KISSPEPTIN AND GNIH CONTROL OF GNRH IN FEMALE MAMMALS

M.J. Zamiri
Department of Animal Science, College of Agriculture, Shiraz University, Shiraz, Iran
mjzamiri@gmail.com

Introduction

Since the discovery of kisspeptin and gonadotropin-inhibitory hormone (GnIH) our understanding of the vertebrate reproductive physiology has greatly increased. Gonadotropin-releasing hormones (GnRH) is a hypothalamic decapeptide secreted into the hypothalamo-hypophyseal portal system in the median eminence. Pulsatile secretion of GnRH is prerequisite to secretion of gonadotropins (FSH and LH) from the gonadotropes in the pars distalis of the adenohypophysis, which control gonadal function in both males and females. Control of secretion of gonadotropins occurs vial the feedback actions of the gonadal hormones. Estradiol, depending on its blood concentration, may exert either a negative or positive feedback on gonadotropin (Gn) secretion, partly through its action of GnRH neurons and partly on the pituitary gland. A low level of estradiol decreases Gn secretion; however, in most mammals, estradiol secretion during the follicular phase of the ovarian cycle reaches to a peak level, which causes a sudden surge of gonadotropin secretion by exerting a positive feedback effect on the hypothalamus. In mammals, progesterone exerts a negative effect on Gn secretion. Because GnRH neurons do not express receptors for estradiol (ERα), androgens, and progesterone (PR), these hormones may affect the GnRH neurons through acting on various interneurons, known to be associated with the GnRH neurons. The axonal terminals of many interneurons are in close contact, and some of them also form synapses with the GnRH neurons.

Kisspeptin

A group of interneurons, known as kisspeptin (Kiss-1) neurons, have been proposed to mediate the effect of estradiol on the GnRH surge. In the mouse, these neurons have been localized by using immunohistochemical methods in the anteroventral-periventricular (AVPV) and arcuate (ARC) nuclei of the hypothalamus, which are associated with the surge and pulsatile secretion of GnRH, respectively (Figure 1). Most Kiss-1neurons in AVPV and ARC contain PR and ERα receptors. In sheep, estradiol acts on the mediobasal hypothalamus (MBH) to induce the GnRH surge. Kisspeptin (Kiss-1) is encoded by *Kiss-1* gene, and acts by binding to its receptor (Kiss-1r) which is G-protein coupled receptor 54. The Kiss-1neurons (also designated as KDN neurons) in the mouse ARC, but not in AVPV, also express dynorphin A and nurokinin B. It is suggested that many factors affecting reproduction act through Kiss-1 neurons, including environmental cues, endogenous rhythms, leptin, stress and others (Figure 2). GnRH neurons contain very few progesterone receptors; therefore, the effect of progesterone on GnRH secretion is likely mediated through interneurons. Several hypothalamic neurons are known to contain PR, including the neurons producing glutamate, gamma-aminobytyric acid, dopamine, and norepinephrine; which have been implicated as mediators of progesterone action on GnRH neurons (Dungan et al., 2006; Estrada et al., 2006; Franchini et al., 2006; Caraty et al., 2010; Wakabayashi et al., 2010).

Gonadotropin-inhibitory hormone

Gonadotropin-inhibitory hormone (GnIH) is another hypothalamic neuropeptide with inhibitory action on the GnRH neurons. The peptide was first discovered in the quail but subsequent studies

identified several of its orthologs, known as arginine-phenylalanine-amide related peptides (RFRP), in the human, cattle (RFRP-1, RFRP-2, RFRP3), rodents, and sheep (RFRP-1, RFRP-3). GnIH neurons have been identified in the paraventricular nucleus (birds) and DMH (Rat, hamster, mouse, sheep). At least 40% RFRP neurons in hamsters were reported to express ERα. The RFRP neurons in the rat express glucocorticoid receptors, which may indicate a mediatory role on reproductive processed in the stressed animals. Similarly, the presence of melatonin receptors on RFRP neurons in seasonal breeders, such as hamsters and sheep, suggests a role for RFRP peptides in the control of seasonal reproduction, probably by acting on the Kiss-1 neurons (Figure 3). GnIH receptors have been found on GnRH neurons (hamster), various cell types in gonads, and probably on adenohypophseal gonadotropes (Bentley et al., 2010; Smith and Clarke, 2010; Tsutsui et al., 2013).

