Neuroendocrine System in Seasonal Breeder: Focusing on the Reproductive Activity of Male Golden Hamster

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ABSTRACT : The reproduction of animals is a way to maintain their species and demands a large amount of energy. The golden hamsters are seasonal breeders whose reproductive activities are regulated by photoperiod (length of day time in a day). The photic information received is transported to the pineal gland via many steps. Melatonin produced by the pineal gland affects the reproductive neuroendocrine system to manage reproductive activities. The major regulator neurons, secreting gonadotropin-releasing hormone, integrate all kinds of information to govern the reproductive frame hypothalamus-pituitary-gonad axis. The elements impinging on the neurons are recently outspread. Thus the present review is to briefly survey the elements discovered newly and subjected to the active research realm and their correlations, focusing on the regulation of reproduction in mainly male golden hamsters as a representative animal.

Key words : Reproduction, Photoperiod, Melatonin, Kisspeptin, GnIH.

GENERAL REPRODUCTIVE FRAME IN MAMMALS

It has been well established that the reproductive activities are regulated by the hypothalamus-pituitary-gonad (HPG) axis in mammals. The hypothalamus integrates signals from a large area of systems via direct and indirect ambient inputs (Bliss et al., 2010). Gonadotropin-releasing hormone (GnRH), a hypothalamic decapeptide, is expressed in a discrete population of neurosecretory cells located throughout the basal hypothalamus of the brain. It is released into the hypothalamus-pituitary portal vessel in a pulsatile manner. The secreted GnRH is transported to the anterior pituitary gland where the hormone exerts its effects on the gonadotropes. As a consequence, the gonadotropins follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are synthesized and secreted into the systemic circulation. They induce gametogenesis (spermatogenesis in males and oogenesis in females) and gonadal steroidogenesis. The gonadal steroid hormones in turn act to regulate GnRH synthesis and release via a negative feedback system between the gonads and the brain.

SEASONAL REPRODUCTION

In order to assure that each generation of a species survives to the next, most animals in temperate zone have developed a “reproductive strategy”, which is seasonality because they are exposed to yearly fluctuations of ambient photoperiod, temperature, precipitation, and food availability. Whereas the non-seasonal breeding animals such as mouse and rat show year-round active reproductive capacity and give rise to litters regardless of the time of a year. Photoperiod is a major environmental signal used to time the sexual activity in the seasonal breeders (Reiter, 1980; Choi, 1996), although other species may also use different factors. A principal reason that reproduction is dependent on the changing day length is that this factor is predictable from year to year. Although other environmental factors also change throughout the course of each year, their stability is not as precise as the photoperiod. An annual cycle of reproductive activity

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endows organisms with the advantage of limiting birth to a time of year when chances for survival are maximized.

As a representative species, hamsters demonstrate seasonal breeding pattern. The golden hamster (or Syrian hamster, *Mesocricetus auratus* as a scientific nomenclature) is a well known member of the rodent subfamily Cricetinae. It uses the photoperiod as an ambient cue, conducting to the annual reproductive cycle (Gaston & Menaker, 1967; Elliott, 1976). The annual reproductive capability is divided into 4 phases; the photosensitive phase, regressing phase, regressed phase, and photorefractory phase (Choi, 1996). Under natural environment, the golden hamsters are reproductively active during spring and summer, which is referred to as the photosensitive phase, until the autumnal equinox in September. The hamsters undergo the course of gonadal regression as the photoperiod shortens with gradually fewer and fewer hours of daylight (regressing phase). The resulting phenomenon is a gonadal atrophy and the sexual involution is remained in winter (regressed phase). The gonad begins to restore the sexual activity from the late winter. This change reflects the spontaneous alteration of reproductive endocrine system because exposure of the animals to constant darkness at this time of the year does not suppress the development of the gonadal recrudescence. The step gaining the automatic reproductive activity is called photorefractory phase. Thereafter hamsters are capable of reproducing and the cyclic phases are repeated annually.

