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Review Article

Recent Progress and Perspective in GnIH Research

Kazuyoshi Tsutsui* and Takayoshi Ubuka

Laboratory of Integrative Brain Sciences, Department of Biology and Center for Medical Life Science, Waseda University, Tokyo, Japan

***Corresponding Author:** Kazuyoshi Tsutsui, Professor, Laboratory of Integrative Brain Sciences, Department of Biology, Waseda University, Center for Medical Life Science of Waseda University, Shinjuku-ku, Tokyo, Japan.

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Abstract

Since the discovery of gonadotropin-releasing hormone (GnRH), a neuropeptide stimulating gonadotropin release, GnRH was assumed the only neuropeptide regulating gonadotropin release in vertebrates. However, a neuropeptide inhibiting gonadotropin release named gonadotropin-inhibitory hormone (GnIH) was recently discovered as a new key regulator of reproduction in vertebrates. GnIH acts on GnRH neurons and gonadotropes via GnIH receptor to inhibit gonadotropin synthesis and release. Demonstration of the inhibitory actions of GnIH has proved that GnRH is not the sole hypothalamic neuropeptide controlling reproduction in vertebrates. Thus, GnIH research has advanced our understanding of the neuroendocrine control of reproductive physiology and behavior. This review describes recent progress in GnIH research on reproductive neuroscience and perspective of GnIH research.

Keywords: *Gonadotropin-Inhibitory Hormone (GnIH); Gonadotropin-Releasing Hormone (GnRH); Gonadotropins; Reproduction; Reproductive Behavior*

Introduction

Optimal reproductive functioning requires coordinated integration of multiple neurochemical regulatory inputs to the hypothalamo-pituitary-gonadal (HPG) axis. Scharrer proposed a seminal concept "neurosecretion" indicating that hypothalamic neurons that terminate in the neurohypophysis produce and release neurohormones that act on endocrine organs in the 1920s. Bargmann established this new concept in 1949. Subsequently, important hypothalamic neuropeptides, such as oxytocin and vasopressin, were identified as the neurohormones secreted from the neurohypophysis in mammals.

On the other hand, Harris (1948) thought secretion of anterior pituitary hormones such as gonadotropins, i.e. luteinizing hormone (LH) and follicle-stimulating hormone (FSH), thyroid stimulating hormone (TSH), adrenocorticotropic hormone (ACTH) and growth hormone (GH) may be regulated by neurohormones produced by hypothalamic neurons that secrete these neurohormones from the median eminence (ME) into the hypophysial portal system. Schally's and Guillemin's groups finally discovered neurohormones, thyrotropin-releasing hormone (TRH), gonadotropin-releasing hormone (GnRH) and growth hormone-inhibiting hormone (somatostatin) and demonstrated this seminal hypothesis. A Nobel Prize was given to Schally and Guillemin for their contributions to "Neuroendocrinology" in 1977.

At the beginning of the 1970s, GnRH, a hypothalamic neuropeptide that stimulates the release of gonadotropins, i.e. LH and FSH from gonadotropes in the anterior pituitary was discovered in mammals by Schally's and Guillemin's groups. Subsequently, it has been shown that GnRH is conserved among vertebrates. We believed that GnRH is the only hypothalamic neuropeptide that regulates gonadotropin release in vertebrates based on extensive GnRH studies over the next three decades after the discovery of GnRH.

In 2000, however, a hypothalamic neuropeptide that inhibits gonadotropin release was discovered by Tsutsui's group in quail, an avian species, which they named gonadotropin-inhibitory hormone (GnIH) [1]. A new research era of reproductive neuroendocrinology was opened by the discovery of GnIH. Tsutsui's group was successful enough to show that GnIH is conserved among vertebrates including humans and acts as a key neurohormone inhibiting reproduction (for reviews, see [2-15]). Tsutsui's group have further shown that GnIH has important functions in addition to the control of reproduction [16,17]. GnIH acts on the pituitary and the brain to regulate reproduction. However, it now appears that GnIH also regulates various behaviors including reproductive behavior through changes in the biosynthesis of neurosteroids in the brain [17]. Thus, extensive GnIH research has progressed our understanding of reproductive physiology and behavior controlled by the neuroendocrine system (for reviews, see [2-5,7-14,18,19]).

Herein this review describes recent progresses in GnIH research on reproductive neuroscience and perspective of GnIH research based on recent GnIH studies.

