

The Effect of Leptin on the Hypothalamic-Pituitary Gonadal Axis and Puberty

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ABSTRACT

Leptin is a hormone secreted by adipose tissue. Many researches done on leptin revealed that leptin plays a key role in regulation of energy, food intake and neuro-endocrine system. One of the neuro-endocrine axis that expresses the effect of leptin is the reproductive system i.e. hypothalamic-pituitary gonadal (HPG) axis. As several studies demonstrated, leptin affects HPG axis at different levels. Hypothalamus, a center for feeding and endocrine system, is the major target site for expression of the effect of leptin, as this area of the brain contains leptin receptors. So, these receptors for leptin may mediate endocrine functions and HPG axis is one of them. There are a number of studies done to come across the effect of leptin on HPG axis and all of them evidenced that leptin has direct and indirect effect on HPG axis and gonadotropin releasing hormone (GnRH) is one of the key sites. But there are arguable findings among these researches regarding mechanism of action for leptin. Even though many experiments demonstrated that leptin may directly affects GnRH through its receptor on GnRH, there are some that showed the effect of leptin on GnRH is indirect i.e. through GnRH synapsing neurons.

The other target area for leptin is anterior pituitary. It is demonstrated that leptin receptors are also found in anterior pituitary and administration of leptin stimulated luteinizing hormone (LH) and follicle stimulating hormone (FSH) secretion from anterior pituitary. In addition, leptin receptors are located in gonads, injection of leptin to different experimental animals showed reversal of sterility and inhibition of steroidogenesis.

On the other hand, many researches done to reveal the correlation between leptin and puberty, the results are controversial. As many findings demonstrated, increase in leptin concentration just before the onset of puberty is seen in humans and rats. On the contrary, some researches evidenced that there is no any correlation between level of leptin and onset of puberty and also there are findings showed the effect of leptin is permissive rather than primary triggering factor for the onset of puberty.

Keywords: Anterior pituitary; Follicle stimulating hormone (FSH); Gonadotropin releasing hormone (GnRH); Gonads; Hypothalamic-pituitary Gonadal (HPG) Axis; Hypothalamus; leptin receptors; Leptin; Luteinizing hormone (LH); Steroidogenesis.

INTRODUCTION

The obese or ob gene was first discovered in 1950 by a group of researchers. Since the mutation of this gene caused excessive obesity in the mice, these mice called ob/ob mice. However, the physiology was yet unknown. But after successive trial, in 1994 a molecular

genetist Jeffery Friedman cloned the ob gene in mice and its homology in human. Then he purified the ob gene product, a hormone he called Leptin. [1] The name Leptin is from a Greek root 'leptos' meaning thin, [2] because it decreased food intake and body weight when administered in mice. [3-5] On the other hand, obesity in db/db mice

was linked to a defect of the leptin receptor (LEPR), [6] because the diabetes or db gene encodes the receptor for the obese (ob) gene product.

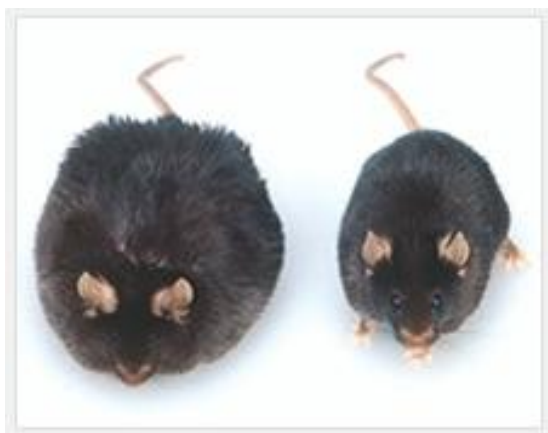


Fig.1. A mouse (left) with a defect in the ob gene that encodes for leptin comparing to the normal mouse (right). (Source: <http://newswire.rockefeller.edu/Leptin/> Accessed date: February, 2017)

Leptin secretion

Leptin is an adipocytes hormone which is a 167 amino acid peptide and circulates as a 16-kD protein partially bound to plasma proteins. Human leptin is 84% identical to mouse leptin and 83% identical to rat leptin. [7] In one of these studies, the proportion of bound leptin was reported to be higher in lean (45%) compared with obese (20%) individuals. [8] Structural analysis indicates that leptin is similar to cytokines. [9] It signals nutritional status to

the central nervous system (CNS) and peripheral organs.

