic elevation of plasma metastin concentrations in human pregnancy: metastin as a novel placenta-derived hormone in humans // J. Clin. Endocrinol. Metab.–2003.–**88**, N 2.–P. 914–919.
55. *Guimiot F., Chevrier L., Dreux S., Chevenne D., Caraty A., Delezoide A. L., de Roux N.* Negative fetal FSH/LH regulation in late pregnancy is associated with declined kisspeptin/KISS1R expression in the tuberal hypothalamus // J. Clin. Endocrinol. Metab.–2012.–**97**, N 12.–E2221–2229.
56. *Terao Y., Kumano S., Takatsu Y., Hattori M., Nishimura A., Ohtaki T., Shintani Y.* Expression of KiSS-1, a metastasis suppressor gene, in trophoblast giant cells of the rat placenta // Biochim. Biophys. Acta.–2004.–**1678**, N 2–3.–P. 102–110.
57. *Qiao C., Wang C. H., Shang T., Lin Q. D.* Clinical significance of KiSS-1 and matrix metalloproteinase-9 expression in trophoblasts of women with preeclampsia and their relation to perinatal outcome of neonates // Zhonghua Fu Chan Ke Za Zhi.–2005.–**40**, N 9.–P. 585–590.
58. *Farina A., Sekizawa A., Purwosunu Y., Rizzo N., Banzola I., Concu M., Morano D., Giommi F., Bevini M., Mabrook M., Carinci P., Okai T.* Quantitative distribution of a panel of circulating mRNA in preeclampsia versus controls // Prenat. Diagn.–2006.–**26**, N 12.–P. 1115–1120.
59. *Armstrong R. A., Reynolds R. M., Leask R., Shearing C. H., Calder A. A., Riley S. C.* Decreased serum levels of kisspeptin in early pregnancy are associated with intra-uterine growth restriction and pre-eclampsia // Prenat. Diagn.–2009.–**29**, N 10.–P. 982–985.
60. *Smith M. S., True C., Grove K. L.* The neuroendocrine basis of lactation-induced suppression of GnRH: role of kisspeptin and leptin // Brain Res.–2010.–**1364**.–P. 139–152.
61. *Evans J. J., Anderson G. M.* Balancing ovulation and anovulation: integration of the reproductive and energy balance axes by neuropeptides // Hum. Reprod. Update.–2012.–**18**, N 3.–P. 313–332.
62. *Wagner G. C., Johnston J. D., Clarke I. J., Lincoln G. A., Hazlerigg D. G.* Redefining the limits of day length responsiveness in a seasonal mammal // Endocrinology.–2008.–**149**, N 1.–P. 32–39.
63. *Castellano J. M., Navarro V. M., Fernandez-Fernandez R., Nogueiras R., Tovar S., Roa J., Vazquez M. J., Vigo E., Casanueva F. F., Aguilar E., Pinilla L., Dieguez C., Tena-Sempere M.* Changes in hypothalamic KiSS-1 system and restoration of pubertal activation of the reproductive axis by kisspeptin in undernutrition // Endocrinology.–2005.–**146**, N 9.–P. 3917–3925.
64. *Greives T. J., Mason A. O., Scotti M. A., Levine J., Ketterson E. D., Kriegsfeld L. J., Demas G. E.* Environmental control of kis-

speptin: implications for seasonal reproduction // Endocrinology.–2007.–**148**, N 3.–P. 1158–1166.
65. *Revel F. G., Ansel L., Klosen P., Saboureau M., Pevet P., Mikkelsen J. D., Simonneaux V.* Kisspeptin: a key link to seasonal breeding // Rev. Endocr. Metab. Disord.–2007.–**8**, N 1.–P. 57–65.
66. *Smith J. T., Clay C. M., Caraty A., Clarke I. J.* KiSS-1 messenger ribonucleic acid expression in the hypothalamus of the ewe is regulated by sex steroids and season // Endocrinology.–2007.–**148**, N. 3.–P. 1150–1157.
67. *Castellano J. M., Bentsen A. H., Sanchez-Garrido M. A., Ruiz-Pino F., Romero M., Garcia-Galiano D., Aguilar E., Pinilla L., Dieguez C., Mikkelsen J. D., Tena-Sempere M.* Early metabolic programming of puberty onset: impact of changes in postnatal feeding and rearing conditions on the timing of puberty and development of the hypothalamic kisspeptin system // Endocrinology.–2011.–**152**, N 9.–P. 3396–3408.