Discovery of GnIH as a new key regulator of reproduction

History of GnIH discovery

In 2000, Tsutsui's group successfully isolated a novel neuropeptide having a C-terminal RFamide motif, Ser-Ile-Lys-Pro-Ser-Ala-Tyr-Leu-Pro-Leu-Arg-Phe-NH2 (SIKPSAYLPLRFamide), from the quail brains by using high-performance liquid chromatography (HPLC) and a competitive enzyme-linked immunosorbent assay with an antibody against RFamide [1]. In fact, this novel RFamide peptide suppressed gonadotropin release from the cultured quail anterior pituitary [1]. This is the first hypothalamic neuropeptide in any vertebrate that inhibits gonadotropin release [1]. This novel RFamide peptide was named GnIH based on its localization in the hypothalamo-hypophysial system and its action on gonadotropin release [1] (Figure 1). In birds GnIH neuronal cell bodies and terminals exist in the paraventricular nucleus (PVN) and ME, respectively [1]. The chicken LPLRFamide peptide that was reported to be the first RFamide peptide isolated in vertebrates is identical to the C-terminal structure of quail GnIH. However, the chicken LPLRFamide peptide can be part of the chicken GnIH peptide SIRPSAYLPLRFamide that was identified in a recent study [20].

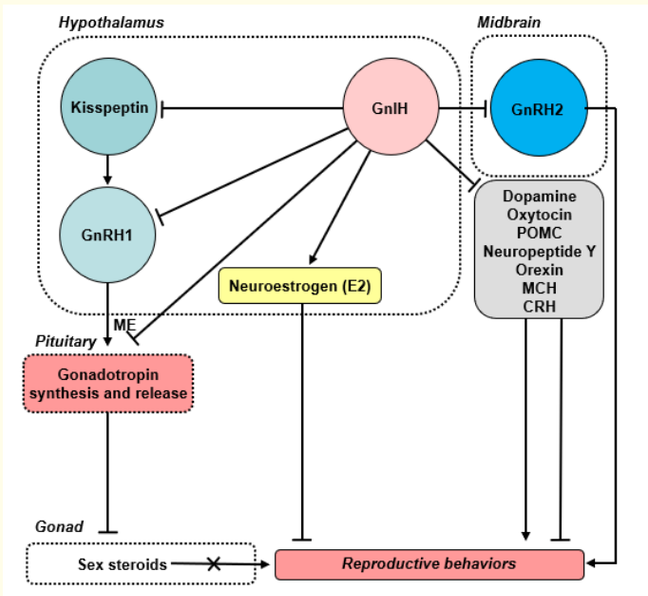

Figure 1: *GnIH actions on the regulation of reproductive physiology and behavior. GnIH is a novel hypothalamic neuropeptide inhibiting gonadotropin synthesis and release by the anterior pituitary. GnIH acts as a key regulator in the control of reproduction and reproductive behaviors. GnIH neuronal cell bodies are localized in the paraventricular nucleus (PVN) in birds and the dorsomedial hypothalamic area (DMH) in mammals. Terminals of GnIH neurons are located in the median eminence (ME) and GnRH1 neurons in the preoptic area (POA) in birds and mammals. GnIH receptor is expressed in gonadotropes and GnRH1 neurons in birds and mammals. Therefore, GnIH inhibits gonadotropin synthesis and release by directly inhibiting gonadotropes in the pituitary and by inhibiting the activity of GnRH1 neurons in the POA via GnIH receptor. GnIH neurons project not only to GnRH1 neurons but also to kisspeptin neurons in the hypothalamus in mammals. Kisspeptin neurons express GnIH receptor. GnIH participates not only in neuroendocrine functions but also in behavioral regulation in birds and mammals. GnIH inhibits reproductive behaviors, such as sexual and aggressive behaviors by acting within the brain. Furthermore, GnIH inhibits reproductive behaviors by stimulating the biosynthesis of neuroestrogen (E2) in the POA. GnIH neurons further project to many other neurons in the brain suggesting multiple actions of GnIH.*

A cDNA encoding the precursor for GnIH was identified in quail [21] and other avian species after the discovery of GnIH (for reviews, see [3,9-13]). One GnIH and two GnIH-related peptides (GnIH-RP-1 and GnIH-RP-2) that possess a common C-terminal LPXRFamide (X = L or Q) motif are encoded in the GnIH precursor in all avian species studied. GnIH was further isolated as a mature peptide in starlings [22], zebra finches [23], chicken [20] and GnIH-RP-2 was also isolated in quail [21].

