KiSS-1/GPR54 mRNA expression in pituitary gland and the relationship between KiSS-10 and luteinizing hormone secretion from pituitary cells of cyclic and PCOS-affected sows

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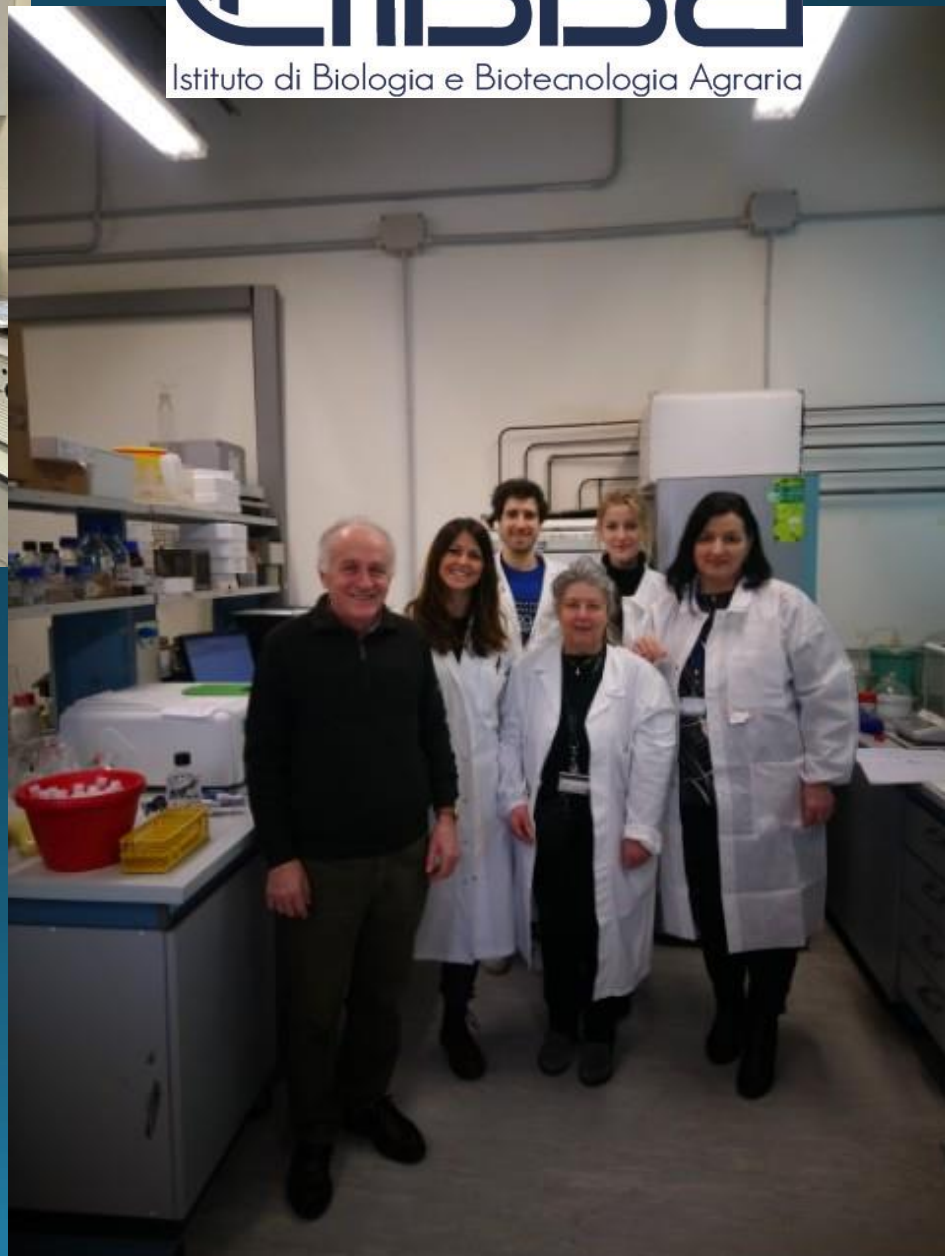
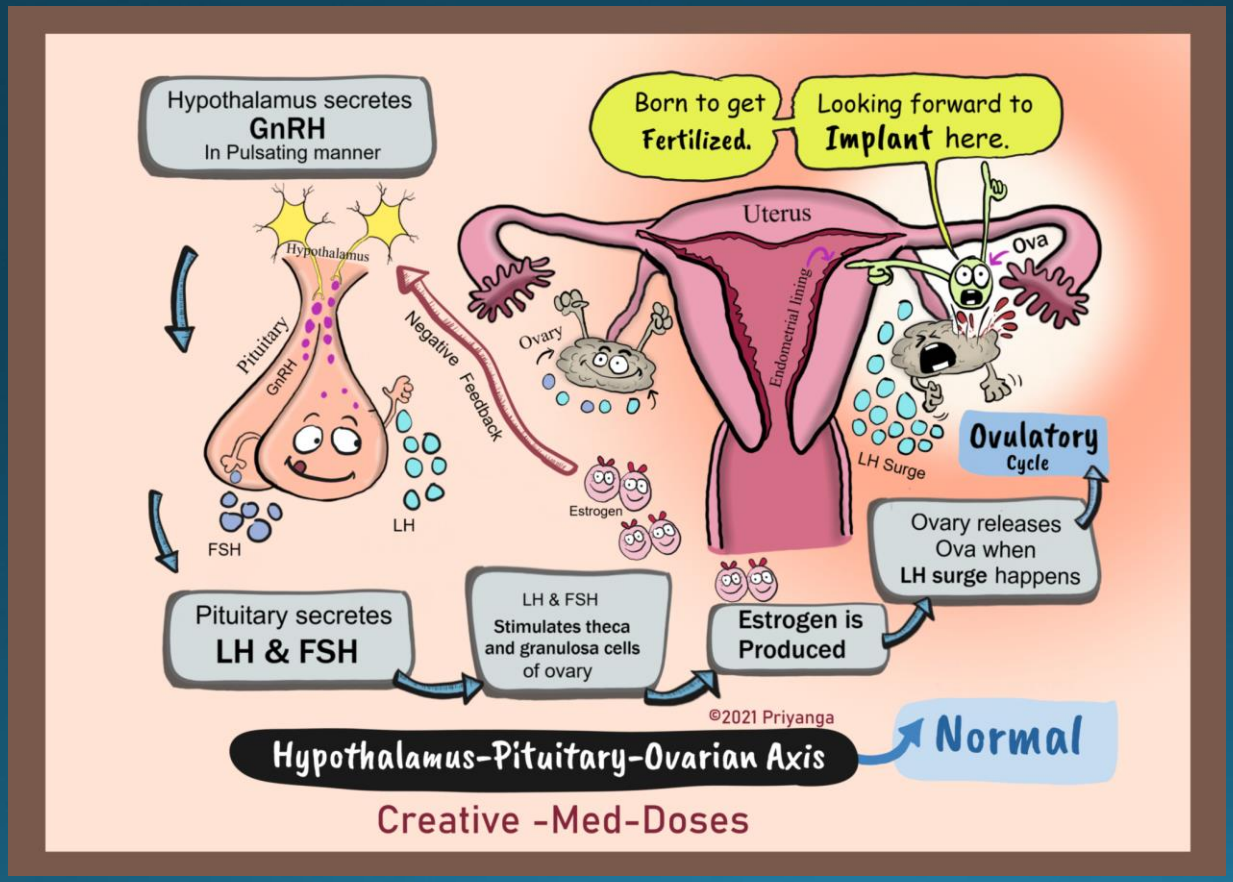