68. *Castellano J. M., Bentsen A. H., Mikkelsen J. D., Tena-Sempere M.* Kisspeptins: bridging energy homeostasis and reproduction // Brain Res.–2010.–**1364**.–P. 129–138.
69. *Meczekalski B., Podfigurna-Stopa A., Riccardo Genazzani A.* Why kisspeptin is such important for reproduction? // Gynecol. Endocrinol.–2011.–**27**, N 1.–P. 8–13.
70. *Brennan A. M., Mantzoros C. S.* Drug Insight: the role of leptin in human physiology and pathophysiology – emerging clinical applications // Nat. Clin. Pract. Endocrinol. Metab.–2006.–**2**, N 6.–P. 318–327.
71. *Wang M. Y., Chen L., Clark G. O., Lee Y., Stevens R. D., Ilkayeva O. R., Wenner B. R., Bain J. R., Charron M. J., Newgard C. B., Unger R. H.* Leptin therapy in insulin-deficient type I diabetes // Proc. Natl Acad. Sci. USA.–2010.–**107**, N 11.–P. 4813–4819.
72. *Mars M., de Graaf C., de Groot C. P., van Rossum C. T., Kok F. J.* Fasting leptin and appetite responses induced by a 4-day 65 %-energy-restricted diet // Int. J. Obes. (Lond).–2006.–**30**, N 1.–P. 122–128.
73. *Margetic S., Gazzola C., Pegg G. G., Hill R. A.* Leptin: a review of its peripheral actions and interactions // Int. J. Obes. Relat. Metab. Disord.–2002.–**26**, N 11.–P. 1407–1433.
74. *Anifandis G., Koutselini E., Louridas K., Liakopoulos V., Leivaditis K., Mantzavinos T., Sioutopoulou D., Vamvakopoulos N.* Estradiol and leptin as conditional prognostic IVF markers // Reproduction.–2005.–**129**, N 4.–P. 531–534.
75. *Lo K. M., Zhang J., Sun Y., Morelli B., Lan Y., Lauder S., Brunkhorst B., Webster G., Hallakou-Bozec S., Doare L., Gillies S. D.* Engineering a pharmacologically superior form of leptin for the treatment of obesity // Protein Eng. Des. Sel.–2005.–**18**, N 1.–P. 1–10.
76. *Hausman G. J., Barb C. R., Lents C. A.* Leptin and reproductive function // Biochimie.–2012.–**94**, N 10.–P. 2075–2081.
77. *Louis G. W., Greenwald-Yarnell M., Phillips R., Coolen L. M., Lehman M. N., Myers M. G. Jr.* Molecular mapping of the neural pathways linking leptin to the neuroendocrine reproductive axis // Endocrinology.–2011.–**152**, N 6.–P. 2302–2310.
78. *Hausman G. J., Barb C. R.* Adipose tissue and the reproductive axis: biological aspects // Endocr. Dev.–2010.–**19**.–P. 31–44.
79. *de Roux N., Genin E., Carel J. C., Matsuda F., Chaussain J. L., Milgrom E.* Hypogonadotropic hypogonadism due to loss of function of the KiSS1-derived peptide receptor GPR54 // Proc. Natl Acad. Sci. USA.–2003.–**100**, N 19.–P. 10972–10976.
80. *Funes S., Hedrick J. A., Vassileva G., Markowitz L., Abbondanzo S., Golovko A., Yang S., Monsma F. J., Gustafson E. L.* The KiSS-1 receptor GPR54 is essential for the development of the murine reproductive system // Biochem. Biophys. Res. Commun.–2003.–**312**, N 4.–P. 1357–1363.
81. *d'Anglemont de Tassigny X., Fagg L. A., Dixon J. P., Day K., Leitch H. G., Hendrick A. G., Zahn D., Franceschini I., Caraty A., Carlton M. B., Aparicio S. A., Colledge W. H.* Hypogonadotropic hypogonadism in mice lacking a functional Kiss1 gene // Proc. Natl Acad. Sci. USA.–2007.–**104**, N 25.–P. 10714–10719.
82. *Lapatto R., Pallais J. C., Zhang D., Chan Y. M., Mahan A., Cerrato F., Le W. W., Hoffman G. E., Seminara S. B.* Kiss1$^{-/-}$ mice exhibit more variable hypogonadism than Gpr54$^{-/-}$ mice // Endocrinology.–2007.–**148**, N 10.–P. 4927–4936.