Since GnIH inhibits gonadotropin release in most avian species studied GnIH is considered to be a new key regulator of avian reproduction (for reviews, see [3,9-13]) (Figure 1). To investigate the biological action of GnIH *in vivo*, chronic GnIH administration to mature male quail was further conducted [24]. Chronic GnIH administration decreases the expressions of common α, LHβ and FSHβ subunit mRNAs and circulating LH concentration. Furthermore, in mature male birds chronic GnIH administration induces testicular apoptosis and regression of seminiferous tubules [24]. In immature male birds, chronic GnIH administration inhibits testicular growth [24]. These findings demonstrate that GnIH suppresses gonadal development and maintenance by decreasing gonadotropin synthesis and release (Figure 1).

Structure and biological action of GnIH

Tsutsui's group further identified GnIHs in mammalian and primate hypothalamus to extend avian findings to other vertebrates [25-29]. As avian GnIH and GnIH-RPs the identified mammalian and primate GnIHs also have C-terminal LPXRFamide (X = L or Q) motif (for reviews, see [3,4,9-13]). Mammalian GnIHs are also called RFamide-related peptide 1 and 3 (RFRP-1 and -3). When avian GnIH was centrally or peripherally administered to Syrian hamsters it inhibits LH release [25]. In Siberian hamsters centrally administered hamster GnIHs (RFRP-1 and -3) inhibits LH release [28]. In rats, centrally administered rat GnIH (RFRP-3) inhibits LH release [30] and GnRH-stimulated gonadotropin release [31]. Mammalian GnIH (RFRP-3) also reduces LH pulse amplitude and GnRH-elicited gonadotropin synthesis and release in sheep [32] and cows. The structure of human GnIH (RFRP-3) is the same as ovine GnIH (RFRP-3) [27]. Therefore, the biological action of human/ovine GnIH (RFRP-3) on the ovine pituitary was examined in collaboration with Clarke's and Bentley's groups. GnRH-stimulated secretions of LH and FSH were both inhibited by human/ovine GnIH (RFRP-3) [32]. Based on these findings, it now appears that mammalian and primate GnIHs suppress gonadotropin synthesis and release as well as GnRH-elicited gonadotropin secretion (for reviews, see [2-4,9-13]) (Figure 1).

GnIHs exist in vertebrate brains from fish to humans (for reviews, see [3-13,15,18]). Sawada., *et al.* (2002b) found that goldfish GnIH precursor cDNA encodes three GnIHs, gfLPXRFa-1, -2 and -3 [33]. Both inhibitory and stimulatory effects of goldfish GnIHs (gfLPXRFa-1, -2 and -3) administration on gonadotropin synthesis and release were shown depending on reproductive conditions.

Agnathans are the most ancient lineage of vertebrates. Therefore, Tsutsui's group searched for the presence of agnathan GnIH in collaboration with Sower's and Nozaki's groups. Based on the existence of the gene encoding GnIH in sea lamprey, Osugi., *et al.* (2012) cloned lamprey GnIH precursor cDNA that encodes three GnIHs in sea lamprey [34]. Then, Osugi., *et al.* (2012) isolated these mature GnIHs in the sea lamprey brain by immunoaffinity purification and identified them by mass spectrometry [34,35].

Progress in GnIH research on reproductive neuroscience

Discovery of GnIH receptor

Tsutsui's group identified the receptor for GnIH in quail to understand the mode of GnIH action on gonadotropin secretion. The identified GnIH receptor, GPR147, is also called neuropeptide FF receptor 1 (NPFF1), which is member of the G-protein coupled receptor superfamily [36]. Yin., *et al.* (2005) clarified that membrane fraction of GnIH receptor cDNA transfected COS-7 cells binds GnIH and GnIH-RPs with high affinity [36]. Therefore, GnIH can act directly on gonadotropes to reduce gonadotropin release in birds through GnIH receptor expressed in gonadotropes (for reviews, see [2-4,9-13,19]) (Figure 1). Furthermore, GnRH1 neurons also express GnIH receptor and GnIH neurons project to GnRH neurons in birds [22,37] (Figure 1). Accordingly, GnIH can act on gonadotropes and GnRH1 neurons to inhibit gonadotropin secretion in birds (for reviews, see [2-4,9-13,19]) (Figure 1).