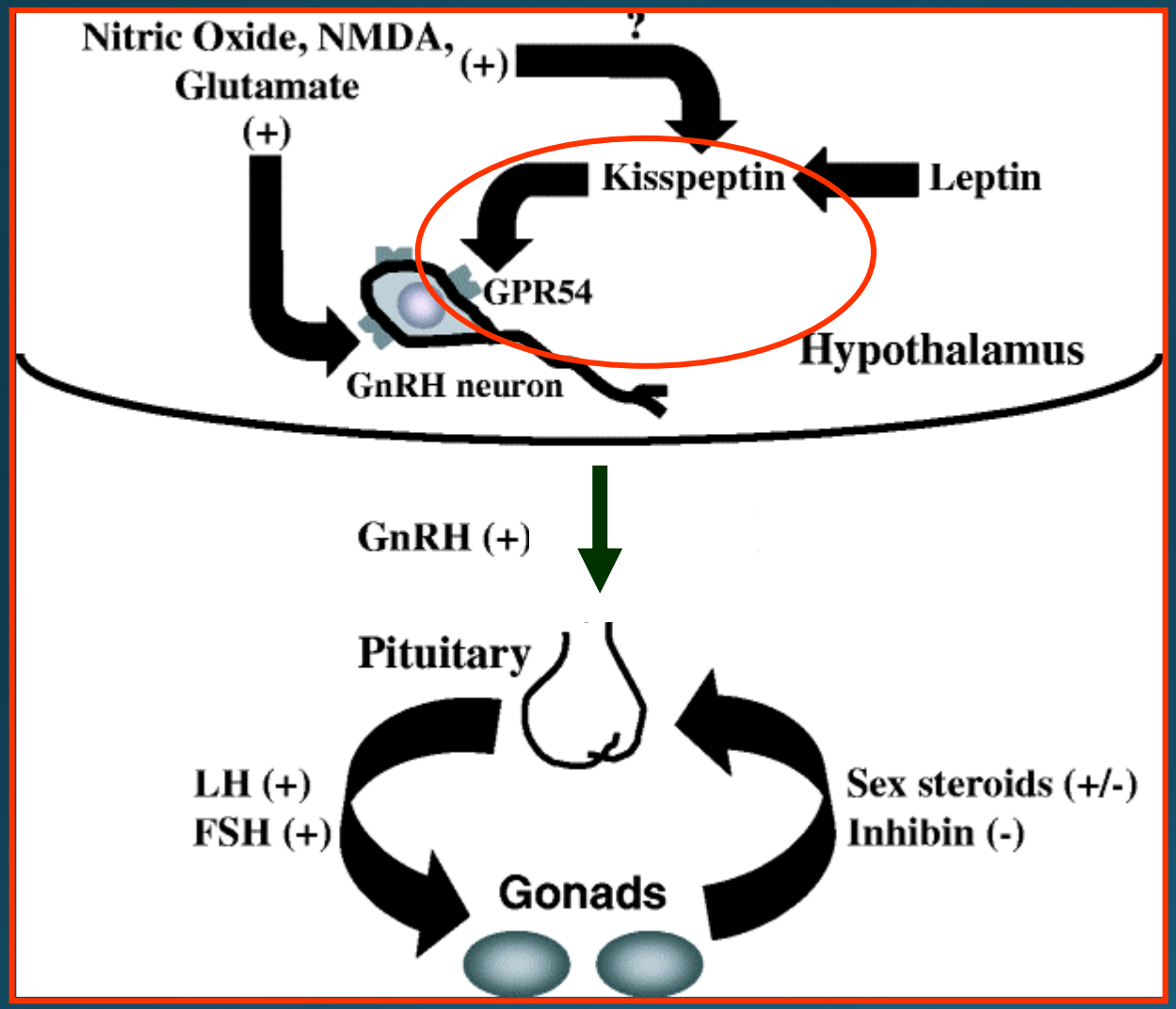
UNIWERSYTET PRZYRODNICZY W LUBLINIE

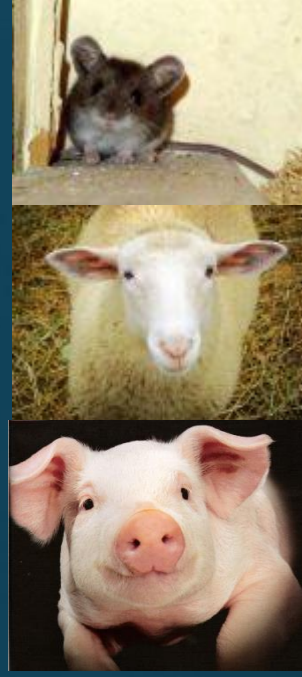
The principal role of the KiSS-1/GPR54 system

in the control
of the hypothalamic-pituitary-ovarian axis



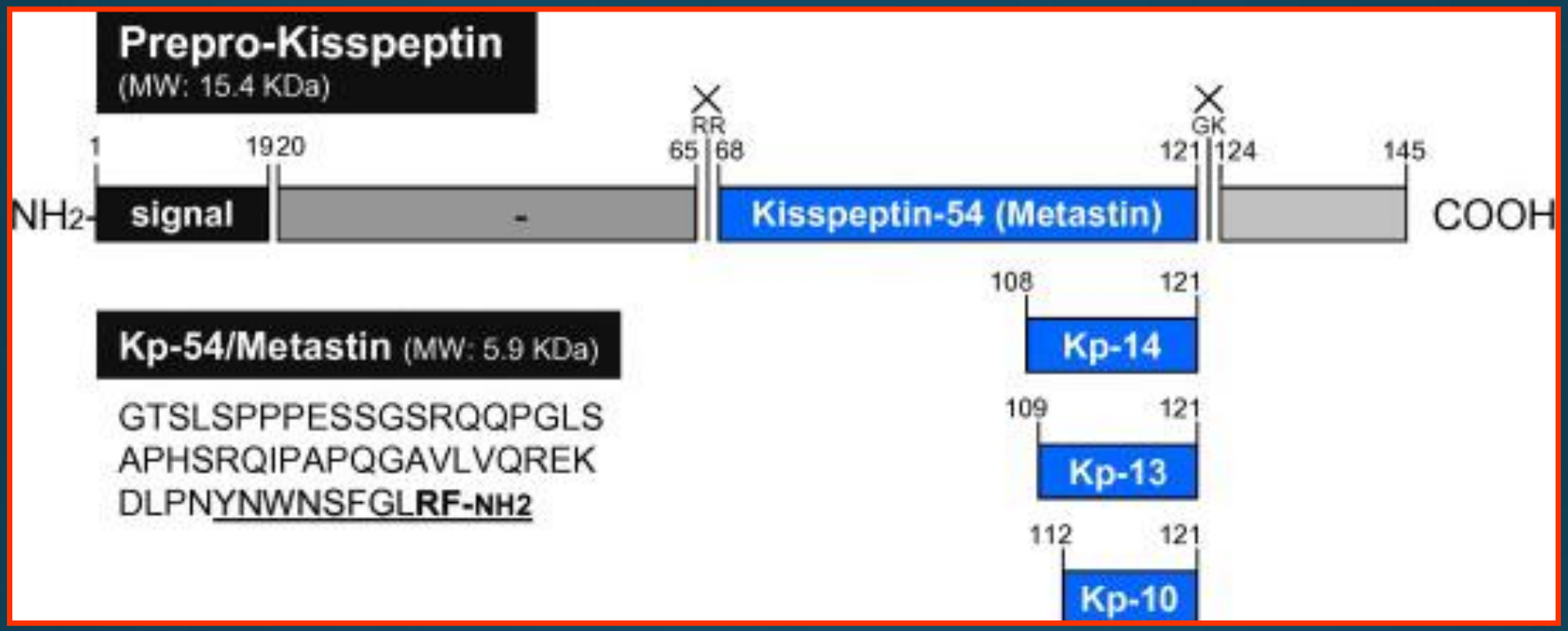
Hypothalamic-Pituitary-Ovarian axis - Creative Med Doses





GPR54 – G protein-coupled receptor

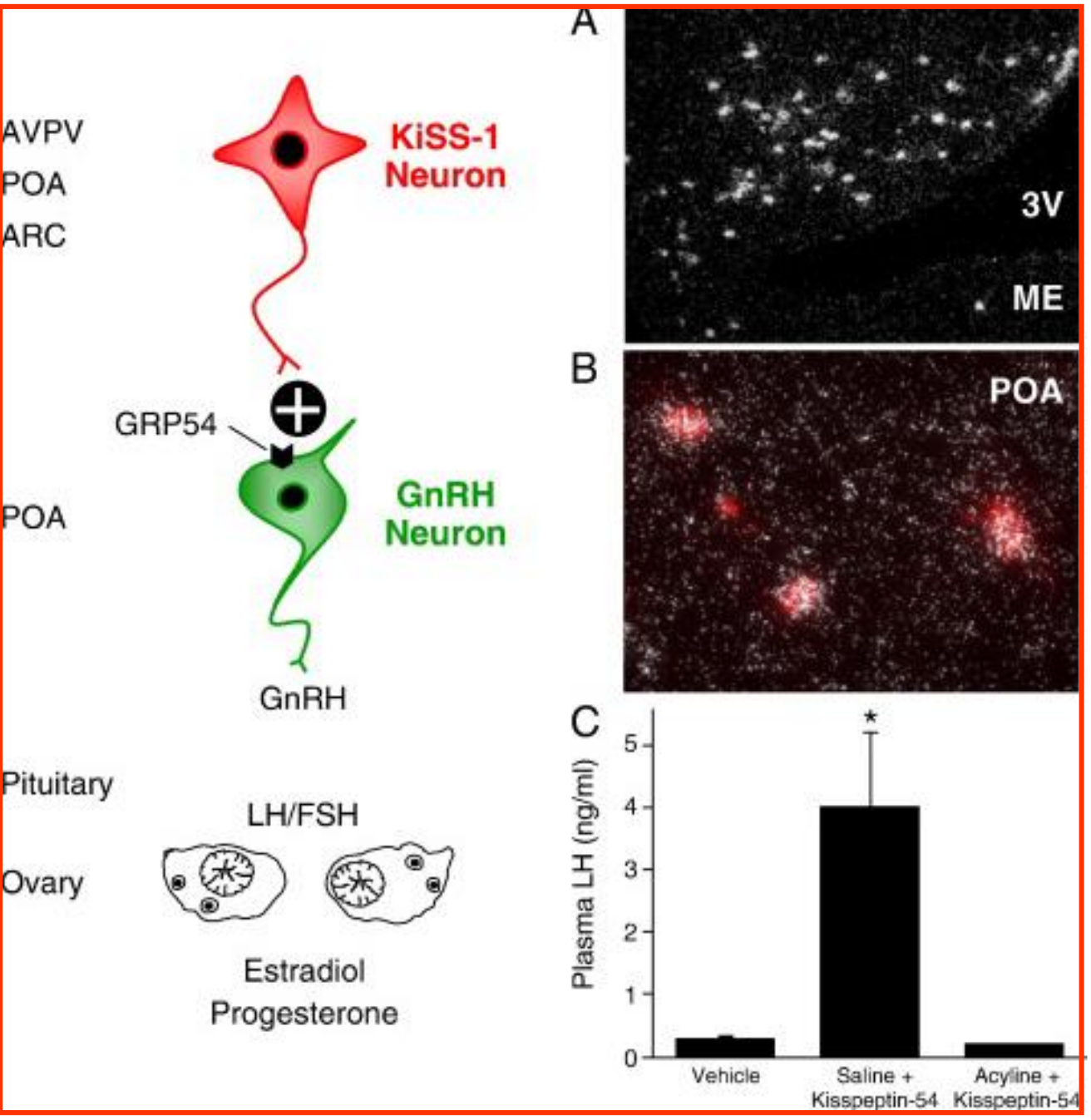
Kuohung W. et al.: Rev. Endocr. Metab. Disord. 7 (4), 2006



