BioTechnologia vol. 93(4) • pp. 361-369 • 2012
Journal of Biotechnology, Computational Biology and Bionanotechnology OPINIONS

A brief overview of the process of the elucidation of GnRH structure (1971)

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I do not know how I may appear to the world;
but to myself I seem to have been only like a boy,
playing by the seashore, and diverting myself,
in now and then finding a smoother pebble
or a prettier shell than ordinary,
whilst the great ocean of truth lay all
undiscovered before me.
Sir Issac Newton,
shortly before his death in 1727 at the age of 84

Abstract

The delineation of the primary structure of the gonadotropin-releasing hormone in 1971 released an avalanche of research on a wide spectrum of aspects concerning releasing hormones and their receptors. Today there are over 100 000 publications on the subject. It should be pointed out that, when this success was achieved, analytical tools and molecular methodology were at a semi-primitive stage in comparison to the present time. Therefore, we should show our respect to the pioneers of neuroendocrinology.

Key words: GnRH, GnRH structure, A.V. Schally, R. Guillemin, Nobel 1977

Abbreviations

GnRH	–	or (LHRH, LRF) neurohormonal decapeptide, synthesized in hypothalamus which have the releasing properties of gonadotropins (LH and FSH) from the anterior pituitary cells
LH	–	luteinizing hormone
FSH	–	follicle stimulating hormone
GnRH receptor	–	receptor protein for GnRH, bound to protein G in the pituitary cell membrane
Protein G	–	protein bound to receptor of rhodopsin type superfamily of receptors in cells
Primary structure of peptide or protein	–	sequence of particular amino acid residues in the chain, it determines both spatial folding and properties
TRH	–	hypothalamic peptide (tripeptide) releasing thyrotropin
ACTH	–	adrenocorticotropin
RIA	–	radioimmunoassay method
CNS	–	central nervous system

Introduction

The pituitary is a small endocrine gland situated at the bottom of the brain and surrounded by the sphenoidal bone on which the brain rests. It consists of two parts, the anterior and posterior lobes, which differ functionally, morphologically, and embryologically. It is known that the pituitary secretes several hormones. These hormones travel through the blood stream to their target organs and tissues, including the peripheral endocrine glands, where they stimulate the secretion of the sex hormones, adrenal cortical hormones and other hormones. The hormones of these endocrine glands regulate different bodily processes such as reproduction, metabolism, the response to stress and also growth and lactation.

Close to the pituitary gland is the hypothalamus, an area of the diencephalon lying at the base of the brain below the thalamus, from which its name derives. The hypothalamus is the part of brain nearest to the pituitary gland, and therefore its function is to act as a link between the central nervous system (CNS) and the endocrine system.

The median eminence of the hypothalamus is connected to the pituitary by a stalk. Since about 1945, scientists have been focusing on obtaining evidence that this area controls anterior pituitary gland activity. Anatomical studies have provided evidence that there is no nerve connection from the hypothalamus to the anterior pituitary; it has been suggested that control is effected hrough the hypophyseal portal blood supply, a well-organized system of blood vessels between the median eminence and the pituitary, and mediated by neurohormonal substances synthesized in the hypothalamus and stored in the median eminence (Campbell et al., 1961; Green and Harris, 1947; Guillemin and Rosenberg, 1955; Harris, 1955; Harris and Jacobsohn, 1952; Igarashi and McCann, 1964; McCann et al., 1960; Courrier et al., 1961). The credit for establishing the concept of hypothalamic neurohumoral control of anterior pituitary secretions must be given to Geoffrey W. Harris, then at the Maudsley Hospital in London in the 1950s, and later head of the Department of Physiology in Cambridge. The central tenet of Harris' proposal for neurohumoral control of the pituitary function was that the unusual capillary system existing between the ventral hypothalamus and the anterior lobe of the pituitary could be the conduit for substances of hypothalamic origin that enable the release of each and every pituitary hormone upon reaching the parenchyma of the gland (Harris, 1955). The early evidence for this theory of hypothalamic control of the pituitary was based on the results of various experimental approaches, including studies on the function of gonads, thyroid, and adrenals after electrical stimulation or lesions of discrete brain areas, disruption of the portal blood vessels between the hypothalamus and the pituitary by sectioning the pituitary stalk, and transplantation of the pituitary to remote sites. Observations of the effects of external environmental factors, such as light, on the reproductive cycles of animals also implied the role of the CNS in the control of the release of gonadotropins. The hypophyseal portal system was found in humans and mammals, as well as in lower vertebrates (Schally el al., 1977).