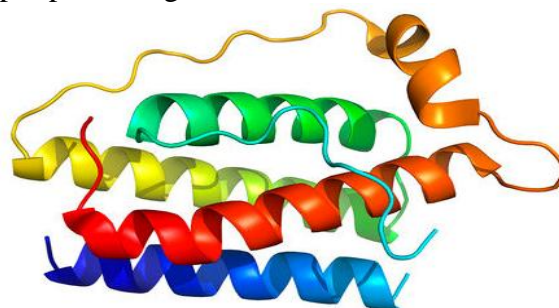


Fig.2. A Model for Secondary Structure of Leptin (source: <http://www.sciencephoto.com/media/7818>)

Leptin is also synthesized in the gastrointestinal tract, skeletal muscle, placenta [10-12] and in the brain. [13, 14] As findings demonstrated in humans and ob/ob mice, the rate of leptin production is directly related to fat mass [15] and leptin mRNA in adipose tissue. [16] Peripheral leptin concentrations also found decreased in response to fasting. [17] Furthermore in human females, weight loss resulted in decrease in leptin level, while weight gain significantly increased circulating leptin concentrations. [18,19] Leptin secretion is also regulated by other factors (Table 1).

Regarding pattern of leptin secretion in, humans, it is demonstrated that leptin is secreted in a circadian and pulsatile manner with a nocturnal rise. [20,21]

Table 1. Factors That Regulate Leptin Expression (Source: Rexford and Jeffrey, 2000)

Site	Increase	Decrease
Adipose tissue	Overfeeding Obesity (except ob mutation) Insulin Glucocorticoids Acute infection Cytokines (TNF- α , IL-1, LPS)	Fasting Testosterone Beta-adrenergic agonists Thiazolidinediones (in vitro) ? Thyroid hormone Cold exposure
Placenta	Insulin Glucocorticoids Hypoxia	Smoking Low birth weight
Skeletal muscle (rat)	Glucosamine Glucose Lipids	
Stomach fundus (rat)		Feeding Cholecystokinin

Leptin receptors and signal transduction

There are six varieties of the Leptin receptors (LEPR, OB-R), “a” to “f”, have been identified. [22] LEPRa, LEPRb, LEPRc, LEPRd and LEPRf have transmembrane

domains; however, only the 'long receptor,' LEPRb, has intracellular motifs necessary for activation of the Janus kinase-signal transducers and activators of transcription (JAK-STAT) signal transduction pathway.

LEPRe lacks both trans-membrane and intracellular domains and circulates as a 'soluble receptor'. [23]

Short-form LEPRs (LEPRa, LEPRc, LEPRd, and LEPRf in mice) and the long-form LEPR (LEPRb in mice) contain exons 1-17 of LEPR and therefore have identical

extracellular and transmembrane domains as well as the same first 29 intracellular amino acids. Short-form LEPRs contain exons 1-17 and terminate 3-11 amino acids after the splice junction for total intracellular domain lengths of 32-40 amino acids. [23]

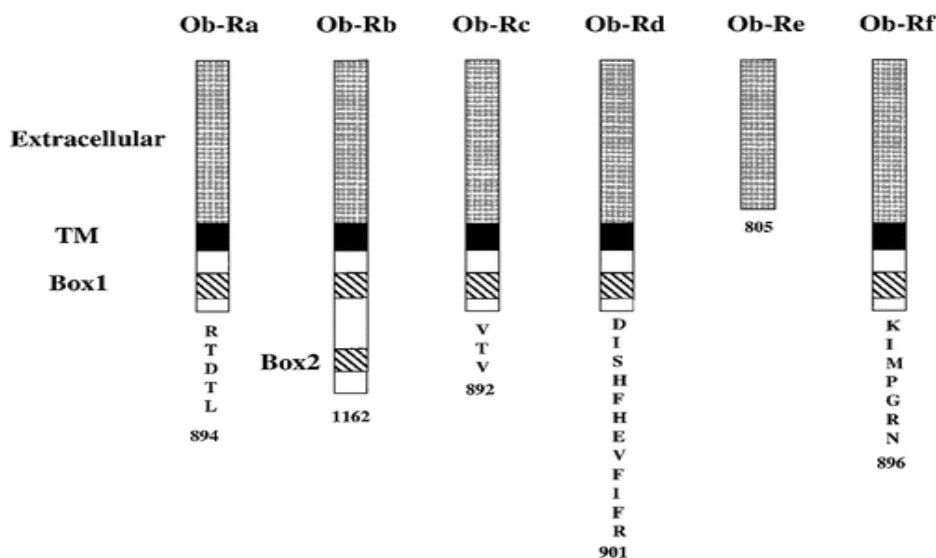


Fig.3. Different Leptin Receptor (Ob-R) Isoforms (source: Rexford SA and Jeffrey SF; 2000)