The seasonal alteration of reproductive situation in the golden hamsters can be reproduced in the laboratory regardless of the time of a year with adequately controlled lighting regimen (Stetson & Watson-Whitmyre, 1986). Adult male hamsters maintain reproductive activity when they are housed in LD (long day, $\geqq$12.5 hours of light per day) including constant light, while SD (short day, <12.5 hours of light per day) including constant darkness causes the testes to regress. The time for the gonad to involute in SD takes at least 8 weeks, which corresponds to the regressing phase in natural photoperiod. And the gonadal recrudescence is also witnessed although animals are kept in SD for an extended period (Stetson et al., 1977; Hong & Stetson, 1988). It takes 20 to 25 weeks of SD.

PINEAL GLAND

The pineal gland was thought to be the seat of the soul in the 16th century, indicating it's importance! But it has been considered as a vestigial organ until melatonin was isolated and characterized from the beef (Lerner et al., 1958). The discovery of the chemical structure of melatonin in mammals served to trigger for the investigation of many other biological activities.

Among the actions of the pineal gland, much concern have been taken on the regulation of reproductive activity. When the pineal gland is removed from the golden hamsters, the photoperiodic effect of SD that genuinely causes gonadal regression in pineal intact hamsters is prevented (Stetson & Watson-Whitmyre, 1986), resulting in preservation of active reproductive function. After the artificial induction of gonadal involution by SD exposure, pinealectomy induces a restoration of reproductive function (Matt & Stetson, 1980), similar to that observed in the pineal intact hamsters transferred from SD to LD. Properly timed administration of melatonin secreted by the pineal gland to pinealectomized hamsters produce gonadal regression (Stetson & Watson-Whitmyre, 1986; Maywood et al., 1991; Grosse et al., 1993). When the production of melatonin is considered to be affected by the light arriving at the pineal gland, the interference of the neural pathway anywhere between retina and the pineal gland inhibits gonadal regression induced by SD in golden hamsters. Taken together, the results indicate that the pineal gland, through melatonin, mediates the photoperiodic effect on reproduction.

MELATONIN

Melatonin (N-acetyl-5-methoxytryptamine) is produced in the pineal gland and transported into circulatory system, which means no specific blood vessel carrying blood to

the specific region. Melatonin is a product of tryptophan metabolism by the pineal gland. The pineal gland (epiphysis cerebri) facilitates uptake of tryptophan into the pinealocyte by a neural amino acid transport mechanism (Sugden, 1989). Tryptophan is ultimately converted into melatonin by several enzymes including N-acetyltransferase. Melatonin then is circulated and excreted through urinary function following modification in the liver into the 6-hydroxy-melatonin (Choi, 1996). The N-acetyltransferase is an enzyme affected by the signals of light, and activated in the absence of light. Thus the enzyme is activated at night, which elevates the level of melatonin in the blood. In other words, the duration of increased pineal and serum melatonin is proportional to the length of dark period (Stetson and Watson-whitmyre, 1986).

When animals are relocated from LD to SD, the pineal melatonin content expands gradually in both way along with the length of darkness. Even in constant darkness, the animals show a cyclic pattern of melatonin comparable to the fluctuation of melatonin of animals exposed to light-dark cycle (Rollag et al., 1980). The exposure of animals to light at night during melatonin levels are elevated abruptly curtails pineal melatonin production. The resulting output is a rapid decline of tissue and blood melatonin levels. These observations indicate that melatonin synthesis within the pineal is controlled by the light.

When melatonin is injected daily into the hamster, it causes the gonad to regress in only evening treatment, but not in the morning treatment (Stetson & Tay, 1983; Choi, 2001). this result is very similar to the exposure to SD in terms of time required. A daily injection of melatonin in pinealectomized animals does not cause testicular involution. But two or three injections daily induce gonadal involution (Stetson & Watson-Whitmyre, 1986), demonstrating that melatonin can exert an anti-gonadotropic action.