RF-amide family

Common sequence **Arg-Phe-NH_2C**

Roa J. et al.: , Frontiers in Neuroendocrinology 29, 2008



A – KiSS-1 mRNA in sheep ARC neurons (silver grains)

B - co-expression of GnRH (red) and GPR54 (silver grains) in POA neurons of rats

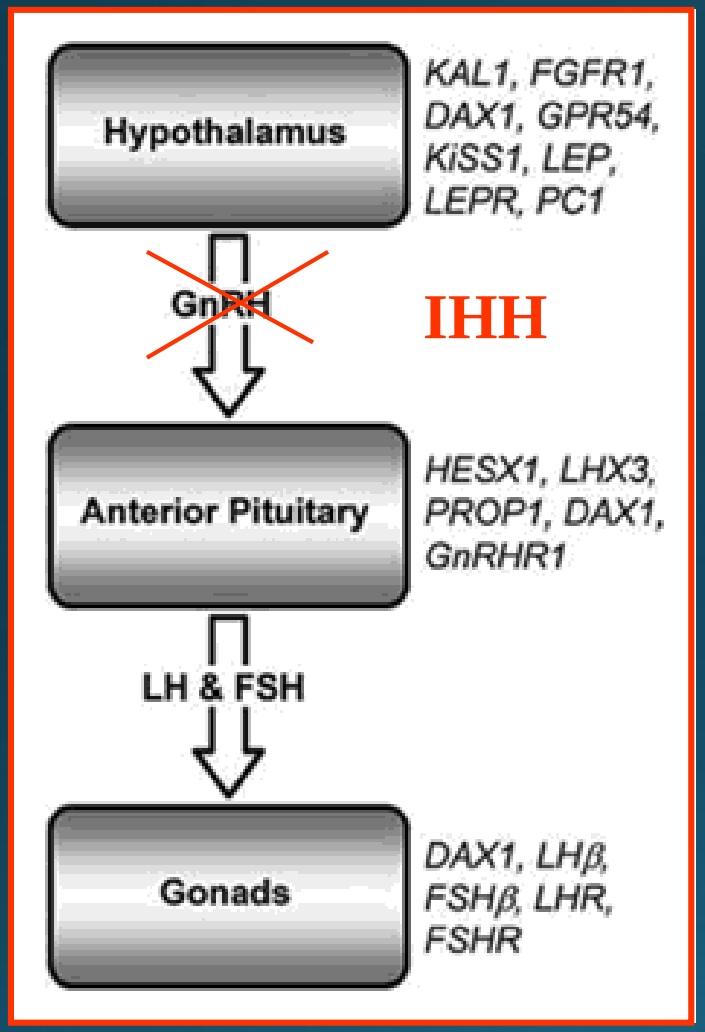
C – effect of kisspeptin-54 on LH concentration in peripheral blood of rats

Kisspeptin expression:

- hypothalamus – AVPV, POA, ARC
- amygdala
- pituitary gland
- ovaries
- testes
- placenta
- pancreas
- liver
- small intestine

GPR54 expression:

- hypothalamus – AVPV, POA, ARC
- amygdala
- pituitary gland
- ovaries
- testes
- placenta
- pancreas
- small intestine
- heart
- skeletal muscle
- kidneys
- lungs
- thymus

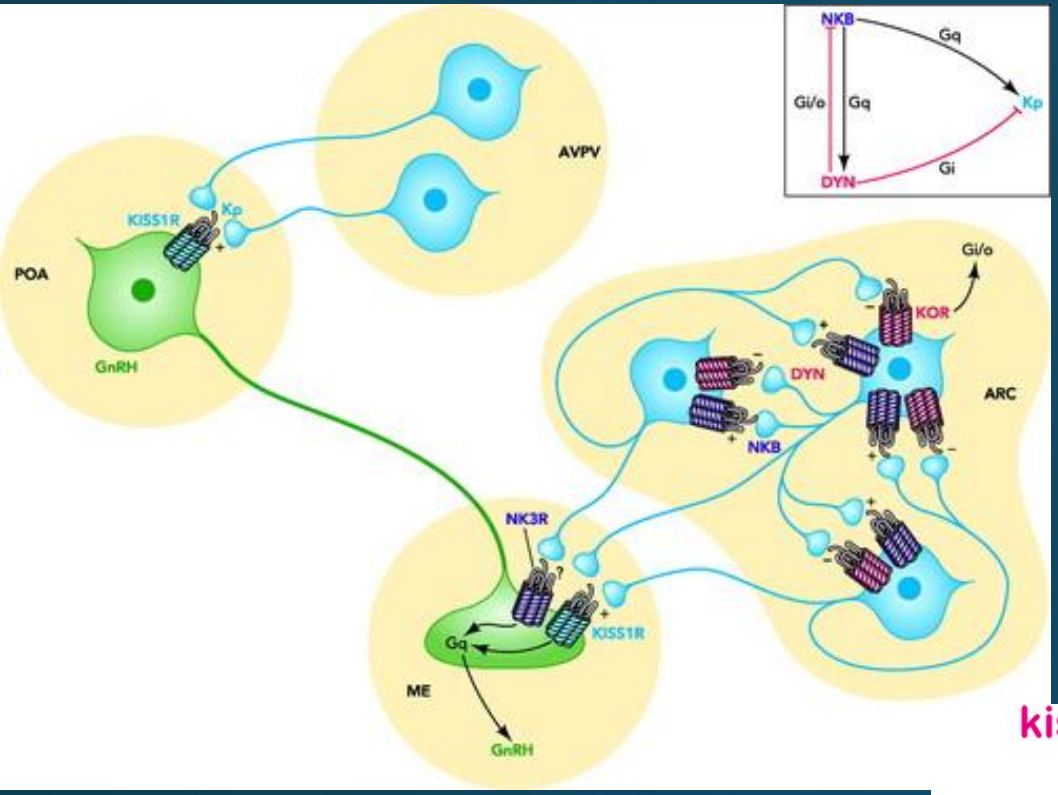


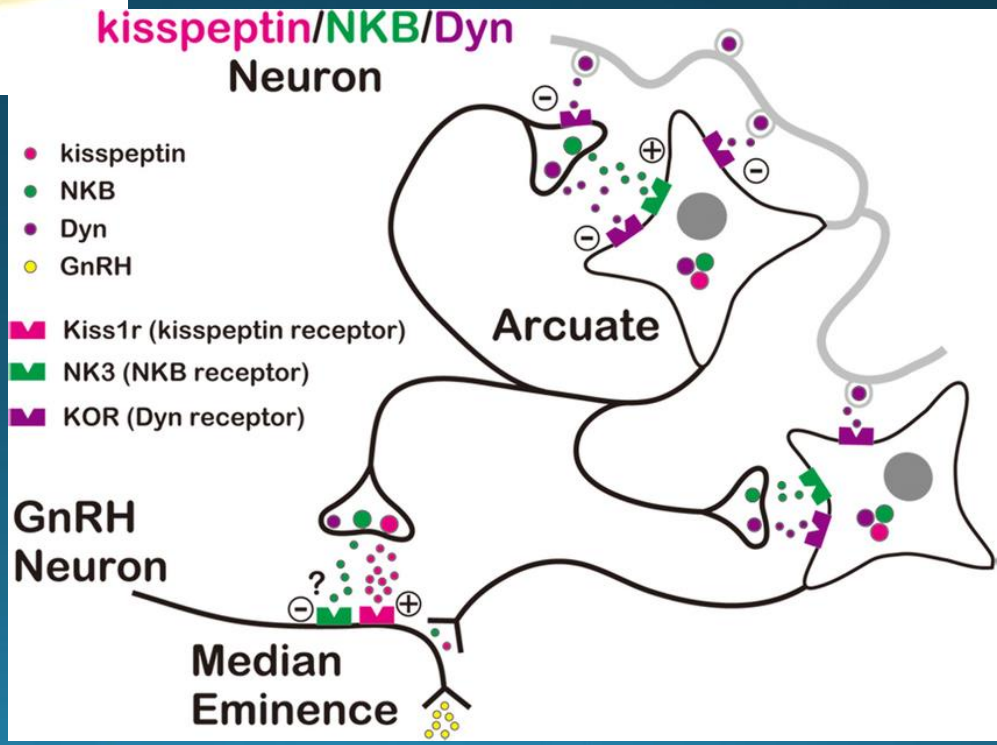
Symptoms of isolated secondary hypogonadism (IHH - isolated hypogonadotrophic hypogonadism):