Although the results of many anatomical, physiological and pharmacological studies had supported the neurohumoral concept of the regulation of the pituitary gland through the portal blood system of pituitary gland, there had been no direct evidence for the existence of hypothalamic hormones involved in the release of pituitary hormones. The demonstration in 1955 of the existence of a corticotropin-releasing factor (CRF) enabled subsequent discoveries of the hypothalamic regulatory substances (Saffran and Schally, 1955; Saffran et al., 1955).

I should also mention the names of two outstanding scientists – pioneers of neuroendocrine research: Samuel M. McCann from the United States and Marian Jutisz from France.

McCann was one of the outstanding researchers in neuroendocrinology and studies on releasing factors. His achievements in neuroendocrinology are significant; he introduced the first biological method for releasing factor identification, which was utilized mostly by scientists prior to the introduction of radioimmunoassay (RIA).

Marian Jutisz was also an outstanding researcher in neuroendocrinology, focusing on the hypothalamus and anterior pituitary. In 1959, when he worked at the College de France with Robert Courrier, a member of the French Academy of Sciences, he began to mention the neurohormonal theory developed by Green and Harris (Green and Harris, 1947) during his lectures, while Courrier would also recall the experiments conducted by Guillemin (Guillemin et al., 1957) and Saffran and Schally (Saffran and Schally, 1955; Saffran et al., 1955) on the partial purification of CRF (corticotropin releasing factor). Courrier then decided to invite Guillemin to his laboratory in Paris. After Guillemin's arrival, Jutisz worked together with him on the purification of factor releasing LH (LRF). The experiments evidenced that both GnRH and TRH are peptides (Courrier et al., 1961). In the meantime Roger Guillemin decided to return to Houston in the United States. He returned to the US in November 1963 taking with him a very talented technical worker and all the protocols concerning the purification of peptides. After his departure, Courrier and Jutisz decided to work only on GnRH and the mechanism of its action.

My research into LHRH began in October 1962, when I joined the scientific staff of Professor E. Domański at the Institute of Animal Physiology and Nutrition at Jabłonna. I started immediately on the isolation and puri-

fication of this releasing hormone from ovine hypothalamus, at my disposal were no more than 5 000 hypothalami. My work had dual aims: to purify and characterize the peptide as far as possible and also to provide purified material to Domański for physiological experiments. The results of my work were published in 3 papers on purification and structural analysis (Kochman, 1966; Kochman, 1969; Kochman and Domanski, 1969) and in a further 3 on the physiological action of this purified peptide before structure elucidation (Domański and Kochman, 1968; Domański et al., 1964; Domański et al., 1966).

However, from the mid 1960s the only two research teams competent and enthusiastic enough to research the possibility and availability of the many hundred thousands of hypothalami for the isolation and purification of LH-RH (GnRH), and ready to determine the structure of this neurohormone, were those of Schally and Guillemin. Schally's group elucidated GnRH in 1971. In 1977, Schally and Guillemin received the Nobel Prize in medicine for his outstanding scientific achievement.

The next two sections of this article are based on the story written and realized by these two distinguished scientists.

Andrew V. Schally and Roger Guillemin

Andrew (Andrzej) Schally was born in Wilno on 30 November 1926 as the son of a Polish General, Kazimierz Schally, who defended Poland in 1939. Young Andrew was also destined to be a military officer. However, the war changed these plans. At first, he, his mother and sister Halina were moved to a camp for the families of Polish Officers in Craiova in Rumania, where Andrew and his sister attended a Polish School. At the age of 15 he was already certain that he wanted to study chemistry and become a scientist. In 1946 his family landed in Edinburgh, where Andrew, then 20, had to learn a new language and adapt to a new culture.

His career path diverged from that envisaged for him by his father. After 3 years of chemical studies at London University he found a job as an assistant technical worker at the National Institute of Medical Research in Mill Hill, which was one of great centers of biological research in England. There he worked for Donald Eliott, a great authority on protein chemistry.

Years later, when describing that period of Schally's working career, Elliot said that Schally performed experiments far better than he himself. However, and this should be stressed, his role was only that of an assistant technical worker. Andrew Schally said later that his work in that Institute determined his scientific personality.