Lesion of the suprachiasmatic nucleus (SCN) blocks gonadal regression in hamsters exposed to SD (Bittman et al., 1991). This outcome is interpreted as a disrupting effect of the retinal-pineal neural pathway by the lesions of the SCN and an interfering effects with appropriate nocturnal melatonin secretion. There are also experimental findings that SCN lesions eliminate the circadian rhythm of pineal N-acetyltransferase activity and of melatonin production normally rising at night (Roseboom et al., 1996). Lesions of SCN fail to prevent reproductive responsiveness to some types of exogenous melatonin administration. On the other hand, lesions of the anterior hypothalamic region of golden hamster prevent the effects of melatonin on the reproductive system. From various experiments, therefore, possible action sites of melatonin are remarked in the hypothalamus.

TARGETING OF MELATONIN

Numerous localizations of melatonin binding sites are observed mainly within the hypothalamus in the brain and par tuberalis of the pituitary (Gauer et al., 1993). Such receptors are characterized by high-affinity and highly species-specific distribution. And receptor density in the par tuberalis of different species of animals exhibits seasonal variations. Bindings are greater in the evening than in the morning. High density of melatonin binding in the rat SCN is demonstrated in the late dark period and early light period compared to other time periods. Melatonin binding in the rat SCN and pars tuberalis is displayed an opposite rhythm to serum melatonin, with a peak in the late light phase and a trough in the dark phase. Both high and low affinity of melatonin bindings are shown with respect to the light-dark cycle in hamsters.

Melatonin receptor is cloned from the *Xenopus laevis* dermal melanophores in the end (Ebisawa et al., 1994). Subsequently other types of melatonin receptor are identified in human retina and brain and chicken brain. The receptors are members of G protein-coupled receptor superfamily with high percentage of amino acid homology with each other.

Gonadal regression caused by SD exposure or melatonin treatment is accompanied by a marked decrease in plasma

FSH, LH, and prolactin which precede testicular atrophy (Pickard & Silverman, 1979; Steger et al., 1985; Choi, 1996). In SD animal, the diminution of serum gonadotropins appears to be due to the suppression of hypothalamic GnRH release. The treatment of sexually inactive animals with GnRH elevates serum LH levels to those of LD animals treated with GnRH. In *in vitro* culture of the anterior pituitary, the administration of GnRH given at one hour intervals increases FSH and LH in a similar way in both LD animals with sexually active testes and SD animals with regressed testes. Thus the inhibitory photoperiod appears to result in reduced GnRH production and/or secretion, indicative of target site of melatonin. During the process of photorefractory phase, serum levels of pituitary hormone in relation to reproduction return to those characteristic of LP animals.

Furthermore, pinealectomy that preserves active testes in golden hamsters, regardless of photoperiod, is associated with high levels of LH, whereas pineal-intact animals on SD show a decrease of gonadotropins. With respect to the fact that serum gonadotropins directly reflect the release of GnRH, the suppression of GnRH release by SD appears to be achieved by the mediation of melatonin in the neuroendocrine system regulating reproduction in golden hamsters. There is no report of melatonin binding sites on the GnRH neurons themselves. Therefore it is likely that melatonin somehow affects the GnRH neurons via the other elements in the brain.

KISSPEPTIN

Kisspeptin is originally discovered as a metastasis-suppressor gene (Lee et al., 1996; Lee & Choi, 2005; Oakley et al., 2009). It is introduced to the reproductive endocrine system in which mutations in kisspeptin receptor are associated with the idiopathic hypothalamic hypogonadism (de Roux et al., 2003). The GPR54 is an orphan G protein-coupled membrane receptor, now called "Kiss1r" for its role as a kisspeptin receptor. An activating mutation was reported for the kisspeptin receptor in the human, which leads to precocious puberty (Teles et al., 2008).