- low levels of gonadotropins
- low levels of ovarian steroid hormones
- reduced ovarian weight
- narrowing of the lumen of the uterine horns
- only primary and secondary follicles are present in the ovaries
- high number of atretic follicles
- infertility

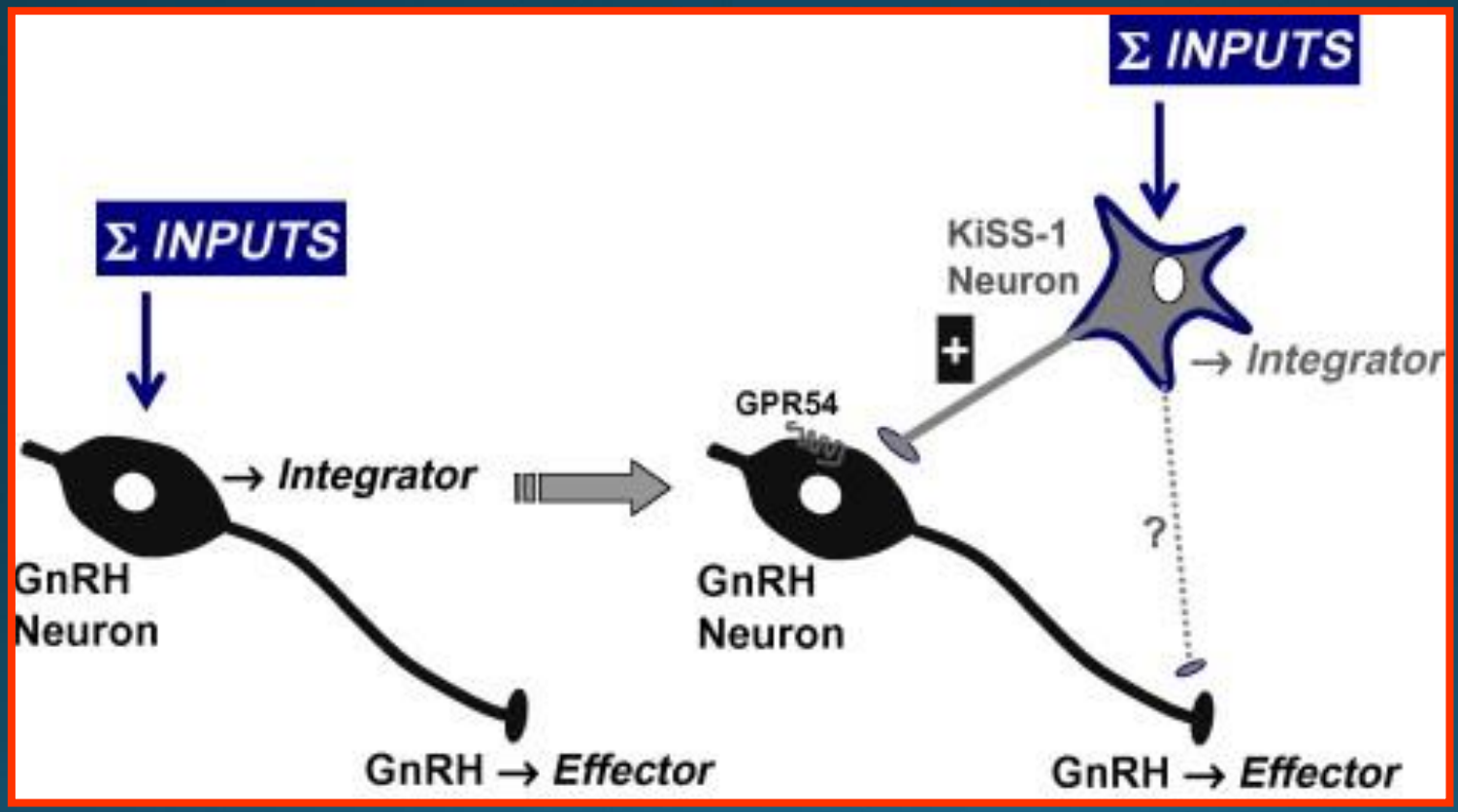
The contribution of kisspeptin in the regulation of hypothalamic-pituitary-ovarian axis