In April 1952, Schally left London and went to Montreal. Again, his appointment was as an assistant technical worker at the Allan Memorial Institute of Psychiatry at McGill University. His chief was Murray Saffran, a young biochemist whose role in Schally's scientific life was very important. It was similar to the role that Fortier had in Guillemin's life, in spite of the fact that Guillemin largely overlooked the role that Fortier had played in his life and career. However, Saffran soon went abroad to the Laboratory of Herman Kalckar to replace James Watson, who later determined the structure of DNA.

On returning to Montreal, Saffran found his new technical worker as a diligent, hard working young man, full of enthusiasm, and happy. The director of the Institute, R. A. Cleghorn, was very interested in the Harris theory of neurohormonal influence on the pituitary, and discussed it with Saffran, who, as a biochemist, decided to isolate and determine the structure of hormones, which at that time was a contentious issue among human physiologists. Aware of Selye's research , he chose the hormone acting on stress, which, in response to it, releases corticotropin.

In 1955, Saffran published two important papers (Saffran and Schally, 1955; Saffran et al., 1955), in which he demonstrated the presence of a hypothalamic substance which he called a factor releasing corticotropin. Saffran proved to be generous, adding Schally's name as co-author, contrary to the practice that assistant technical workers were not considered authors. This decision by Saffran had a decisive effect on the further scientific career of Schally, and as Saffran said later: "The first important discovery I made was to give a scientist from the east an open road everywhere in America and he will reach the goal some time later".

Roger Guillemin was born on 11 January 1924 in Dijon, France, where his father was a supplier of instruments and as a means of transport had at his disposal only a bicycle. The University of Dijon had a Medical Faculty and Roger began studying there, but his studies were interrupted after his participation in the Resistance.

The two professors from the Medical Faculty in Dijon tried to convince him to pursue a scientific career and advised him to focus on endocrinology. However, in France after the war the prospects for work in a labo-

ratory were very limited. His opportunity arrived in 1948 when he participated in a Scientific Conference in Paris concerning the reaction of organisms to stress. The conference was organized by a great scientist from Canada, Hans Selye. After the Conference Roger asked Selye to accept him as trainee. Selye agreed and offered him 120 dollars per month for work in his newly founded Institute in Montreal. Guillemin arrived at the Institute full of hope but after two months it was clear that he was not as good as the other young researchers in the laboratory. Selye was not interested in educating the young man who had not had a chance to gain a good education in Dijon during the Nazi occupation. Roger had to return to France at the end of the same year. He arrived in Bourgogne, where he began to work as a doctor in his native city. His career as a scientist restarted owing to the kindness of a student from the Selye's Institute, Claude Fortier, who was again, on a study placement at Selye's Institute. He wrote a letter to Guillemin and proposed collaboration on the subject of his thesis (Wade, 1981). The subject of Fortier's scientific interest was the relationship between the brain and the pituitary. He was fascinated by the theory of Harris which stated that the pituitary and the rest of the body were controlled by the influx of substances going from the brain. Fortier asked Guillemin to come and work with him.

In 1950, just before finalizing his thesis, Guillemin fell seriously ill. At that time Fortier helped him very much. He suggested the introduction of cortisone and antibiotics into his treatment. His nurse, Lucienne Billard, subsequently became his wife and Fortier was the godfather of their first child. Guillemin was able to return to the laboratory again and then quickly forgot the help and support that Fortier gave him when he was ill and in need.

Guillemin looked for a new place where he could continue his research. In 1953, he received a position at the Department of Physiology in the Faculty of Medicine at Baylor University in Texas.

Working in Houston, he visited the laboratory of another French scientist, Charles Pomerat, who was working on tissue culture. Pomerat introduced him to a young student who was working on pituitary tissue cultures. Guillemin was then told that the pituitary tissues in the culture did not synthesize the hormones which they normally synthesize, *in situ*. To verify this it was possible only to have a culture of the pituitary and hypothalamic tissue together as a control of the secretion of the pituitary hormones. The idea was fascinating but Pomerat did not show even the slightest interest in this study. However, Pomerat mentioned to Guillemin the Harris's existing idea concerning the hypothalamic substances of.

Guillemin wished to verify Pomerat's thesis and the student, Barry Rosenberg, came to Guillemin's laboratory and they worked together on this interesting subject. Guillemin chose cells that produced ACTH. When the cells were alone in a culture containing ACTH, the ACTH secretion dropped almost immediately.