In the following sections, we report the findings of the research carried out in the Department of Animal Science, Shiraz University during the past few years.

Salehi et al. (2013) determined *KiSS-1* gene expression at the transcriptional level and *RFRP-3* gene expression at the transcriptional and translational levels in the rat hypothalamus during the estrous cycle. Expression of *KiSS-1* mRNA and *RFRP-3* mRNA was studied by RT-PCR, and expression of *RFRP* peptide was studied using immunohistochemistry. Expression of *KiSS-1* mRNA during estrus was lower than other phases of the cycle, and expression of *RFRP-3* mRNA during proestrus was lower than diestrus. The ratio of *RFRP-3/KiSS-1* mRNA at proestrus was smaller than at estrus and diestrus. Almost all neurons expressing *RFRP* in the DMH were bipolar. The number of *RFRP* neurons during diestrus and late estrus were greater than in early estrus and proestrus (Salehi et al., 2013; Jafarzadeh Shirazi et al., 2013). It was concluded that changes in *RFRP-3/KiSS-1* gene expression ratio during the ovarian cycle of may be involved in regulation of GnRH secretion and controlling of the ovarian cycle in rats.

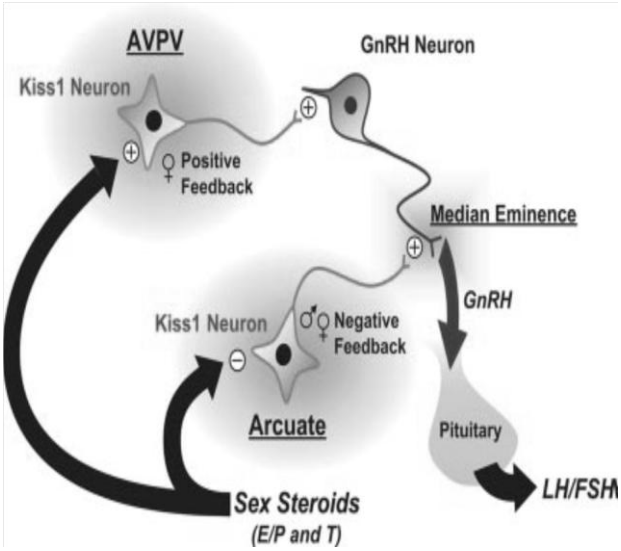

Figure 1. Feedback control of GnRH secretion through kisspeptin neurons (Kiss1) located in the anterovetral-periventricular (AVPV) and arcuate (ARC) nuclei in mice.

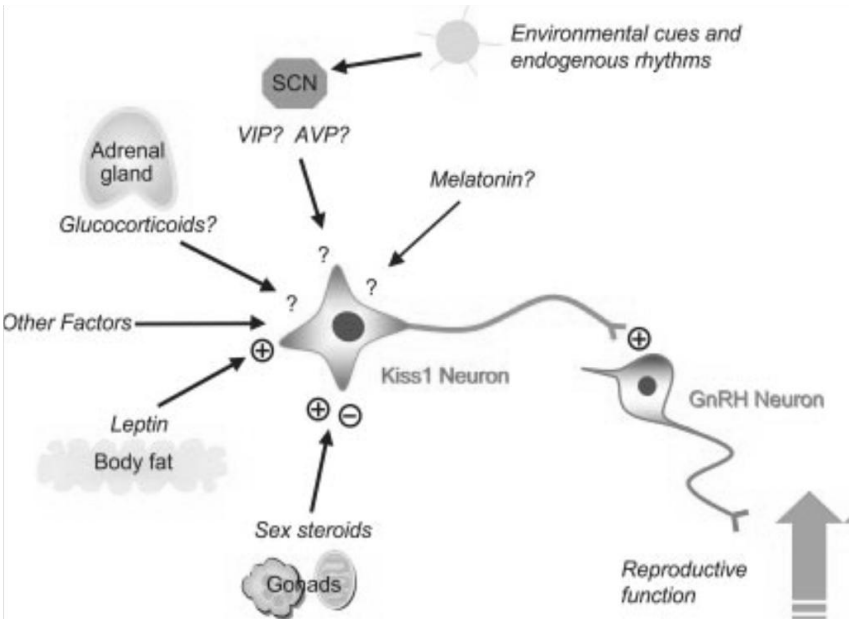

Figure 2. Factors influencing reproduction through kisspeptin (Kiss-1) neurons.