I. HYPOTHALAMUS

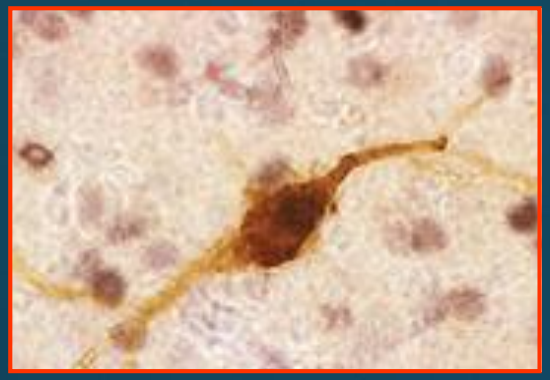




DOI: 10.1523/JNEUROSCI.5848-09.2010



Roa J. et al.: , Frontiers in Neuroendocrinology 29, 2008

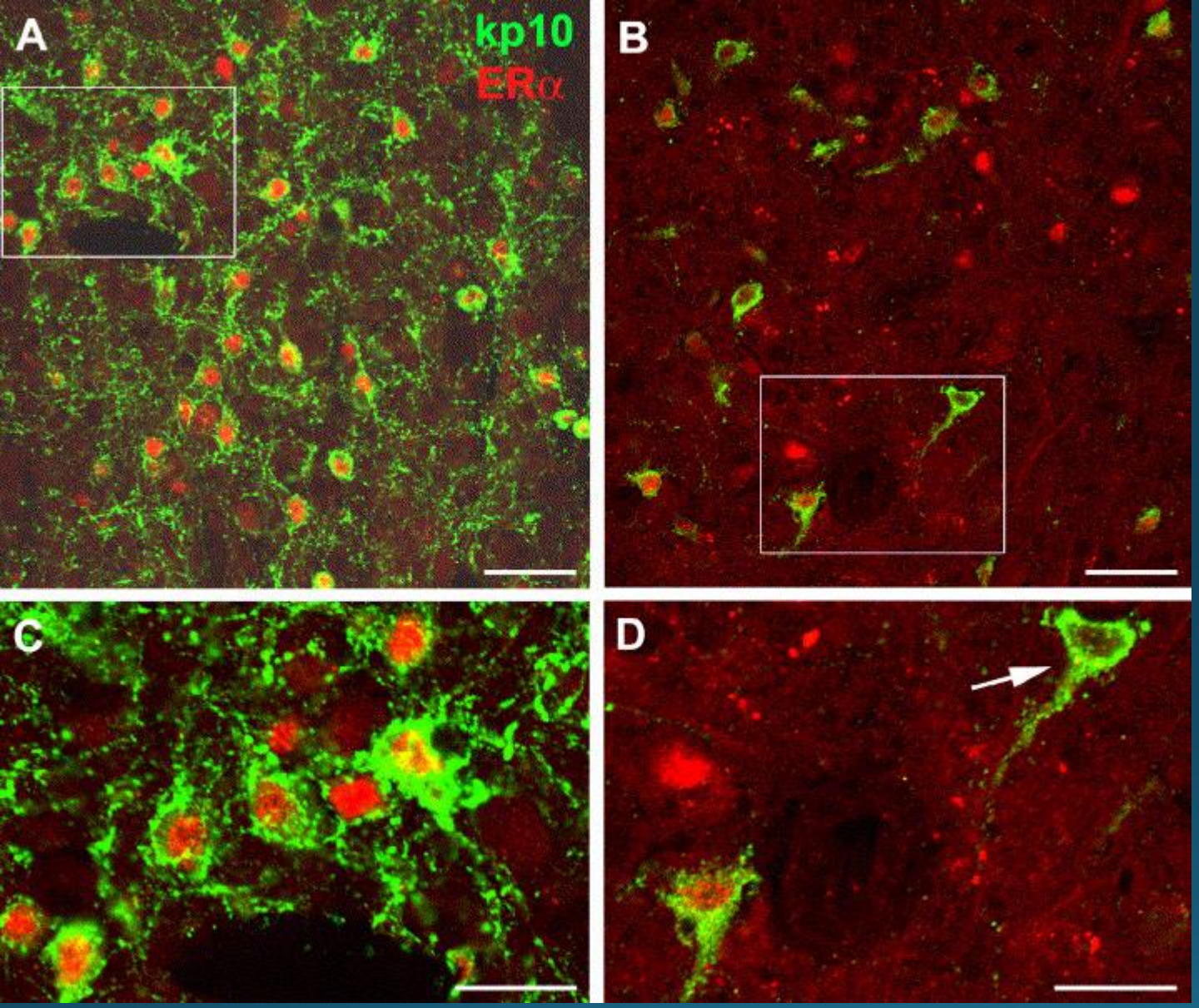


GnRH neurons

90% - the presence of kisspeptin

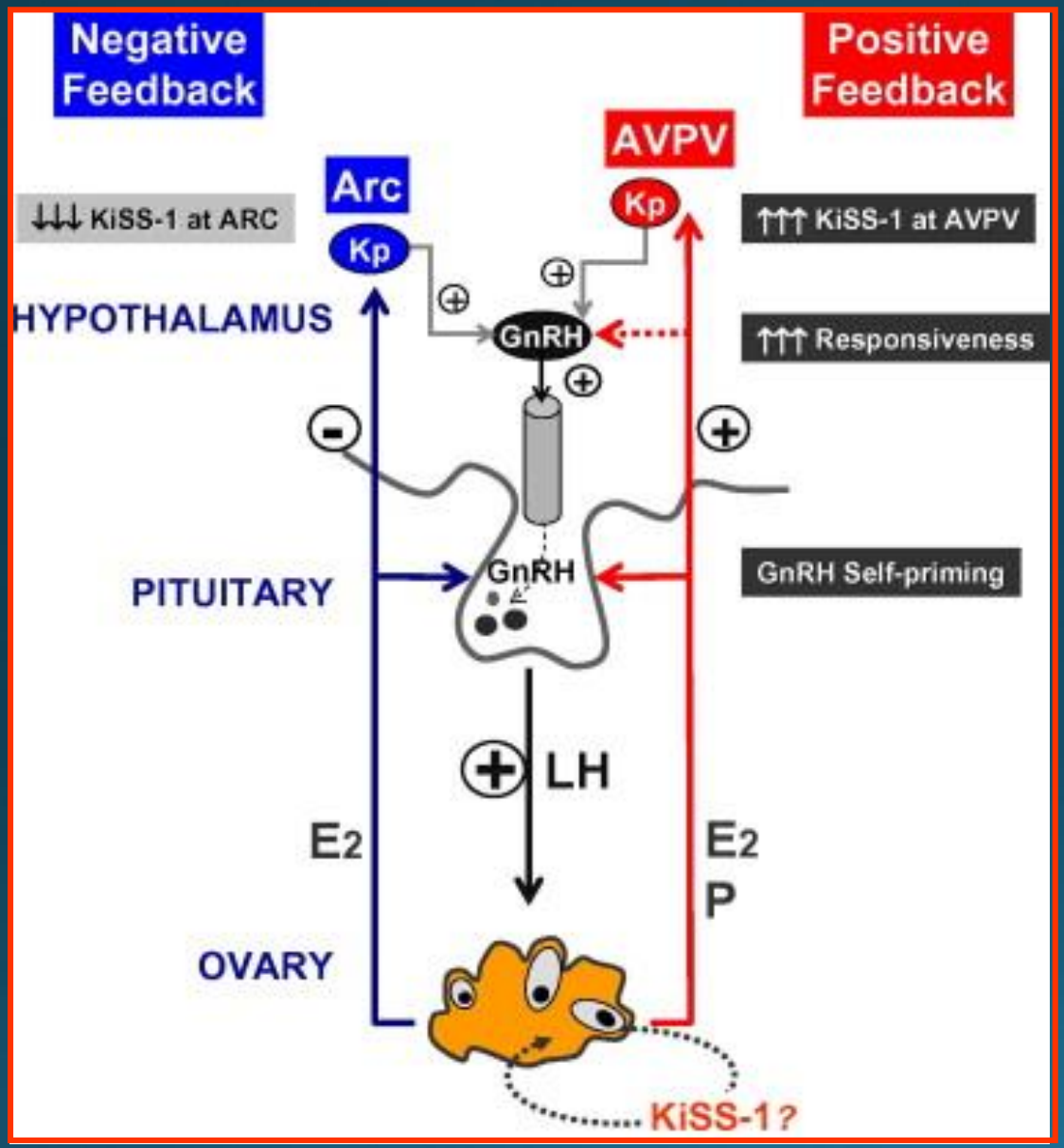
77% - expression of GPR54

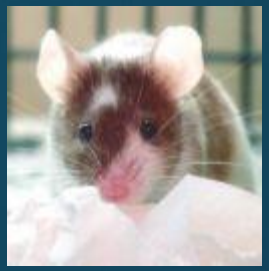
86% - increase in expression of the Fos protein under the influence of kisspeptin



Localization of kisspeptin-10 (green) and ER receptors (red) in arcuate nucleus neurons (A and C) and preoptic area (B and D) in a sheep (double immunofluorescence labeling). In the arcuate nucleus, in contrast to the preoptic area, most kp-10ir neurons show high nuclear immunoreactivity for ER.

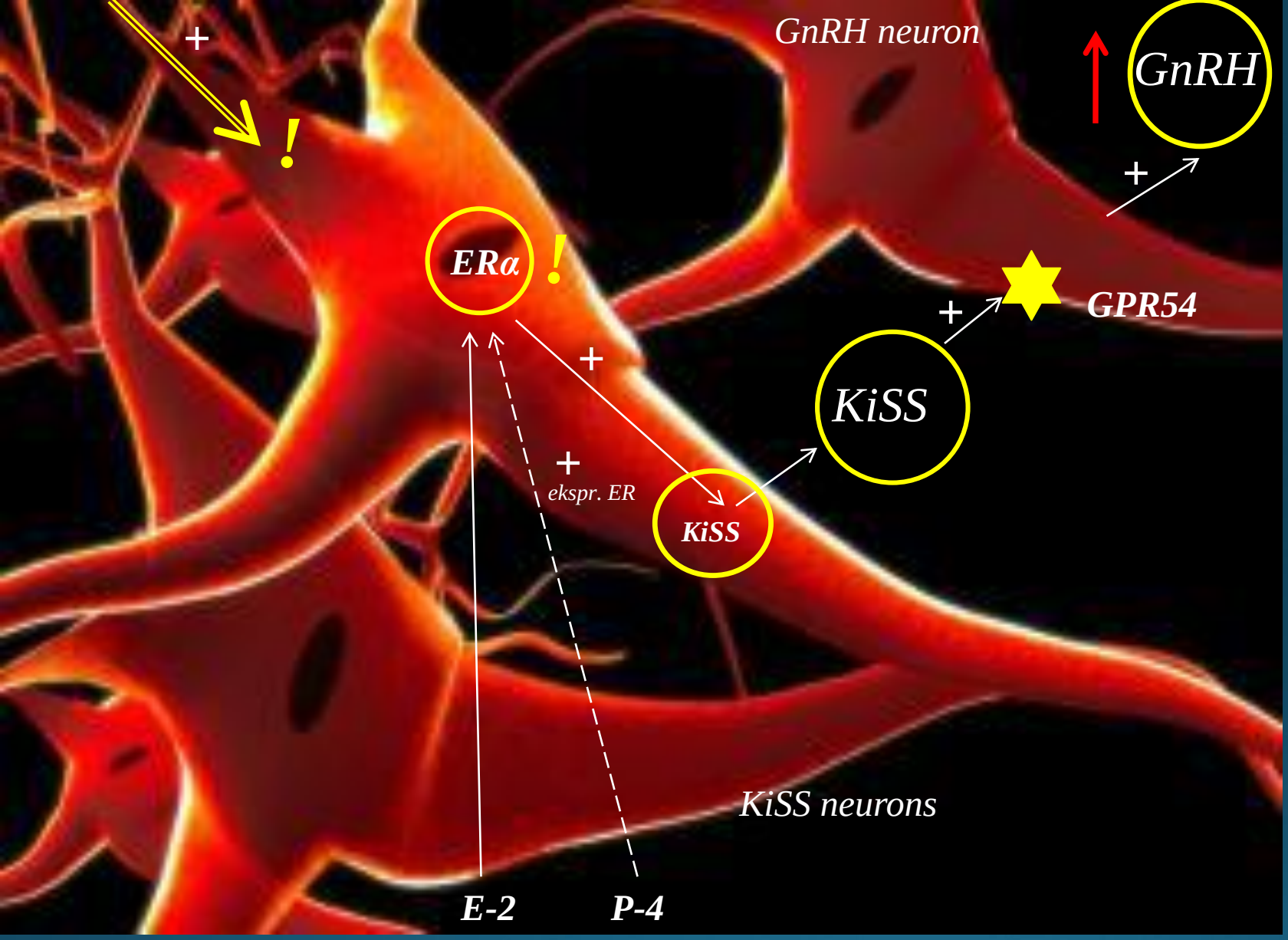
Franceschini I. et al.: Neuroscience Letters 401, 2006