Kisspeptin receptor has been described to be expressed in GnRH neuron, indicating that these cells are almost certainly direct targets for kisspeptin action (Gottsch et al., 2004; Irwig et al., 2004; Han et al., 2005). In particular, kisspeptin-immunoreactive fibers are found in the medial preoptic area, anterior hypothalamic area, paraventricular nucleus, and arcuate nucleus, which are the regions involved in the regulation of reproductive system. It has also been found that kisspeptin immunoreactive fibers terminate in close proximity to GnRH fibers in the median eminence and kisspeptin causes GnRH release from the median eminence *in vitro* (Richard et al., 2008; Kim et al., 2012). Therefore, kisspeptin appears to be involved in the regulation of reproductive function at levels of both hypothalamus and pituitary.

GONADOTROPIN INHIBITING HORMONE (GnIH)

On the basis of large range of investigation performed in mammals, GnRH has been known as an unique regulator to synthesize and release the gonadotropins. However, a hypothalamic factor that inhibits the HPG axis is identified in the quail 12 years ago and named gonadotropin inhibiting hormone (GnIH) (Tsutsui et al., 2000). Since then GnIH has been identified in chick, sparrow, and starling and found to exert its effects on the GnRH neurons via GPR 147 receptor to control the reproductive endocrine system by reducing the synthesis and release of gonadotropins from the pituitary (Ciccone et al., 2004; Osugi et al., 2004; Yin et al., 2005; Tsutsui et al., 2007; Ubuka et al., 2008).

The equivalent findings for mammals have been reported where they show the presence of orthologues of GnIH in the brains of various species (Clark et al., 2009; Smith & Clarke 2009). These mammalian forms of the peptide have been called RF-amide related peptides (RFRP). There exist multiple forms of GnIH in aves and mammals. In mammals, the GnIH (RFRP) gene encodes at least two peptides and

they are named RFRP-1 and RFRP-3. RFRP-2 has also been identified in human and bovine. The mammalian forms of GnIH originate from the same region of the hypothalamus, the paraventricular/dorsomedial hypothalamic area, and appear to have similar functions to the avian form.

GnIH immunoreactive cells are detected in the diencephalon, pons, and medulla of the mouse brain (Ukena et al., 2001). GnIH-expressing cells are condensed dorsomedial hypothalamic nucleus, with some in the posterior hypothalamus. In the rat with the same manner, cells are observed in the dorsomedial nucleus, ventromedial nucleus, and tuberomammillary nucleus (Johnson et al., 2007). GnIH precursor is identified in the cells that were confined to the dorsomedial nucleus of the rat brain (Rizwan et al., 2009).

Chronic treatment of mature birds with GnIH for 2 weeks decreased plasma testosterone concentrations as well as the synthesis and release of gonadotropins in a dose-dependent manner (Ubuka et al., 2006). An anterior pituitary hormone LH is well known to stimulate the synthesis and release of testosterone in the Leydig cells in vertebrates. Thus the decrease of testosterone after GnIH treatment is likely to be a result of the decrease in LH synthesis and release. On the other hand, there is a possibility of direct action of GnIH on the testes. GnIH administration via osmotic pump induces testicular apoptosis and attenuated spermatogenic activity in mature birds (Ubuka et al., 2006). It is thus thought that the decrease in testosterone in blood is the major cause of testicular apoptosis. And it is found that the expression of GnIH in the hypothalamus increases at the onset of testicular regression in adult bird exposed to SD photoperiod. With this result and the plentiful of other data, the increase in GnIH activity could be one of the main cause of gonadal atrophy in aves.

Like birds, the expression of mammalian GnIH homologs (RFRPs) appear to be involved in photoperiod-mediated changes in reproductive functioning. In golden hamsters RFRP cell bodies are localized to the dorsomedial hypothalamus, which is a key brain region mediating the influence of melatonin on SD-induced gonadal regression. Thus RFRP is considered as a putative element in the course of receiving and transmitting the photoperiodic information via melatonin.