In pigs, long form of leptin receptor, Ob-Rb, was expressed in the hypothalamus, cerebral cortex, amygdala, thalamus, cerebellum and anterior pituitary. In addition, Ob-Rb was expressed in ovary, uterine body, testes, liver, kidney, pancreas, adrenal gland, heart, spleen, lung, intestine, bone marrow, muscle and adipose tissue. However, expression was absent in the thyroid, thymus, superior venacava, aorta, spinal cord and oviduct.

In similar experiment in human fetus, Ob-Rb was expressed in brain, intestine, muscle, fat, heart, liver and umbilical cord. [24-27] In addition, In human brain it is found that leptin receptors /LEPR/ are localized in the choroid plexus epithelium, ependymal lining, and neurons of the hypothalamic nuclei (arcuate, suprachiasmatic, mamillary, paraventricular, dorsomedial, supraoptic and posterior), inferior olivary nuclei and cerebellar Purkinje cells. [28] It is suggested that LEPR are localized in the choroid plexus may be involved in transport of leptin across the

blood brain barrier. [29, 30] In the hypothalamus, the OB-Rb variant is the predominant isoform expressed, with high expression noted in the arcuate nucleus (ARC), ventromedial nucleus (VMN) and paraventricular nucleus (PVN) from studies done in rats and mouse, and these areas are known to be involved in the regulation of feeding and reproduction [31] also in anterior pituitary. [32-34]

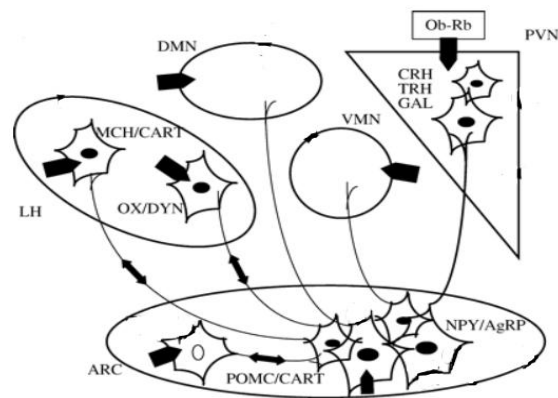


Fig.4. Localization of Leptin Receptors in the Varieties of Hypothalamic Area. ARC, arcuate nucleus; PVN, paraventricular nucleus; LH, lateral hypothalamus; VMN, ventromedial nucleus; DMN, dorsomedial nucleus. (source: B Beck; 2006)

Both leptin and its receptor share structural and functional similarities with the interleukin-6 family of cytokines. [35] Stimulation of the long form activates signal transducer and activator of transcription (STAT) proteins both in vivo and in vitro, whereas the short form is apparently incapable of signaling through this pathway. [36] Works done on signaling pathways for leptin implicated that Janus kinase (JAK) family members, STAT, as well as mitogen-activated protein kinases (MAPK) pathways in leptin receptor are responsible to mediate signal transduction. [37-39]

Study on the pathways responsible for mediating the actions of leptin has shown that STAT-3 induces gene transcription of the suppressor of cytokine signaling-3 (SOCS-3). [40] Over expression of SOCS-3 results in the inhibition of leptin-induced tyrosine phosphorylation of JAK-2, thus preventing the activation of the JAK/STAT pathway following the addition of leptin. [41]

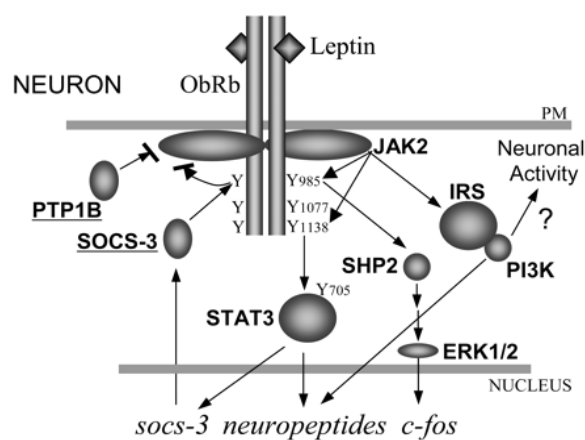


Fig.5. Cellular Signal Transduction of Leptin (source: Christian and Barbara. 2004)