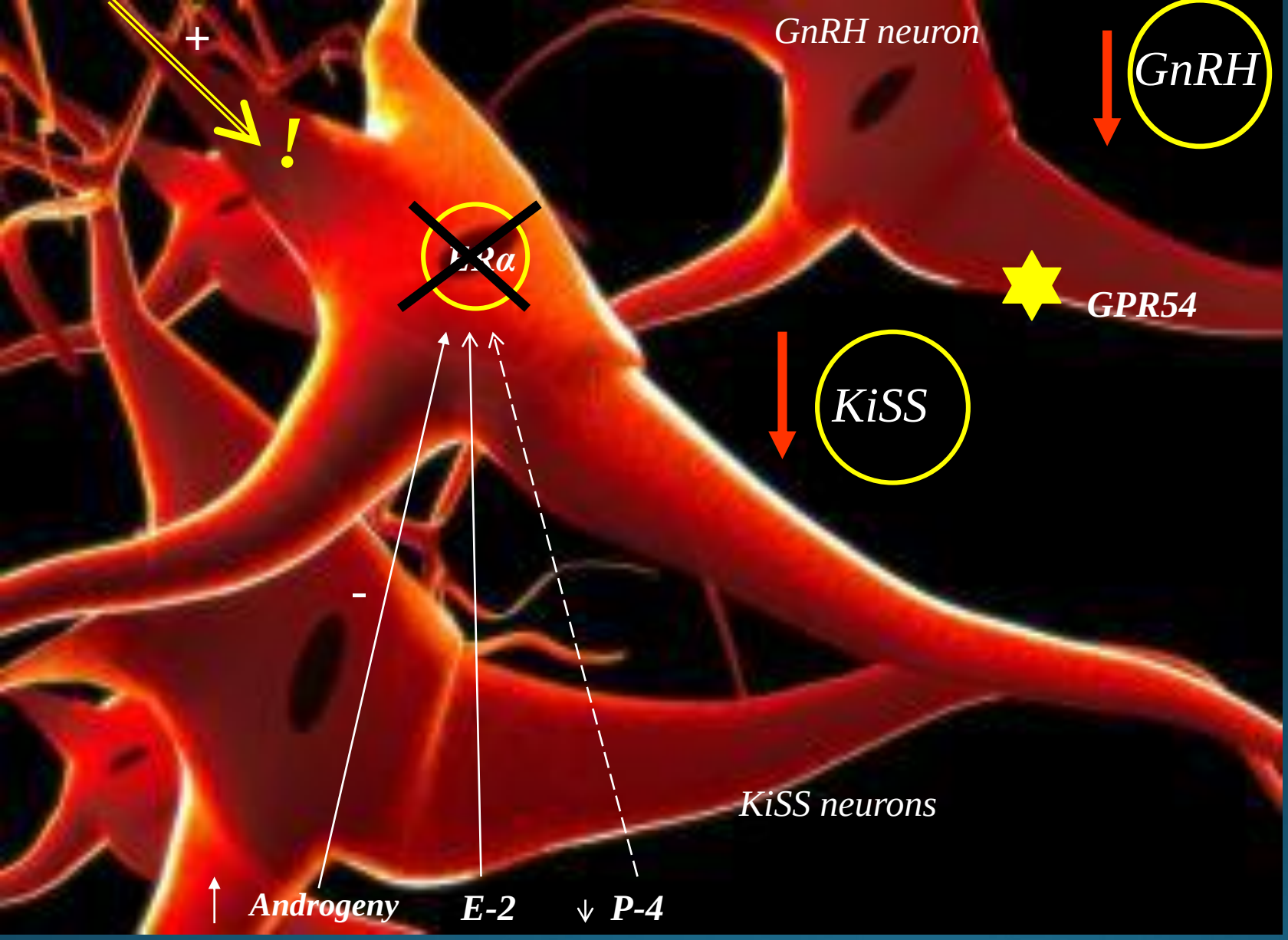


Mechanism of negative and positive estradiol feedback involving kisspeptins in rodents.

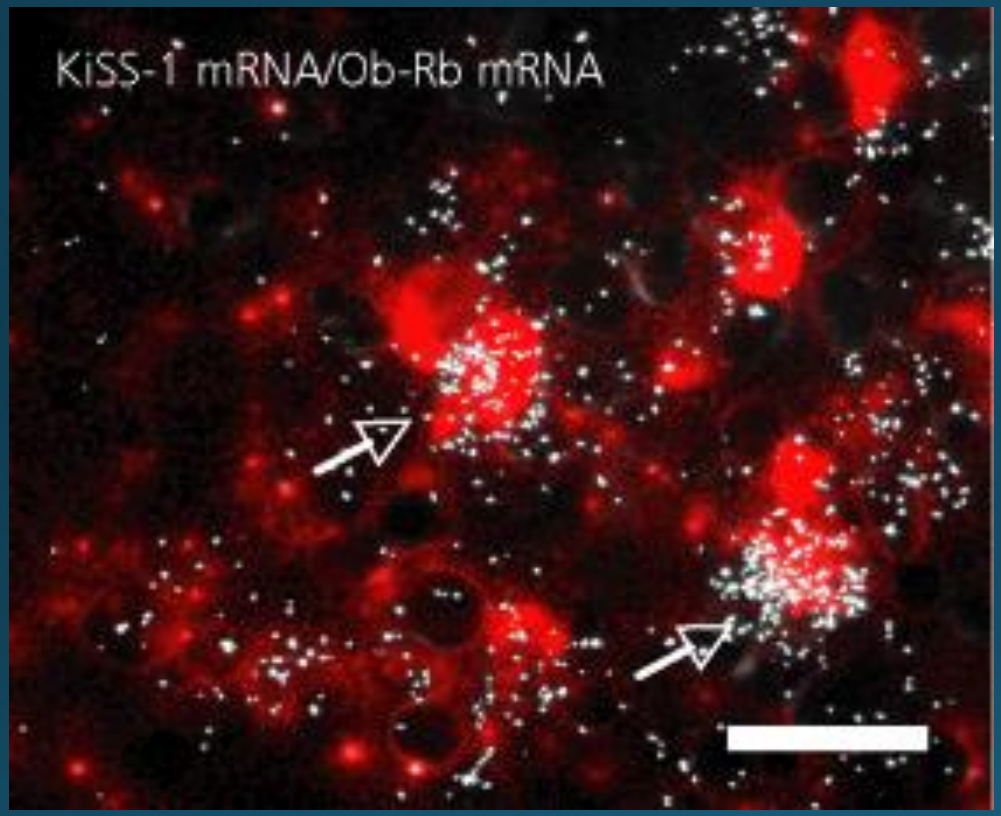
Roa J. et al.: , Frontiers in Neuroendocrinology 29, 2008



Contribution of the KiSS-1/GPR54 system to stimulating the preovulatory GnRH surge in response to 17β-estradiol



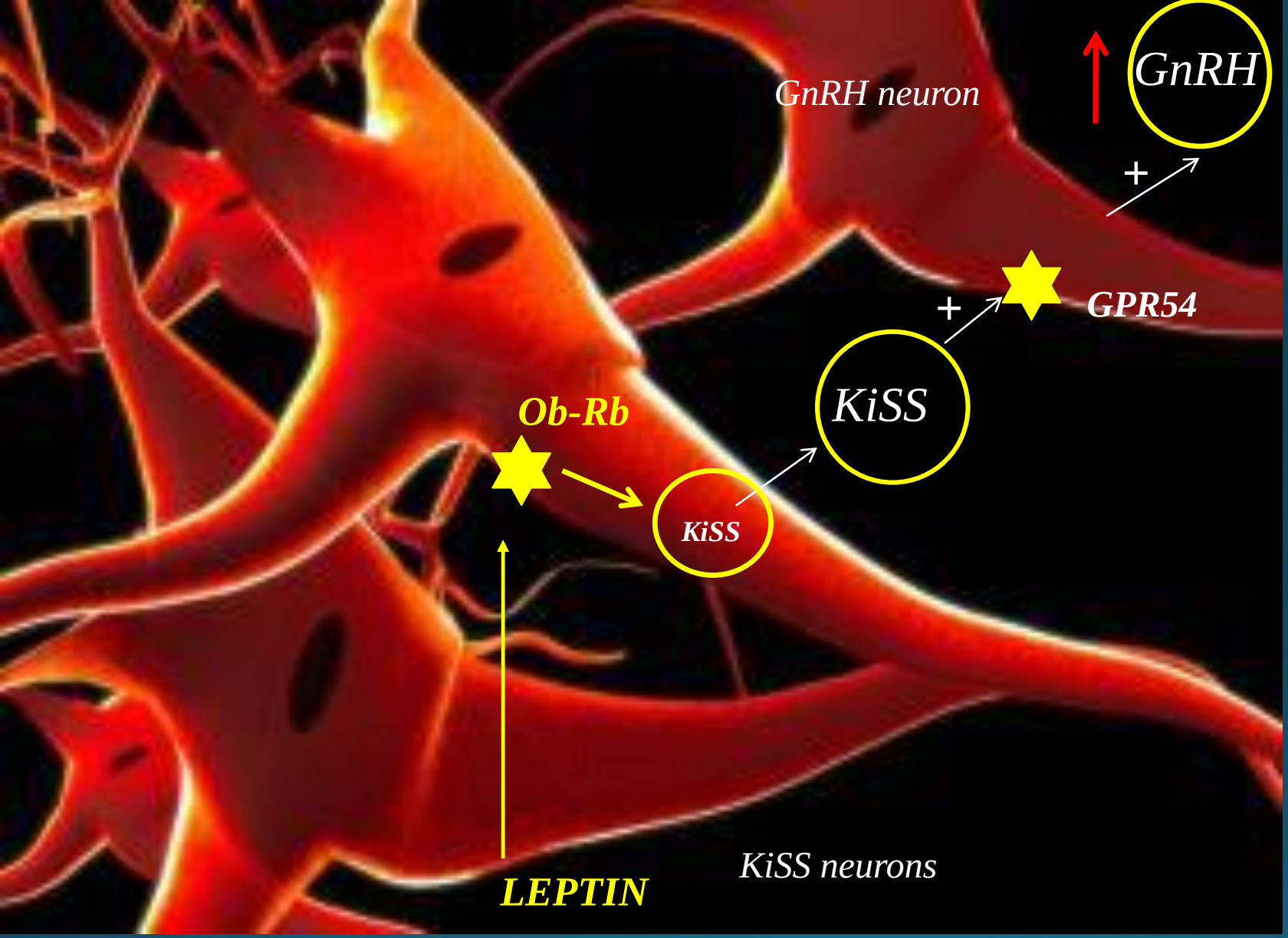
Mechanisms responsible for the suppression or lack of preovulatory GnRH surge related to regulation of kisspeptin neurons activity by ovarian steroid hormones