In mammals, Hinuma., *et al.* (2000) identified OT7T022 as the receptor for RFRP, mammalian GnIH, which is identical to GPR147. Two GPCRs for NPFF, NPFF1 (identical to GPR147) and NPFF2 (identical to GPR74), were found by Bonini., *et al.* (2000). It is known that NPFF that has a C-terminal PQRFamide motif and modulates pain sensitivity. As described above, it is considered that the GnIH (LPXRFamide peptide) and NPFF (PQRFamide peptide) genes are paralogous [34,35]. It is also considered that GPR147 and GPR74 genes are made by gene duplication. The binding affinities of GnIH and NPFF for GPR147 and GPR74 were investigated. The results suggested that GnIH has a higher affinity for GPR147, whereas NPFF has potent agonistic activity for GPR74. Taken together, these findings indicate that GPR147 (NPFF1, OT7T022) is the primary receptor for GnIH.

Molecular mechanism of GnIH action on target cells

GnIH signaling pathways were investigated by Tsutsui's group using the mouse gonadotrope cell line, LβT2 to clarify the molecular mechanisms of GnIH actions. Son., *et al.* (2012) first showed that GnIH receptor mRNA is expressed in LβT2 cells [38]. Mouse GnIHs effectively reduce cAMP production, extracellular signal-regulated kinase (ERK) phosphorylation, and LHβ expression and LH release stimulated by GnRH. Gonadotropin gene expression stimulated by GnRH is suppressed by inhibitors for adenylate cyclase (AC) and protein kinase A (PKA), but not for protein kinase C (PKC). Therefore, GnIH suppresses GnRH-stimulated gonadotropin gene expression by inhibiting GnRH actions on the AC/cAMP/PKA-dependent ERK pathway [38]. This inhibitory pathway of mouse GnIH action was also shown in the GnRH neuronal cell line GT1-7 expressing GnIH receptor stimulated by vasoactive intestinal polypeptide (VIP) [39].

Kisspeptin has a stimulatory action on GnRH neurons in mammals, which is opposite to GnIH. GnIH neurons may suppress both GnRH1 neurons and kisspeptin neurons because GnIH neurons project to GnRH1 and kisspeptin neurons (for reviews, see [2-4,9-13]) (Figure 1). Projection of GnIH neurons to GnRH2 neurons as well as many other neurons suggest multiple actions of GnIH (for reviews, see [2-4,9-13]) (Figure 1).

Multiple actions of GnIH

GnIH action on reproductive behaviors

In estrogen-primed female white-crowned sparrows GnRH2 enhances copulation solicitation induced by the song of males. Since GnIH neurons terminate in close proximity of GnRH2 neurons and GnRH2 neurons express GnIH receptor in songbirds [22], it is possible that GnIH inhibits copulation solicitation by inhibiting the activity of GnRH2 neurons in songbirds [40] (Figure 1). GnIH RNA interference (RNAi) suppresses resting time, spontaneous production of complex vocalizations, but stimulates agonistic vocalizations [41]. The results imply that GnIH RNAi induces arousal. Recently, Ubuka., *et al.* (2014) have further demonstrated that GnIH inhibits aggressive behavior in male quail [17]. Therefore, GnIH inhibits not only reproduction but also sexual and aggressive behaviors (for reviews, see [2,12,18,19]) (Figure 1).

In rats, Johnson., *et al.* (2007) showed that ICV administration of GnIH inhibits male sexual behavior [30]. In female hamsters ICV administration of GnIH suppresses sexual motivation and vaginal scent marking [42]. GnIH administration modifies fos expression in the medial POA, medial amygdala and bed nucleus of the stria terminalis, key neural loci implicated in female sexual behavior [42]. Therefore, GnIH is suggested to be an important key regulator of female proceptive sexual behavior and motivation (Figure 1). Accordingly, GnIH acts in the brain to regulate socially motivated behavior in mammals and birds.

GnIH action on neurosteroid biosynthesis

Interactions of neuropeptides and neurosteroids may modulate brain functions. Ubuka., *et al.* (2014) determined that GnIH stimulates cytochrome P450 aromatase (P450arom) activity and increases synthesis of neuroestrogen in the quail brain [17] (Figure 1). GnIH stimulation of neuroestrogen synthesis suppresses aggressive behavior [17] (Figure 1). These results establish that GnIH regulates aggressive behavior by modifying steroidal milieu in the brain.