It was the year 1954, Guillemin remembered the date well, when the results of the second experiment provided confirmation that only in the presence of fragments from the hypothalamus did the pituitary cells begin normal secretion . Guillemin understood the importance of this experiment. Some months later, he came across nearly identical experiments reported by Saffran and Schally (Saffran and Schally, 1955). Luckily, Guillemin had published the preliminary version of this experiments in December 1954.

In answer to the invitation from Roger Courrier, a member of the French Academy of Sciences, Guillemin arrived in Paris, bringing his family, and worked together with Courier and Jutisz at the beginning of the 1960s. He held the latter's competence in high esteem but was also of the opinion that the biologist is the important scientist while the chemist's task is only to perform the work.

Guillemin decided to return to Houston and in 1963 obtained US Citizenship.

It took Guillemin some time to set up a laboratory in Houston in 1963. He decided to work even faster than before. On behalf of the National Institutes of Health he ordered a collection of a half-million ovine hypothalami from a slaughterhouse. They were transported to Houston and he was considering collecting more in the United States. Then he tried to construct a team. He also believed that this time, for isolating the released factors, a specialist in chemistry may be needed. Roger Burgus became responsible for this area and he became the soul of the group.

Then the busy work proceeded, including the day to day organization of work, conduct of logical experiments and drawing conclusions; all these elements led from the discovery of the primary structure of the first releasing hormone to the next and then one after another.

Guillemin loved to dominate. He was never an easy co-worker for fellow scientists. He was a man of calculation, an organizer and master in utilizing the scientific competences of others. He constructed a machine in order to reach a goal, but he expressed neither pleasure nor satisfaction. The Nobel Prize medal he was awarded stands on his desk to remind him of what he battled for (Wade, 1981).

The analyses leading to the elucidation of GnRH structure in Schally's Laboratory – Arimura's story

From 1965, the main physiologist in the Schally group was Akira Arimura, the head of Japanese scientists working at the forefront and responsible for decisive experiments. In the 60s, Andrew Schally succeeded in purifying 250 μg from 160 000 porcine hypothalami. Akira Arimura, a physiologist, and a chemist Yoshihiko Baba worked on the determination of LHRH structure. The analytical instruments were very old and although they tried very hard, the available material and obsolete instruments gave them no chance to successfully finish the work. Schally asked Akira Arimura if he knew any extremely competent Japanese chemists who would be able to determine the structure of LHRH using only 250 μg of purified material in hand. Arimura wrote a letter to Professor Seiichi Inayama who worked in Keio University School of Medicine, who had an excellent awareness of the ability of Japanese scientists. Inayama first asked the Committee of Professors at Tokyo University and received the answer that it was impossible to characterize the structure of LHRH using such a small amount of material because the currently available methods required much more material for such analysis. However, Seiichi did not give up and continued searching. When he read a report of a new method for identifying the C-terminus of a peptide using selective ^{3}H-labeling, he thought the method which required a very small amount of peptide could be used for deter-mination of the structure of LHRH. The method was developed by Hisayuki Matsuo from Osaka. Matsuo accepted the invitation sent by Andrew Schally (Arimura, 1991).

Dr Matsuo, a star of Japanese science, arrived with his wife in New Orleans on New Year's Eve 1970. He was very shocked by the outdated analytical instruments in the laboratory, but very surprised and very impressed by Andrew Schally's bluntness and the trust he showed in him when he instantly made his whole stock of purified LHRH available to him. But there was another shock to follow. Neither the Veterans Administration (VA) nor Tulane University had the license needed to order 0.5 Ci tritiated water, the minimum ordering amount. The officials of the Veterans Administration Hospital told Arimura that it would take a long time, several months to a year, to obtain the license. Matsuo could not use his method for selective tritium labeling unless he had titrated water. Arimura, very desperate, asked Ernest A. Daigneault, Professor of Pharmacology at Lousiana State University (LSU) Medical School for help. He instantly helped to solve this problem. He not only agreed to purchase the radioisotope at LSU, but also permitted Matsuo to perform his first experiment at his laboratory under LSU license (Arimura, 1991).