The effect of leptin on HPG axis

Leptin level communicates whether there is sufficient energy available to undertake energy-demanding physiological functions, including reproduction. Distribution of Ob-R and its mRNA through Hypothalamic-pituitary-gonadal axis has been examined in several species, including mouse, [42] rat [43,44] and human. [45] The Ob-R has been found at all points along the HPG axis. Several groups have documented

evidence for expression of Ob-R mRNA in the gonads of mice, rats, and humans. [46,47] This leptin receptor localization in the hypothalamic-pituitary gonadal axis has led to the suggestion that leptin may have an important reproductive neuro-endocrine role.

The association between leptin and reproduction is mainly derived from researches done on relation of leptin and reproductive hormones. For example, a study done in healthy cycling women shows there is a positive correlation between leptin pulsatility, LH and estradiol plasma level. [48] In addition, findings from studies done on both ob/ob female and male mice showed the administration of recombinant leptin significantly affected the reproductive axis and restored fertility in both sexes. [49] Besides, it corrected sterility which resulted ovulation, pregnancy and parturition in the female ob/ob mice which further asserts leptin has influence on multiple stages of reproductive axis. [50] On the other hand, leptin treatment led to pubertal development in leptin deficient children, [51] which further confirms the critical role of leptin in reproduction.

The effect of leptin on GnRH

The long LEPR, LEPRb, is enriched in the hypothalamus, particularly, in the arcuate, dorsomedial, ventromedial and ventral premamillary nuclei which entail the role of leptin in feeding behavior and hormone regulation. [52] From study done on rats, leptin significantly increases GnRH secretion in vitro from hypothalamic area and also FSH and LH secretion. [53] In pigs, existence of Ob-R (Ob-Rb) in the hypothalamus and pituitary and the fact that leptin increased LH secretion from pituitary cells and GnRH release from hypothalamic tissue [54] suggests that leptin acts through the hypothalamic-pituitary axis. Since, in dose related manner, leptin has been shown to stimulate GnRH secretion from the hypothalamus, [55, 56] it has been reported that leptin may signal GnRH containing neurons directly.

On the contrary, experiments performed in rat showed there is little or no expression of Ob-R in GnRH neurons. [57] However, this evidence still shows there could be a possibility for leptin to affect GnRH directly. Furthermore, the presence of long LEPRb different nuclei of the hypothalamus raised an idea that other neurons may be intermediaries in the signal transduction pathway between leptin and GnRH release. [58]

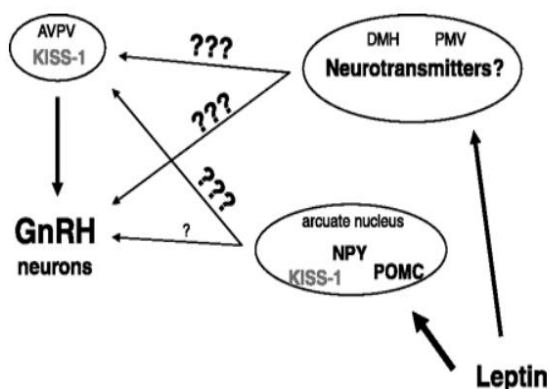


Fig.6. Leptin-Kiss-1 Regulation of GnRH. (source: Jennifer et al. 2008)

Neurons from these LEPRb-expressing regions project to GnRH neurons and play roles in reproduction, including the ARC, medial preoptic area (MPOA) and the PMv. One of these neurons is Kiss-1 neuron. Leptin regulates expression of hypothalamic kisspeptin-1 (Kiss-1), which regulates GnRH secretion. [59,60] Cocaine and Amphetamine-Regulated Peptide (CART) is also a facilitator of GnRH expression, and the large population of CART neurons in the ARC and PMv that project onto GnRH neuron-containing regions are key sites of direct or indirect leptin regulation. [61-63]