83. *Navarro V. M., Fernandez-Fernandez R., Castellano J. M., Roa J., Mayen A., Barreiro M. L., Gaytan F., Aguilar E., Pinilla L., Dieguez C., Tena-Sempere M.* Advanced vaginal opening and precocious activation of the reproductive axis by KiSS-1 peptide, the endogenous ligand of GPR54 // J. Physiol.–2004.–**561**, Pt 2.–P. 379–386.
84. *Clarkson J., Herbison A. E.* Postnatal development of kisspeptin neurons in mouse hypothalamus; sexual dimorphism and projections to gonadotropin-releasing hormone neurons // Endocrinology.–2006.–**147**, N 12.–P. 5817–5825.
85. *Han S. K., Gottsch M. L., Lee K. J., Popa S. M., Smith J. T., Jakawich S. K., Clifton D. K., Steiner R. A., Herbison A. E.* Activation of gonadotropin-releasing hormone neurons by kisspeptin as a neuroendocrine switch for the onset of puberty // J. Neurosci.–2005.–**25**, N 49.–P. 11349–11356.
86. *Stevenson T. J., Hahn T. P., Macdougall-Shackleton S. A., Ball G. F.* Gonadotropin-releasing hormone plasticity: A comparative perspective // Front Neuroendocrinol.–2012.–**33**, N 3.–P. 287–300.
87. *Richard N., Corvaisier S., Camacho E., Kottler M. L.* KiSS-1 and GPR54 at the pituitary level: overview and recent insights // Peptides.–2009–**30**, N 1.–P. 123–129.
88. *Migaud H., Ismail R., Cowan M., Davie A.* Kisspeptin and seasonal control of reproduction in male European sea bass (*Dicentrarchus labrax*) // Gen. Comp. Endocrinol.–**179**, N 3.–P. 384–399.
89. *Kauffman A. S., Park J. H., McPhie-Lalmansingh A. A., Gottsch M. L., Bodo C., Hohmann J. G., Pavlova M. N., Rohde A. D., Clifton D. K., Steiner R. A., Rissman E. F.* The kisspeptin receptor GPR54 is required for sexual differentiation of the brain and behavior // J. Neurosci.–2007.–**27**, N 33.–P. 8826–8835.
90. *Gottsch M. L., Cunningham M. J., Smith J. T., Popa S. M., Acohido B. V., Crowley W. F., Seminara S., Clifton D. K., Steiner R. A.* A role for kisspeptins in the regulation of gonadotropin secretion in the mouse // Endocrinology.–2004.–**145**, N 9.–P. 4073–4077.
91. *Messager S., Chatzidaki E. E., Ma D., Hendrick A. G., Zahn D., Dixon J., Thresher R. R., Malinge I., Lomet D., Carlton M. B., Colledge W. H., Caraty A., Aparicio S. A.* Kisspeptin directly stimulates gonadotropin-releasing hormone release via G protein-coupled receptor 54 // Proc. Natl Acad. Sci. USA.–2005.–**102**, N 5.–P. 1761–1766.
92. *Navarro V. M., Castellano J. M., Fernandez-Fernandez R., Tovar S., Roa J., Mayen A., Barreiro M. L., Casanueva F. F., Aguilar E., Dieguez C., Pinilla L., Tena-Sempere M.* Effects of KiSS-1 peptide, the natural ligand of GPR54, on follicle-stimulating hormone secretion in the rat // Endocrinology.–2005.–**146**, N 4.–P. 1689–1697.
93. *Navarro V. M., Castellano J. M., Fernandez-Fernandez R., Tovar S., Roa J., Mayen A., Nogueiras R., Vazquez M. J., Barreiro M. L., Magni P., Aguilar E., Dieguez C., Pinilla L.,Tena-Sempere M.* Characterization of the potent luteinizing hormone-releasing activity of KiSS-1 peptide, the natural ligand of GPR54 // Endocrinology.–2005.–**146**, N 1.–P. 156–163.
94. *Thompson E. L., Patterson M., Murphy K. G., Smith K. L., Dhillo W. S., Todd J. F., Ghatei M. A., Bloom S. R.* Central and peripheral administration of kisspeptin-10 stimulates the hypothalamic-pituitary-gonadal axis // J. Neuroendocrinol.–2004.–**16**, N 10.–P. 850–858.