Modification of neurosteroid production by GnIH is a novel regulatory mechanism of aggressive behavior. It is well known that unlike female quail sexually mature male quail fight with intense aggressiveness. Aggressive behavior is known to be depended on testicular androgen in male quail [43]. However, generally no correlation is observed between aggressiveness and testosterone (T) concentration in the blood [43]. Although aggression in males is not activated by non-aromatizable androgens, such as dihydrotestosterone (DHT), it is activated by aromatizable androgens, such as T and androstenedione (AD). Furthermore, P450arom inhibitors blocks T-induced aggression [43]. Therefore, the effect of testicular androgen on aggressive behavior depends on its aromatization into estrogen in the brain (neuroestrogen).

GnIH neurons project to the ME and other brain areas, such as the POA [1,44,45] and the periaqueductal central gray (PAG; [22]) that express GnIH receptor in birds [22,36]. POA and PAG are known to regulate aggressive behavior. The POA is considered to be the most active site of aromatization of testicular androgen by P450 aromatase (P450arom), and neuroestrogen acts directly in the POA to regulate aggressive behavior in male quail. Since GnIH decreases aggressive behavior in male birds as described above [17,40], Ubuka., *et al.* (2014) hypothesized that GnIH may suppress aggressive behavior by modifying the activity of P450arom and neuroestrogen synthesis in the brain (Figure 1). Ubuka., *et al.* (2014) found that GnIH-ir neuronal fibers exist abundantly near P450arom-ir cells and GnIH receptor is colocalized in P450arom-ir cells in the POA [17]. Ubuka., *et al.* (2014) uncovered that GnIH increases P450arom activity and neuroestrogen synthesis through GnIH receptor in the POA [17] (Figure 1). It was further revealed that central administration of higher doses of E2 decreases aggressive behavior [17]. This finding indicates neuroestrogen is essential to activate aggressive behavior, but higher concentrations of neuroestrogen in the brain suppress aggressive behavior. It is therefore considered that GnIH suppresses aggressive behavior by stimulating P450arom activity and neuroestrogen synthesis in the brain over its optimum concentration for the activation of aggressive behavior in male birds [17] (Figure 1).

Regulatory mechanisms of GnIH biosynthesis

Melatonin regulation of GnIH biosynthesis

It is known that nocturnal secretion of melatonin regulates seasonal reproductive activity in vertebrates. Ubuka., *et al.* (2005) discovered that melatonin elimination by pinealectomy plus orbital enucleation (Px plus Ex) decreases GnIH mRNA and GnIH peptide expressions in the quail brain [46]. On the contrary, melatonin administration increases GnIH mRNA and GnIH peptide expressions in the quail brain [46]. Importantly, a melatonin receptor subtype Mel1c exists in GnIH neurons [46]. Accordingly, it is considered that melatonin directly induces GnIH expression in GnIH neurons in quails (Figure 2). Chowdhury., *et al.* (2010) further found that melatonin also increases GnIH release in quail [47] (Figure 2). Based on these findings, melatonin produced in the pineal gland and eyes acts directly on GnIH neurons to stimulate GnIH expression and release in birds [12,13,46,47] (Figure 2).