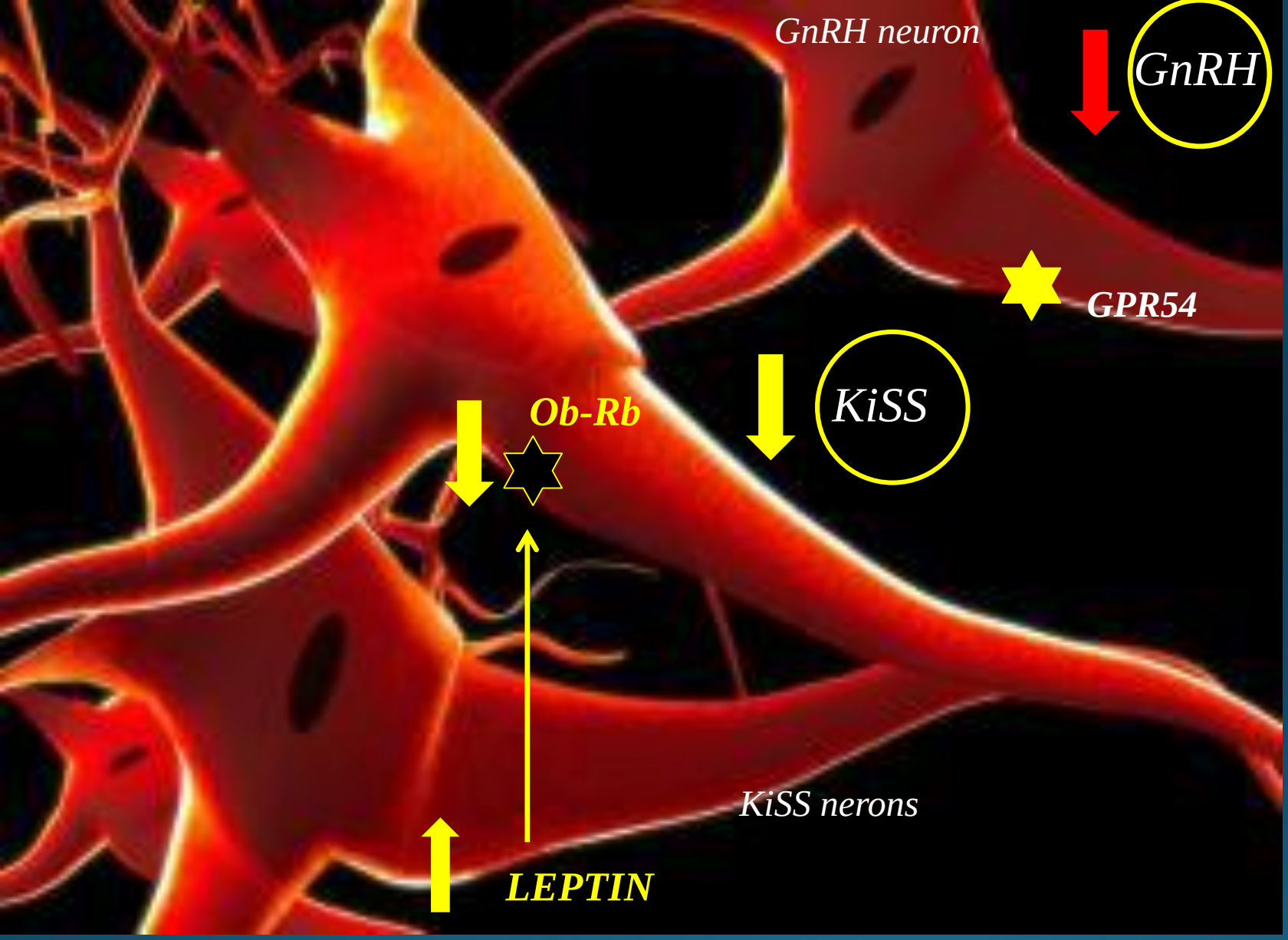
Co-expression of KiSS-1 mRNA (red) and Ob-Rb mRNA (silver grains) in sheep arcuate nucleus.

Approximately 42% of KiSS-1 neurons express Ob-Rb mRNA.

Roa J. et al.: , Frontiers in Neuroendocrinology 29, 2008



The role of leptin in stimulating GnRH secretion *via* the KiSS-1/GPR54 hypothalamic system

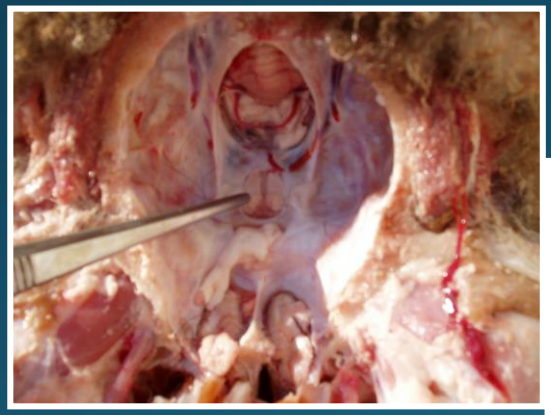


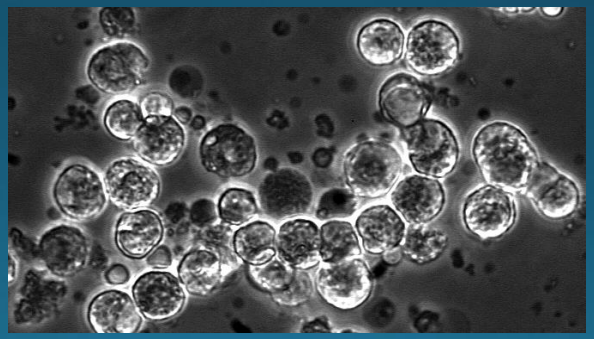
Hyperleptinemia can cause suppression or inhibition of GnRH release

The principal role of the KiSS/GPR54 system

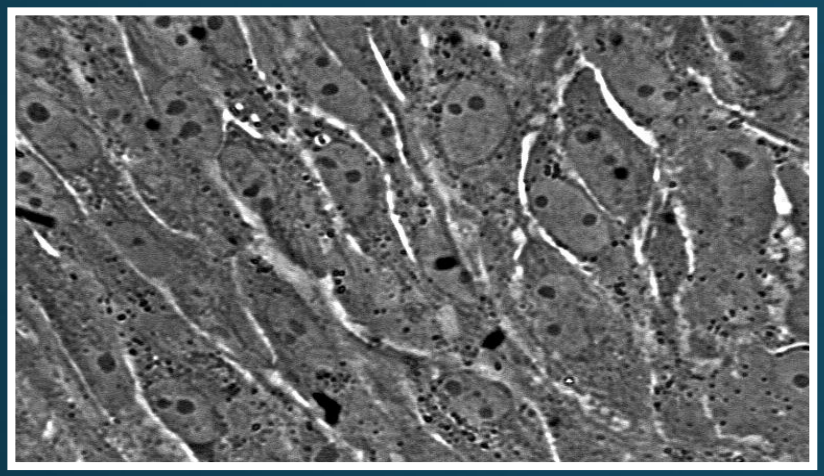
in the control
of the hypothalamic-pituitary-ovarian axis

II. Pituitary gland





Author's pictures (Urszula Kosior-Korzecka)