Whereas long term exposure to inhibitory photoperiod leads to the suppression of RFRP immunostaining and mRNA (Revel et al., 2008). Sixty days of melatonin treatment to LD animals shows analogous consequence, indicating that the pineal hormone melatonin mediates these effects. These disputable results embarrass the efforts reported to reconcile with a role of RFRP in reproductive suppression, as it is lowest during maximal reproductive inhibition. One of the prospects is that golden hamsters require enhanced GnIH expression to suppress GnRH during the initial phase of regression, but that this level of inhibition is not necessary in hamsters with a fully regressed reproductive axis and low testosterone concentrations. Another prospect is that the HPG axis in hamsters with regressed testes is sensitive enough to respond to lowered testosterone, leading to sufficient action of GnIH via feedback route to maintain the involuted testicular function.

Taken together, GnIH appears to inhibit gonadal development and maintenance through a decrease in gonadotropin synthesis and release (Tsutsui et al., 2010). Thus GnIH (RFRP) is thought as a key neuromodulator regulating vertebrate reproduction, if expanded.

Their interaction is now of important to pursue the integrative understanding of seasonal reproduction. The major crucial elements involved in the mechanism of seasonal reproductive system are enlarged by addition of GnIH and kisspeptin, impinging directly on the utmost important GnRH neurons. In short, kisspeptin acts as a pronounced stimulatory regulator of the GnRH system and GnIH a remarkable suppressing regulator.

GnIH has been reported to inhibit kisspeptin-activated GnRH firing rate *in vitro*, indicating the interactions at the cellular level on GnRH target cells. The administration of the kisspeptin receptor antagonist suppresses the LH surge in female rat. In a similar way, treatment of the GnIH receptor antagonist increases the gonadotropin-

releasing influence of kisspeptin. Despite the fact that all experiments on GnIH and kisspeptin indicate that both have profound actions on the HPG axis in mammals, the specific neural loci to integrate and summate their impacts have not been explored the downstream of reproductive function. On the basis of findings reported to date, nevertheless, these two neuropeptides play key roles in reproduction. It is reasonable to surmise that kisspeptin and GnIH serve to work on the pathway of excitatory and inhibitory signals in the regulation of HPG axis.

CONCLUSION

In summary, the discovery of both GnIH and kisspeptin has inevitably altered the working organization of the reproductive system. The neuron secreting GnRH is now directly connected to two elements GnIH and kisspeptin upstream at a viewpoint of structural and functional aspects. GnIH acts on GnRH neurons in the hypothalamus via a novel G protein-coupled receptor to inhibit gonadal development and maintenance by decreasing the synthesis and secretion of gonadotropins. GnIH homologs have also been identified in the hypothalamus of various mammals. The mammalian GnIH homologs act to inhibit gonadotropin release in several mammalian species. The antigonadotropic hormone effects of GnIH suggests that it is able to interfere or prevent GnRH action on gonadotropes. Kisspeptin is also an important element influencing the GnRH neurons, leading to development and up-regulation of the reproductive system in mammals. The activity of kisspeptin neurons via GPR54 is required for the capability of fertility. It has a stimulatory effects on GnRH neurons, indicating the elevated release of GnRH and up-regulation of the HPG axis. On the other hand, GnIH down-regulates the HPG axis at the levels of hypothalamus and pituitary. This distinct opposing roles of these two newly discovered elements suggest that they act as key neurohormones controlling reproductive activity. In the light of the influence of melatonin in seasonal breeders and its potentials impinging on the neurons of both GnIH and kisspeptin, the GnRH neurons are likely to be affected by the melatonin indirectly. Therefore, as a reproductive neuroendocrine course of transporting the information of daily light in animals breeding seasonally, melatonin-GnIH/Kisspeptin-GnRH route could be reckoned to the driving pathway in the reproductive system.

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