95. *Thompson E. L., Murphy K. G., Patterson M., Bewick G. A., Stamp G. W., Curtis A. E., Cooke J. H., Jethwa P. H., Todd J. F., Ghatei M. A., Bloom S. R.* Chronic subcutaneous administration of kisspeptin-54 causes testicular degeneration in adult male rats // Am. J. Physiol. Endocrinol. Metab.–2006.–**291**, N 5.–E1074–1082.
96. *Plant T. M., Ramaswamy S., Dipietro M. J.* Repetitive activation of hypothalamic G protein-coupled receptor 54 with intravenous pulses of kisspeptin in the juvenile monkey (*Macaca mulatta*) elicits a sustained train of gonadotropin-releasing hormone discharges // Endocrinology.–2006.–**147**, N 2.–P. 1007–1013.
97. *Seminara S. B., Dipietro M. J., Ramaswamy S., Crowley W. F. Jr., Plant T. M.* Continuous human metastin 45–54 infusion desensitizes G protein-coupled receptor 54-induced gonadotropin-releasing hormone release monitored indirectly in the juvenile male Rhesus monkey (*Macaca mulatta*): a finding with therapeutic implications // Endocrinology.–2006.–**147**, N 5.–P. 2122–2126.
98. *Caraty A., Smith J. T., Lomet D., Ben Said S., Morrissey A., Cognie J., Doughton B., Baril G., Briant C., Clarke I. J.* Kisspeptin synchronizes preovulatory surges in cyclical ewes and causes ovulation in seasonally acyclic ewes // Endocrinology.–2007.–**148**, N 11.–P. 5258–5267.
99. *Lents C. A., Heidorn N. L., Barb C. R., Ford J. J.* Central and peripheral administration of kisspeptin activates gonadotropin but not somatotropin secretion in prepubertal gilts // Reproduction.–2008.–**135**, N 6.–P. 879–887.
100. *Hashizume T., Saito H., Sawada T., Yaegashi T., Ezzat A. A., Sawai K., Yamashita T.* Characteristics of stimulation of gonadotropin secretion by kisspeptin-10 in female goats // Anim. Reprod. Sci.–2010.–**118**, N 1.–P. 37–41.
101. *Irwig M.S., Fraley G.S., Smith J. T., Acohido B. V., Popa S. M., Cunningham M. J., Gottsch M. L., Clifton D. K., Steiner R. A.* Kisspeptin activation of gonadotropin releasing hormone neurons and regulation of KiSS-1 mRNA in the male rat // Neuroendocrinology.–2004.–**80**, N 4.–P. 264–272.
102. *Parhar I. S., Ogawa S., Sakuma Y.* Laser-captured single digoxigenin-labeled neurons of gonadotropin-releasing hormone types reveal a novel G protein-coupled receptor (Gpr54) during maturation in cichlid fish // Endocrinology.–2004.–**145**, N 8.–P. 3613–3618.
103. *Dungan H. M., Gottsch M. L., Zeng H., Gragerov A., Bergmann J. E., Vassilatis D. K., Clifton D. K., Steiner R. A.* The role of kisspeptin-GPR54 signaling in the tonic regulation and surge release of gonadotropin-releasing hormone/luteinizing hormone // J. Neurosci.–2007.–**27**, N 44.–P. 12088–12095.
104. *d'Anglemont de Tassigny X., Fagg L. A., Carlton M. B., Colledge W. H.* Kisspeptin can stimulate gonadotropin-releasing hormone (GnRH) release by a direct action at GnRH nerve terminals // Endocrinology.–2008.–**149**, N 8.–P. 3926–3932.
105. *Anjum S., Krishna A., Sridaran R., Tsutsui K.* Localization of Gonadotropin-releasing hormone (GnRH), gonadotropin-inhibitory hormone (GnIH), kisspeptin and GnRH receptor and their possible roles in testicular activities from birth to senescence in mice // J. Exp. Zool. A Ecol. Genet. Physiol.–2012.–**317**, N 10.–P. 630–644.
106. *Zhang C., Roepke T. A., Kelly M. J., Ronnekleiv O. K.* Kisspeptin depolarizes gonadotropin-releasing hormone neurons through activation of TRPC-like cationic channels // J. Neurosci.–2008.–**28**, N 17.–P. 4423–4434.