KiSS-10 causes an increase in the concentration of free Ca 2+ ions in about 62% of cells

estrogens increase kiss-1 expression

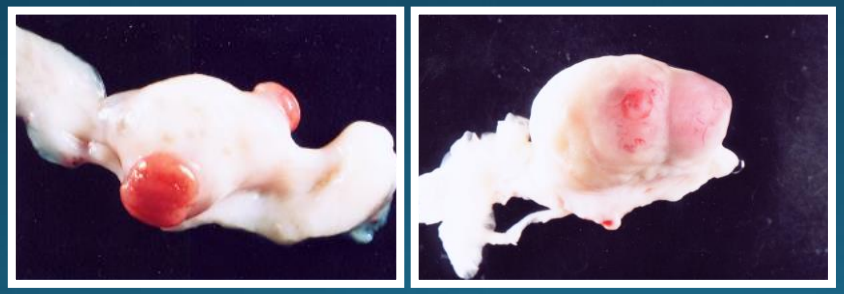
expression of *kiss-1 and gpr54 genes*

Author's photo (Urszula Kosior-Korzecka)

The principal role of the KiSS/GPR54 system

in the control
of the hypothalamic-pituitary-ovarian axis

III. OVARY



Author's pictures (Urszula Kosior-Korzecka)

kiss-1 and *gpr54* expression in theca cells, corpus luteum and interstitial cells

kisspeptins can control ovulation by regulating the activity of proteases

mutations in the *gpr54* gene cause a reduction in 17β-estradiol levels

mutations in the *gpr54* gene cause a reduction in 17β-estradiol levels

kiss-1 expression increases under the influence of preovulatory gonadotropin release

KiSS-1/GPR54 system is a crucial element in a control mechanisms of development and reproductive processes, such as:

initiation of puberty, secretion of gonadotropins and metabolic regulation of fertility.

The theory about the superior role of GnRH, and then leptin, has undergone some modification in recent years after the discovery of kisspeptins and GPR54.

KiSS-1 neurons in the hypothalamus are now considered to be a fundamental element of the HPO axis, involved in both receiving and integrating key signals such as ovarian steroids and metabolic factors.

KiSS-1/GPR54 was considered to be a missing link connecting individual levels of the HPO axis into one coherent and functional system.

Praca oryginalna *Original paper*

Kisspeptin-10 and peptide 234 modulate GnRH--induced follicle-stimulating hormone secretion from anterior pituitary cells of prepubertal lambs in vitro*)

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Received 04.03.2014 *Accepted 08.04.2014*

Kosior-Korzecka U., Radwańska P., Witkowska K., Patkowski K., Wójcik M., Wessely-Szponder J., Bobowiec R.

Kisspeptin-10 and peptide 234 modulate GnRH-induced follicle-stimulating hormone secretion from anterior pituitary cells of prepubertal lambs in vitro

Summary

The aim of the study was to analyze the contribution of kisspeptin-10 (KiSS-10) and peptide 234 (kisspeptin-234, potent neutral antagonist of GPR-54 receptors) to the modulation of GnRH-induced follicle-stimulating hormone (FSH) secretion from anterior pituitary cells of prepubertal ram lambs in vitro. Pituitary cells were cultured in McCoy 5A medium without hormones (the negative control), with GnRH (4×10^{-9} M, the positive control), with GnRH (4×10^{-9} M) and 10^{-11}-10^{-8} M of KiSS-10 or GnRH (4×10^{-9} M), 10^{-11}-10^{-8} M of KiSS-10 and 10^{-7} M of peptide 234. After 6, 12 and 48 h of the experiment, the secretion of follicle-stimulating hormone was determined. The obtained results show that FSH secretion from anterior pituitary cells of ram lambs in vitro was dependent on kisspeptin-10 concentration in the culture medium. Addition of 10^{-11}-10^{-9} M of KiSS-10 caused an increase in FSH secretion ($r = 0.73$, 0.90, and 0.82 after 6, 12 and 48 h, respectively) compared to both the negative and positive control, whereas the highest concentration of KiSS-10 (10^{-8} M) suppressed the secretion of this gonadotropin. The most stimulating effect was observed under the influence of 10^{-9} M of KiSS-10. However, concurrent cell exposure to peptide 234 abolished the stimulating action of kisspeptin-10 on FSH secretion. The negative correlation between FSH secretion and 10^{-11}-10^{-8} M of KiSS-10 in this condition was found ($r = -0.68$, –0.91, and –0.81 after 6, 12 and 48 h, respectively). This confirms that the observed increase in GnRH-induced FSH secretion was a direct effect of KiSS-10 on the anterior pituitary cells of prepubertal ram lambs.

Keywords: kisspeptin-10, peptide 234, follicle-stimulating hormone, anterior pituitary cells

Small Ruminant Research 144 (2016) 6–16

Contents lists available at ScienceDirect

Small Ruminant Research

journal homepage: www.elsevier.com/locate/smallrumres

Relationships between leptin, the KiSS-1/GPR54 system and thyrotropic axis activity in ewe lambs predisposed to the delayed puberty

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ARTICLE INFO

Article history:
Received 8 November 2015
Received in revised form 25 July 2016
Accepted 26 July 2016
Available online 27 July 2016

Keywords:
Leptin
KiSS-1/GPR54 system
Thyrotropic axis
Ewe lambs
Puberty
Laparoscopy

ABSTRACT

In the present study we compared body weight gains, some factors involved in the initiation of sexual maturation (pituitary expression of KiSS-1 and G protein-coupled receptors (GPR54), plasma concentrations of kisspeptin-10 (KiSS-10), leptin, thyroid-stimulating hormone (TSH), free thyroxin (fT4)) and the time of the first ovulation in ewe lambs predisposed to delayed puberty and control animals. The experiment was carried out on 114 ewes and 64 female lambs divided according to their birth type and body weight of their mothers. All ewe lambs were weighed at birth and every two weeks thereafter, until eight months of postnatal age. From four to eight months of postnatal age at monthly intervals, blood samples were collected from the jugular vein of all ewe lambs. Then, daily weight gains were recorded and plasma KiSS-10, leptin, TSH and fT4 concentrations were analysed by ELISA using species-specific antibodies. Starting from six months of age, the pituitary expression of KiSS-1/GPR54 mRNA was determined by Real Time-PCR. The activity of the ovaries was estimated using laparoscopy. The results obtained showed that the time of the onset of puberty in the ewe lambs depended on the mother's body mass, the plasma leptin level, and the birth type (singleton/twin). It was observed that the elevation of leptin concentration up to 3.35 ± 0.26–3.60 ± 0.19 ng/mL was associated with the initiation of puberty. Conversely, the hyperphysiological leptin levels found in ewe lambs, which were twin offspring of fatty sheep, were correlated with puberty delayed until the age of ten months. Moreover, it was found that a significant increase in pituitary KiSS-1 mRNA expression (1.40 ± 0.12–1.63 ± 0.22) (relative KiSS-1 mRNA expression level, ratio of KiSS-1 mRNA/GAPDH mRNA) and plasma KiSS-10 concentration (31.26 ± 1.54 ng/mL–32.24 ± 2.25 ng/mL) was connected with the occurrence of the first ovulation. On the other hand, GPR54 mRNA expression in the pituitary decreased around the time of the first ovulation. Also, the increase in thyroid gland activity was dependent on the mother's body mass as well as birth type and occurred around the time of the first ovulation.

Research in Veterinary Science 105 (2016) 180–187

Contents lists available at ScienceDirect

Research in Veterinary Science

journal homepage: www.elsevier.com/locate/rvsc

Relationships between leptin, KiSS-1/GPR54 expression and TSH secretion from pituitary cells of pubertal ewes *in vitro*

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ARTICLE INFO

Article history:
Received 28 May 2015
Received in revised form 8 February 2016
Accepted 21 February 2016
Available online xxxx

Keywords:
Kisspeptin
Leptin
Thyroid-stimulating hormone
Pubertal ewes
Pituitary cells *in vitro*

ABSTRACT

Kisspeptin and leptin play a crucial role in the puberty of sheep as they initiate the activity of hypothalamic-pituitary-ovarian axis. Also hormones of thyrotropic axis are probably involved in this process. The aim of study was to analyze the impact of leptin on kisspeptin-10 secretion as well as kisspeptin-1 and G protein-coupled receptor (GPR54) mRNA expression in pituitary cells of pubertal ewes *in vitro*. The influence of kisspeptin on TSH secretion was also examined. Cells were cultured in McCoy's 5A medium without hormones; with 10^{-10}–10^{-5} M of leptin; with 10^{-11}–10^{-5} M of kisspeptin-10; with peptide 234 (10^{-7} M, antagonist of GPR54) or 10^{-11}–10^{-5} M of kisspeptin-10 and peptide 234. Then, kisspeptin-10 and TSH secretion as well as KiSS-1 and GPR54 expression were analyzed. We found that leptin directly affected kisspeptin-10 secretion and kisspeptin-1/GPR54 expression in pituitary cells of pubertal ewes. Kisspeptin-10 did not change TSH secretion, except exerting a short-term influence after 2 h.