Proopiomelanocortin (POMC) and Opioid neurons also make direct synaptic contacts with GnRH-containing neurons, [64-66] high expression of Ob-R on POMC neurons in the ARC is observed in rats [67] and modulation of reproduction by the endogenous opioid 6-endorphin and a-melanocyte stimulating hormone (a-MSH) also seen. [68, 69]

Neuropeptide Y (NPY) is another substance that is found in the ARC that

plays a role in feeding and reproduction. NPY has been shown to stimulate GnRH release, an action that may be mediated by synaptic contacts between NPY and GnRH neurons. [70] NPY neurons in the ARC also express Ob-R, [71-73] which supports the possibility that GnRH modulation by NPY and the overall effect of leptin on reproduction through NPY. On top of this, another finding demonstrated that metabolic signals in part are communicated to GnRH neurons via the γ -aminobutyric acid (GABA) neuronal pathway. [74]

Over all, even though there are several studies that showed indirect stimulation of GnRH by leptin via different GnRH synapsing neurons, there are also some that revealed the expression of LEPR on GnRH neurons which asserts direct effect of leptin on GnRH.

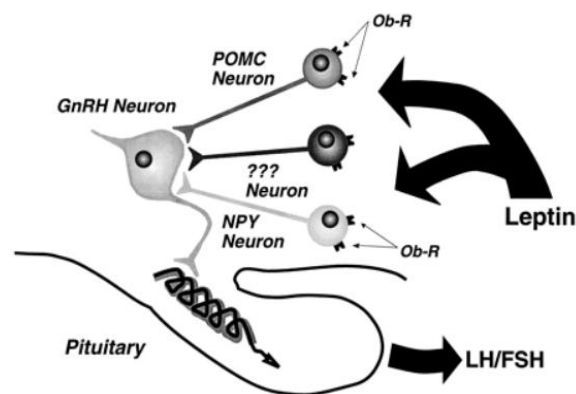


Fig.7. Proposed Model for the Action of Leptin on Neuroendocrine Reproductive Axis. (Source: Matthew et al. 1999)

The effect of leptin on anterior pituitary /LH and FSH secretion

Researches on monkeys ewes demonstrated that anterior pituitary is also contains Ob-R. [75] It is also demonstrated that leptin stimulates GnRH and gonadotropin release from pigs pituitary. [76] In addition, leptin treatment modulates GnRH and pulsatile LH frequency in rats. [77] In these fasted female rats, both leptin concentration and LH pulsatile frequency are decreased. Besides, reduction is arrested by administration of leptin. Another finding from a research done in rodents, rats [78, 79] and male and female mice [80] also

demonstrated administration of exogenous leptin changed gonadal axis and prevented starvation induced delay in ovulation.

In the above experiments, particularly in the mice, leptin administration (50 microg twice daily, ip) to males and females mice increased serum LH and FSH levels.

In addition, fasting in different animals; sheep, [81,82] hamsters [83] monkeys, [84] rats [85,86] and mice, [87] caused suppression of pulsatile LH secretion. Furthermore, the same result is demonstrated in humans [88, 90] following fasting. On the contrary, in female rats, pulsatile LH secretion is reversed by refeeding fasted rats. [91]

The effect of leptin on gonads

There are also many researches done to understand the presence or absence of leptin receptors in mammalian gonads. Using reverse transcription polymerase chain reaction (RT-PCR), leptin receptor

presence has been demonstrated in rat ovarian granulosa cells. [92] Similarly, in other experiment, long and short isoforms of leptin receptors are expressed in leydig cells of rats. [93] Thus, granulosa and leydig cells contain the ability to respond to leptin. In vitro experiments performed on theca, granulosa, and luteinized granulosa cells demonstrated that leptin can have an inhibitory influence on steroidogenesis in bovine and primate models. [94,95] As these findings indicated, leptin does not inhibit steroidogenesis directly rather, it does inhibit various mechanisms that stimulate steroidogenesis. As it is proposed, this can be through inhibition of insulin induced progesterone and estradiol production, and insulin induced progesterone and androstenedione production from bovine granulosa and theca cells, respectively. [95]

On the contrary, in male ob/ob mice, leptin treatment corrected sterility, increased testicular and seminal vesicle weights and increased sperm production. [96]