107. *Quaynor S., Hu L., Leung P. K., Feng H., Mores N., Krsmanovic L. Z., Catt K. J.* Expression of a functional G protein-coupled receptor 54-kisspeptin autoregulatory system in hypothalamic gonadotropin-releasing hormone neurons // Mol. Endocrinol.–2007.–**21**, N 12.–P. 3062–3070.
108. *Dumalska I., Wu M., Morozova E., Liu R., van den Pol A., Alreja M.* Excitatory effects of the puberty-initiating peptide kisspeptin and group I metabotropic glutamate receptor agonists differentiate two distinct subpopulations of gonadotropin-releasing hormone neurons // J. Neurosci.–2008.–**28**, N 32.–P. 8003–8013.
109. *Liu X., Lee K., Herbison A. E.* Kisspeptin excites gonadotropin-releasing hormone neurons through a phospholipase C/calcium-dependent pathway regulating multiple ion channels // Endocrinology.–2008.–**149**, N 9.–P. 4605–4614.
110. *Pielecka-Fortuna J., Chu Z., Moenter S. M.* Kisspeptin acts directly and indirectly to increase gonadotropin-releasing hormone neuron activity and its effects are modulated by estradiol // Endocrinology.–2008.–**149**, N 4.–P. 1979–1986.
111. *Shibata M., Friedman R., Ramaswamy S., Plant T. M.* Evidence that down regulation of hypothalamic KiSS-1 expression is involved in the negative feedback action of testosterone to regulate luteinising hormone secretion in the adult male rhesus monkey (*Macaca mulatta*) // J. Neuroendocrinol.–2007.–**19**, N 6.–P. 432–438.
112. *Rometo A. M., Krajewski S. J., Voytko M. L., Rance N. E.* Hypertrophy and increased kisspeptin gene expression in the hypothalamic infundibular nucleus of postmenopausal women and ovariectomized monkeys // J. Clin. Endocrinol. Metabol.–2007.–**92**, N 7.–P. 2744–2750.
113. *Smith J. T., Dungan H. M., Stoll E. A., Gottsch M. L., Braun R. E., Eacker S. M., Clifton D. K., Steiner R. A.* Differential regulation of KiSS-1 mRNA expression by sex steroids in the brain of the male mouse // Endocrinology.–2005.–**146**, N 7.–P. 2976–2984.
114. *Roa J., Vigo E., Castellano J. M., Gaytan F., Navarro V. M., Aguilar E., Dijcks F. A., Ederveen A. G., Pinilla L., van Noort P. I., Tena-Sempere M.* Opposite roles of estrogen receptor (ER)-alpha and ERbeta in the modulation of luteinizing hormone responses to kisspeptin in the female rat: implications for the generation of the preovulatory surge // Endocrinology.–2008.–**149**, N 4.–P. 1627–1637.
115. *Estrada K. M., Clay C. M., Pompolo S., Smith J. T., Clarke I. J.* Elevated KiSS-1 expression in the arcuate nucleus prior to the cyclic preovulatory gonadotrophin-releasing hormone/lutenising hormone surge in the ewe suggests a stimulatory role for kisspeptin in oestrogen-positive feedback // J. Neuroendocrinol.–2006.–**18**, N 10.–P. 806–809.
116. *Pompolo S., Pereira A., Estrada K. M., Clarke I. J.* Colocalization of kisspeptin and gonadotropin-releasing hormone in the ovine brain // Endocrinology.–2006.–**147**, N 2.–P. 804–810.
117. *Grachev P., Li X. F, Lin Y. S., Hu M. H., Elsamani L., Paterson S. J., Millar R. P., Lightman S. L., O'Byrne K. T.* GPR54-dependent stimulation of luteinizing hormone secretion by neurokinin B in prepubertal rats // PLoS One.–2012.–**7**, N 8.–e44344.
118. *Matvienko M. G., Pustovalov A. S., Buzynska N. O., Dzerzhynsky M. E.* Morphofunctional changes in rat testes under kisspeptin influence against blockade and activation of alpha-adrenergic receptors and melatonin administration // X Int. interdisciplinary sci. conf. of students and young scientists (19–23 March 2012, Kyiv).–Kyiv, 2012.–P. 206–207.
119. *Dzerzhinsky M., Pustovalov A., Matvienko M.* Morphofunctional changes in rat testes under kisspeptin influence against blockade and activation of alpha-adrenergic receptors and melatonin administration // Reproduction in Domestic Animals.–2012.–**47**, N 2.–P. 20.

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