Matsuo confirmed that his new method was good enough to determine the peptide C-terminus using only a few micrograms of lysine vasopressin as a model peptide, which also has amidated C-terminus as would be the case for GnRH. Matsuo made a brave decision to approach determining N- and C-terminal amino acids of fragments obtained from digestion of Schally's purified LHRH by chymotrypsin or thermolysin without further purification. Baba determined the N-terminal amino acid using microscale Edman degradation, and Matsuo determined the C-terminal amino acid using selective tritium labeling. The number of N-terminal amino acids was supposed to be the same as that of C-terminal amino acids, but it was not. The conclusion was that the experiment had gone wrong or one amino acid had been overlooked. Matsuo found that tryptophan, which is destroyed by ordinary acid hydrolysis, had been overlooked. The next conclusion was that GnRH consists not of 9, but 10 amino acids. This information was very important for further research. From a "jigsaw game-like trial" using N- and C-terminal amino acid sequences of mixed enzyme-digested fragments followed by a few steps of Edman degradation, the two most likely candidates for GnRH structure were postulated by Matsuo (Arimura, 1991; Wade, 1981). Schally went with Baba to a meeting in California at that time, Matsuo started to synthesize the first candidate peptide using the new peptide synthesizer just arrived from Japan. After this synthesis, Arimura injected the obtained peptide into assay rats. Blood was collected for LH assays by the RIA method using Niswender's antiserum (Arimura, 1991).

On Sunday, April 25, 1971, Arimura left home and went to the laboratory. He removed test tubes from the refrigerator and centrifuged. Then, he sat in front of the auto-γ-counter and watched the register. When the test tubes were counted the counting started falling, indicating a tremendous release of LH. It was 9:00 a.m. the same day, and it was then that he became the first person in the world to discover the structure and activity of the GnRH molecule. He realised that this was a key moment in the history of neuroendocrinology (Arimura, 1991).

Publications with the details of experimental results appeared very quickly (Baba et al., 1971; Matsuo et al., 1971a, Matsuo et al., 1971b; Schally et al., 1971).

Guillemin's group published their successful work using sheep hypothalami shortly thereafter (Burgus et al., 1972).

Research on GnRH after the elucidation of its structure

The first great achievement in GnRH studies after the elucidation of its primary structure was Kerdelhué et al.'s (1973) discovery of specific antibodies against it and establishing its radioimmunological assay (RIA).

In 1971, Mitnick and Reichlin initiated studies on the biosynthesis of hypothalamic releasing hormones. On the basis of their experiments on the biosynthesis of the thyrotropin releasing hormone (TRH), they reported that this hormone could be synthesized in supernatants of hypothalamic homogenates devoid of cellular organelles and then set forth a claim for a "TRH synthetase": a soluble, enzymatic, RNA-independent system for the biosynthesis of the tripeptide (Mitnick and Reichlin, 1971).

Lipmann used supernatants of hypothalamic homogenates without cellular organelles, similar in composition to those for gramicidine and thyrocidine biosynthesis, but failed to confirm the results obtained by Reichlin. Neither did McKelvy and Grimm-Jørgensen (McKelvy and Grimm-Jørgensen 1975) confirm the findings of Reichlin in their studies on the biosynthesis of TRH, which proved that the chromotographic method used by Reichlin was insufficient to demonstrate the biosynthesis of a releasing hormone.

Several reports have been published on the biosynthesis of LHRH. The studies by Johansson et al. (1972, 1973) on porcine hypothalamic tissue led to the suggestion that mitochondrial-containing fractions could synthesize LHRH and that a protein template mechanism utilizing phospho-pantetheine of mitochondrial origin could be involved in this process. Contrary to these findings, Kochman, Jutisz and Kerdelhué, in very laborious studies using supernatants of hypothalamic homogenates without organelles, slices or dispersed hypothalamic neurons of rat, could not evidence the process of LHRH biosynthesis. Therefore, we decided to follow this process in *in vivo* experiments. We used mature normal and castrated Wistar female rats in which, eight days before experiments, stainless steel cannulae were implanted into the 3rd ventricle.

The biosynthesis was followed and evaluated in the hypothalami of intact and castrated female rats after the infusion of a labelled glycine to the 3rd ventricle. Pretreatment of the cycloheximide of a proportion of the rats was performed. On the basis of a biochemical analysis we suggested that the biosynthesis of LHRH in the hypothalamus involved the ribosomal system (Domański and Kochman, 1978; Kochman et al., 1977; Kochman et al., 1982).

When the mechanism of the GnRH biosynthesis had been well established by the characterization of cDNA for precursors and the isolation of the gene for GnRH (Adelman et al., 1986; Seeburg and Adelman, 1984; Seeburg et al., 1987), the processing of the LHRH precursor was found to take place within the perikarya (Rubin et al., 1987). The peptide GAP is colocalized with LHRH (Sar et al., 1987) and its release from the median eminence varies according to LHRH (Clarke et al., 1987). The important features involved in the physiological regulation of LHRH include a pulsatile release from the hypothalamus to maintain the correct levels of gonadotropins. Gonadal regulation of the release of the hypothalamic gonadotropin-releasing hormone in primates was investigated with great success by the eminent scientist – Tony Plant (Plant, 1986).