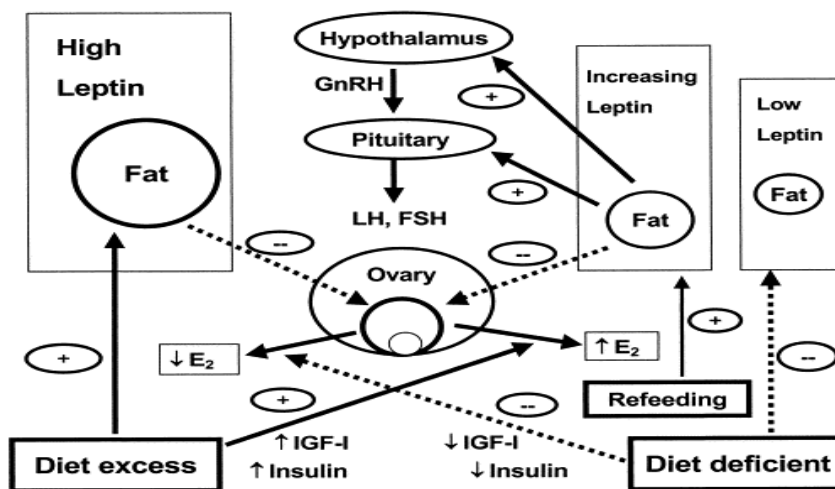


Fig.8. Summary for the Role of Leptin in Regulating Reproductive System. Encircled “-” and dashed line indicates a inhibitory effect; encircled “+” and solid line indicates stimulatory effect.

(Source: LeonJ Spicer.2002)

The effect of leptin on puberty

It is known that in humans onset of puberty is induced by an increase in pulsatile release of GnRH from the hypothalamus. In addition to those researches revealed the effect of leptin on HPG-axis, there are studies done to discover the effect of leptin on puberty. A study in

boys showed elevation of prepubertal leptin levels followed by a rise in testosterone but leptin level decreased after initiation of puberty. [97] In addition, an increase in leptin level is also seen in boys and girls children just before puberty. [98] But, in this study, plasma leptin was higher in girls than boys. In male monkeys [99] and female rats [100] it

also observed that leptin increased prior to the onset of puberty. Besides triggering puberty, leptin injection also caused earlier onset of puberty in normal female mice. [101]

A study done in female mice demonstrated that leptin is not the primary signal to initiate onset of puberty rather it has permissive function. [102] Moreover, research on male rhesus monkeys evidenced that there is no correlation between level of leptin and onset of puberty. [103]

In humans, it is reported that higher serum leptin concentrations is observed before, during and after puberty in girls than boys also in post pubertal girls than prepubertal girls. [104] Regarding the pattern, in both sexes, even though concentration of leptin increased before and during puberty, it lowered after puberty in the boys but it increased in the girls. [105,106]

On the other hand, under nutrition can delay the timing of pubertal onset which is seen in rats. [107] In these rats, earlier onset of puberty and estrus are demonstrated in fed on high-fat than low-fat diets. It can also inhibit reproductive behavior which is observed in hamsters. [108] In humans, weight loss in females can cause amenorrhea and can be restored by weight gain. [109]

CONCLUSION

There are thousands of researches done on the hormone leptin. The effect of leptin on reproduction was one of the target areas of these studies. All findings reviewed for this paper evidenced that leptin has effect on HPG axis, even though some of them are controversial to each other. In addition, among researches done on the effect of leptin on puberty most of them revealed that leptin has effect on puberty. But since there are also studies which stated that leptin has no significant effect on the onset of puberty further studies should be conducted to clearly identify the effect of leptin on puberty.

List of abbreviations

a-MSH α - Melanocyte Stimulating Hormone

ARC -Arcuate Nucleus

CNS -Central Nervous System

CART -Cocaine and Amphetamine-Regulated Peptide

DMN -Dorsomedial Nucleus

FSH -Follicle Stimulating Hormone

GABA - γ -Aminobutyric Acid

GnRH -Gonadotropin Releasing Hormone

HPG-axis Hypothalamic-Pituitary Gonadal Axis

JAK -Janus Kinase

LH -Leutenazing Hormone

LEPR /OB-R Leptin Receptor

MPOA -Medial Preoptic Area

NPY -Neuropeptide Y

PVN -Paraventricular Nucleus

POMC -Proopiomelanocortin

RT-PCR -Reverse Transcription Polymerase Chain Reaction

STAT -Signal Transducers and Activators of Transcription

SOCS-3 -Suppressor of Cytokine Signaling-3

VMN -Ventromedial Nucleus

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