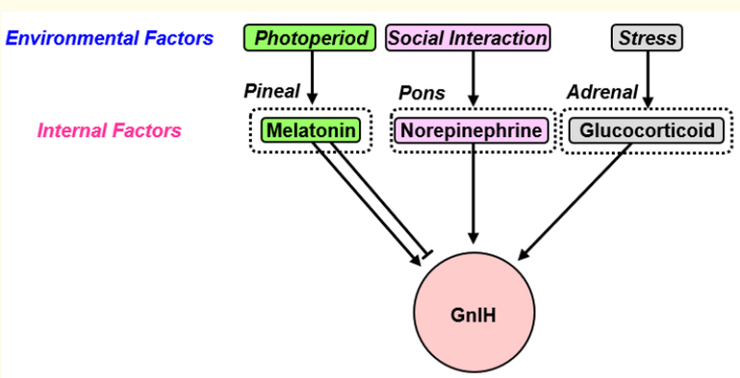

Figure 2: *Regulation of GnIH biosynthesis by environmental and internal factors. The neuroendocrine integration of environmental and internal factors is important for the control of reproduction and reproductive behaviors. Environmental factors include photoperiod, stress and social interaction, whereas internal factors include melatonin, glucocorticoid and norepinephrine (NE). GnIH inhibits the expression and release of gonadotropins and the expression of reproductive behaviors. Expression and release of GnIH are photoperiodically modulated via a melatonin-dependent process in birds and mammals. Melatonin increases GnIH expression in quail and rats, while melatonin decreases GnIH expression in hamsters. Stress increases GnIH expression by the actions of glucocorticoids in birds and mammals. Thus, GnIH is an internal mediator of stress-induced reproductive disruption. The social environment also changes GnIH expression and release by the action of norepinephrine (NE).*

On the contrary, melatonin suppresses the expression of GnIH in Syrian and Siberian hamsters, highly photoperiodic mammals [28] (Figure 2). In sexually quiescent hamsters exposed to SD photoperiods GnIH expression is reduced compared to sexually active hamsters kept under long day (LD) photoperiods. These changes in GnIH expression according to the photoperiod are not observed in Px hamsters. Importantly, melatonin injections to hamsters kept in LD decrease GnIH expression to SD level [28]. Accordingly, it is considered that GnIH expression is photoperiodically regulated depending on melatonin concentration in the brain in birds and mammals (Figure 2).

Glucocorticoid regulation of GnIH biosynthesis

It is known that stress reduces reproduction across vertebrates. Kirby., *et al.* (2009) showed that immobilization stress increases GnIH expression associated with suppression of the HPG axis in rats [48] (Figure 2). Kirby., *et al.* (2009) also found that adrenalectomy blocks the increase in GnIH expression under stress [48]. Because GnIH neurons express glucocorticoid receptor (GR) it is considered that adrenal glucocorticoids act directly on GnIH neurons to increase GnIH expression [48] (Figure 2). These findings indicate that GnIH is an integrator to suppress reproductive function under stress in mammals [48].

Recently, Son., *et al.* (2014) determined that in quail GR is expressed in GnIH neurons in the PVN and a glucocorticoid corticosterone (CORT) increases GnIH expression, indicating that glucocorticoids can directly regulate GnIH expression [49] (Figure 2). Furthermore, Son., *et al.* (2014) clarified how CORT activates GnIH expression using a GnIH neuronal cell line, rHypoE-23 [49]. rHypoE-23 cells express GR and CORT treatment increases GnIH expression [49]. It thus appears that stress reduces gonadotropin secretion by increasing GnIH expression in birds and mammals.

Norepinephrine regulation of GnIH biosynthesis

There are several reports showing that the presence of a female bird rapidly decreases plasma T concentrations in male quail. Tobari., *et al.* (2014) first showed that norepinephrine (NE) increases rapidly in the PVN when the male quail views a conspecific female [16] (Figure 2). When males view a female GnIH expression also increases in the PVN of male quail associated with decreased plasma LH concentrations [16] (Figure 2). Tobari., *et al.* (2014) further found that NE administration to male quail stimulates GnIH release [16]. Importantly, GnIH neurons are innervated by noradrenergic fibers and express α2A-adrenergic receptor in male quail [16]. Accordingly, it is considered that female presence stimulates NE release in the PVN and GnIH release, resulting in decreased circulating LH and T levels in males [16] (Figure 2).

Advancement and perspective of GnIH research

Role of GnIH in hypothyroidism-induced delayed puberty

It is possible that the decrease and increase in GnIH function induce central pubertal disorder and central reproductive dysfunction, respectively. Thyroid disorder is associated with pubertal delay. However, although interactions between the hypothalamo-pituitary-thyroid (HPT) and HPG axes have been suggested the mechanism of thyroid hormone (TH) action on pubertal onset remains unclear (Figure 3). Kiyohara., *et al.* (2017) examined the effect of abnormal thyroid status on pubertal onset and assessed the changes in the HPG axis and GnIH expression in female mice [50]. Female mice with hypothyroidism induced by the long-term treatment of propylthiouracil (PTU) show delayed pubertal onset [50]. Hypothyroid female mice show increased hypothalamic GnIH expression [50]. Furthermore, decreased circulating LH and estradiol-17β (E2) levels associated with the increase in hypothalamic GnIH expression in hypothyroid status [50]. It is therefore concluded that hypothyroidism may delay pubertal onset of female mice by increasing GnIH expression and decreasing circulating LH and E2 levels [50] (Figure 3).