It is a pleasure to mention here that Professor Plant is an Honorary Member of the Polish Society of Neuroendocrinology.

The outstanding discovery after the elucidation of the GnRH structure was the finding and evidencing of the ontogeny of the neurons of the progenitor cells of GnRH which were found in the epithelium of the olfactory placode (Wray et al., 1989; Wray and Hoffman, 1986) and the nervus terminalis (cranial nerve zero or terminal nerve), a differentially organized set of nerve

fibers comingled with chains of GnRH-containing neuronal cell bodies, extending peripherally to the lamina propria of the nasal chemosensory mucosa and centrally to the ventral forebrain, where they start to establish an adult-like distribution. Progenitors of neurons expressing mRNA for GnRH I and GnRH type I receptors, and destined for the preoptic area, migrate from the olfactory placode, crossing into the septal-preoptic area, apparently following gradients of the adhesion molecule (NCAM) and the axonal growth promoting protein, netrin (Schwarting et al. 2004). Some of these early GnRH neurons remain in the nasal cavity, including the olfactory and vomeronasal mucosa, in adult organisms, including humans (Wirsing-Wiechmann, 2001). These peripheral GnRH processes terminate within the lamina propria of the chemosensory mucosa. Type I GnRH receptors are also expressed by chemosensory neurons. Paracrine release of GnRH may possibly influence the chemosensory neurons and therefore the GnRH is able to increase the sodium conductance in olfactory neurons (Wirsing-Wiechmann, 2001). The GnRH in these neurons may be involved, or responsible, for the increased sexual arousal induced by body odors at certain times of the menstrual cycle of women, and be involved in the overall functions of the pheromone (Guillemin, 2005).

Professor Susan Wray is an Honorary Member of the Polish Society of Neuroendocrinology.

Conclusions

The delineation of a GnRH amino acid sequence in 1971 by the two independent research groups of Schally and Guillemin released an avalanche of research on a range of aspects concerning both the decapeptide and its receptor (to date totaling more than 100 000 publications). Thirty structural forms of natural GnRH have been identified and determined in vertebrates and invertebrates. Many vertebrates have three different forms of GnRH and three cognate receptors have been identified with distinct distributions and functions. Human hypothalamic GnRH regulates LH and FSH secretion through the pituitary GnRH type I receptor via activation of the Gq protein. Studies have identified amino acid residues both in the ligand and receptor involved in binding, receptor activation, and translation into intracellular signal transduction. The predominant binding of the GnRH type I receptor in the gonadotrope is through Gq protein stimulation, while signal translation can also be propagated via other G proteins and potentially by G protein-independent means. The possible selection of intracellular signaling may be specifically directed by differences in ligand structure. A second form of GnRH, GnRH II, conserved for more than 400 million years of evolution in all higher vertebrates, including man, is present in extrahypothalamic brain and many reproductive tissues. Its cognate receptor has been cloned from different vertebrate species, including primates. The human gene homolog of this receptor, however, has a frameshift and stop premature codon, and it appears that GnRH II signaling takes place in humans through the GnRH type I receptor. There is a considerable plasticity in the use of different GnRHs, receptors, and signaling pathways for diverse functions.

GnRH and its analogs are used extensively for the treatment of hormone-dependent diseases and in assisted reproductive technology. They may potentially be used as contraceptives in men and women.

Future perspectives

Hundreds of thousands publications on the different aspects of GnRH from structural studies to the precise mode of its action and its application in clinical research have been published. Generally speaking this area has been the most fertile in the whole history of neuroendocrinology.

Human hypothalamic GnRH regulates LH and FSH secretion through the pituitary GnRH type I receptor.

There is a considerable plasticity in the use of different GnRHs, receptors, and signaling pathways for diverse functions. The precise estimation of the molecular mechanisms involved in ligand binding to receptor, subsequent activation, and intracellular signal transduction is essential to an understanding of disease processes. Delineation of the structural elements in GnRH and its receptor, which facilitates differential signaling, will importantly contribute to the development of new interventive analogs. The enormous, broad, multidirectional and profound research on GnRH and its receptor helps us to understand the essence of reproductive mechanisms.

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