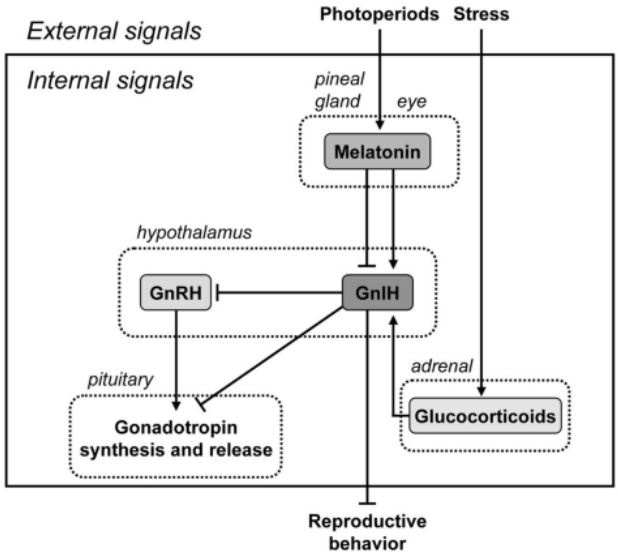

Figure 3. Neuro-integration of environmental and endogenous signals to control reproduction.

Adavi et al. (2011) investigated the effect of suckling on the expression of GnIH in the dorsomedial hypothalamus (DMH) and paraventricular nucleus (PVN) in rats. Postpartum rats were allotted into two groups. Control (non-lactating) rats were separated from their pups upon parturition. Lactating rats were allowed to suckle their pups for 8 days. Number of GnIH neurons in DMH and PVN was estimated using immunohistochemistry on day 8 postpartum. Number of GnIH neurons in DMH and PVN was higher in lactating rats. It was concluded that increased expression of GnIH in rat DMH during lactation may inhibit GnRH/LH secretion, thereby resulting in lactational anestrus.

Nowroozi (2013) determined the effect of litter size and suckling intensity on the expression of KiSS-1 mRNA in lactating rat ATR, using real-time PCR. Three groups of rats, suckling 5, 10 or 15 pups, were allowed to suckle their pups continuously. Three groups with 5 pups were separated from their pups for 6 h on day 8 postpartum, after which their pups were allowed to suckle for 2.5, 5 or 7.5 min., before being killed. Two groups with 10 and 15 pups were separated from their pups for 6 h on day 8 postpartum, after which their pups were allowed to suckle for 5 min. Expression of KiSS-1 mRNA decreased by increases in the litter size and the intensity of suckling stimulus; with suckling intensity having a greater effect. Therefore, inhibition of kisspeptin may be implicated as cause of anestrus in lactating rats.

Zamiri et al. (2012) first described the distribution of of kisspeptin neurons in the arcuate nucleus of the goat during the follicular and luteal phases of the ovarian cycle. This was followed by a more comprehensive experimentation studying the distribution of Kiss-1 (in ARC) and RFRP (in DMH/PVN) neurons in cycling and anestrous goats (Jafarzadeh et al., 2014). Female native does were used during anestrus, and follicular and luteal phases of the ovarian cycle. Diencephalons sections containing rostral, middle and caudal regions of DMH/PVN and ARC were stained for determination of RFRP and kisspeptin immunoreactive neurons. Number of RFRP-ir neurons in the follicular phase was lower than in the luteal phase and anestrus. Irrespective of the ovarian stage, the number of RFRP-ir neurons in the rostral and middle regions of DMH/PVN was greater than in the caudal region. In contrast, number of kisspeptin-ir neurons in the follicular

phase was greater than in the luteal phase and during anestrus. Irrespective of the stage of the cycle, number of kisspeptin-ir neurons in the caudal region of the ARC was greater than in the middle and rostral regions. The RFRP-ir cells were more abundant in the rostral region of DMH/PVN nuclei of the hypothalamus, with greater number being found during anestrus compared to the breeding season. On the other hand, kisspeptin-ir neurons were more abundant in the caudal part of the ARC, with greater number recorded in the follicular phase than during anestrus.

In summary, our data further confirm the findings by other researchers suggesting an important role for hypothalamic kisspeptin and GnIH in controlling GnRH secretion and reproduction in female animals. Considering the complexity of reproductive mechanisms, it is likely that many more brain peptides will be discovered in the future. It remains to be discovered as which one of these neuropeptides is (are) the key regulator of reproductive processes.

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