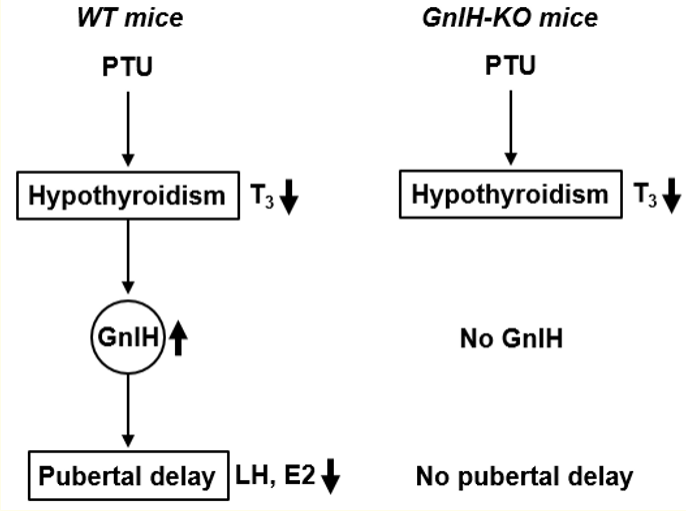

Figure 3: *Role of GnIH in hypothyroidism-induced pubertal delay. Female mice with hypothyroidism with the reduced level of circulating triiodothyronine (T3) induced by the long-term treatment with propylthiouracil (PTU) show delay in pubertal onset. Hypothalamic GnIH expression is increased in hypothyroid female mice. Circulating LH and estradiol-17 (E2) levels are decreased in hypothyroid status concomitant with the increase in hypothalamic GnIH expression. Administration of PTU to GnIH-KO mice also induces hypothyroidism. However, hypothyroidism-induced delayed puberty was not seen in PTU-administered GnIH-KO female mice as observed in wild type (WT) female mice. It is therefore considered that hypothyroidism delays pubertal onset of female mice by the increase in GnIH expression in the hypothalamus and the decrease in circulating LH and E2 levels.*

Kiyohara., *et al.* (2017) further induced hypothyroidism into GnIH-knockout (KO) female mice to examine the involvement of GnIH in pubertal disorder induced by hypothyroidism [50]. PTU administration to GnIH-KO mice induces hypothyroidism with reduced level of circulating triiodothyronine, T_3 [50]. However, delayed puberty was not seen in PTU-administered GnIH-KO female mice as observed in wild type (WT) female mice [50]. It is therefore considered that GnIH mediates delayed pubertal onset in hypothyroid status (Figure 3).

Mechanism of GnIH action on hypothyroidism-induced pubertal delay

It was confirmed that GnIH neurons express both TH receptors (TRα and TRβ) [50]. Although several putative TH-response elements (TREs) were found within 3 kb upstream region from the mouse GnIH ORF, both TRs did not directly bind to these TREs present in the GnIH promoter region in chromatin immunoprecipitation (ChIP) assays [50], indicating that TH (T_3) may act via non-genomic action by membrane TRs. Increased H3 acetylation (H3Ac) is observed in hypothyroid female mice [50]. Therefore, thyroid status may regulate chromatin modification in the GnIH promoter region, which changes GnIH gene expression.

Role of GnIH in reproductive dysfunction by the increase in GnIH expression

GnIH decreases gonadotropin secretion. Previous researches [14,24,50] suggest that significant acceleration in the function of GnIH neurons causes central reproductive dysfunction. We are currently investigating how excessive GnIH expression in the brain induces reproductive dysfunction using mice that overexpress GnIH by treatment with hormone and brain molecules that induce GnIH gene expression (see Chapter Regulatory mechanisms of GnIH biosynthesis).

Conclusion

Discovery of GnIH has shown that GnRH is not the only hypothalamic neuropeptide regulating reproduction. GnIH regulates not only reproduction but also reproductive behaviors. Future studies are needed to clarify how GnIH modifies the neurosteroid milieu in the brain to regulate brain functions. A recent study further indicated that GnIH is involved in pubertal disorder caused by thyroid dysfunction. This is a novel function of GnIH mediating the interaction of the HPT-HPG axes in abnormal puberty. Further researches are needed to develop novel diagnostic methods for reproductive dysfunction focusing on GnIH.

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Disclosure Statement

The authors have nothing to disclose.

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