Neuroendocrinology Letters Volume 45 No. 3 2024
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

REVIEW ARTICLE

The effect of gonadotropin-releasing hormone on the nervous system.

Jorge Juan Alberto Baca-Alonso[1], J. Luis Quintanar[1]

1 Departamento de Fisiología y Farmacología, Centro de Ciencias Básicas, Universidad Autónoma de Aguascalientes, México.

Correspondence to: Dr. J. Luis Quintanar
Laboratorio de Neurofisiología, Depto. de Fisiología y Farmacología. Centro de Ciencias Básicas, Universidad Autónoma de Aguascalientes
TEL: 449-9108423, E-MAIL: jlquinta@correo.uaa.mx,
ORCID: 0000000312577723

Submitted: 2024-02-09 Accepted: 2024-07-28 Published online: 2024-07-30

Key words: **GnRH; neuroendocrinology; neuroregeneration; nervous system; spinal cord; peripheral nerve; neuroprotection; GnRH analogue; leuprolide acetate; regeneration treatment**

Neuroendocrinol Lett 2024; **45**(3):188–196 **PMID:** 39146565 NEL450324R02

Abstract

Gonadotropin-releasing hormone (GnRH) plays a crucial role in regulating the human endocrine system. Synthesized primarily in the hypothalamus, GnRH manages the balance of reproductive hormones. This review highlights GnRH's various functions, particularly its impact on fertility, sexual development, and overall reproductive health through the regulation of gonadal development and function. Beyond its direct role in reproductive processes, GnRH also influences neuroprotection, cognition, and mood regulation, as shown by its activity in different regions of the nervous system. Research into GnRH and its analogs has revealed promising therapeutic potential for treating neurological disorders, indicating its broader impact beyond reproduction. Understanding GnRH's diverse roles not only emphasizes its importance in reproductive physiology but also highlights its involvement in neurological functions. Therefore, exploring the mechanisms behind GnRH's actions opens new avenues for research and therapeutic interventions, promising advancements in both reproductive medicine and neurological health.

Abbreviations:

BDNF	- Brain Derived Neurotrophic Factor
CXCL-1	- Chemokine Ligand 1
CYP19	- Cytochrome p450 Family 19
ESR1	- Estrogen Receptor 1
FSH	- Follicle Stimulating Hormone
GnRH	- Gonadotropin Releasing Hormone
GnRH-R	- Gonadotropin Releasing Hormone Receptor
IFN-γ	- Interferon gamma
IL-1β	- Interleukin 1 beta
LA	- Leuprolide Acetate
LH	- Luteinizing Hormone
NF-κβ	- Nuclear Factor kappa beta
TNF-α	- Tumor Necrosis Factor alpha

INTRODUCTION

Gonadotropin-releasing hormone (GnRH), secreted by the hypothalamus, plays a crucial role in regulating the reproductive system by stimulating the production and release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These gonadotropic hormones travel through the bloodstream to the ovaries in women or the testes in men, where they trigger the production of sex hormones and the maturation of eggs and sperm (Chen & Fernald, 2008).

The production and release of GnRH are regulated by estrogen and testosterone through negative feedback mechanisms that maintain hormonal equilibrium, as shown in Figure 1. Disruption of this delicate balance causes physiological changes in the body, although these changes are not necessarily harmful (Neill *et al.* 2004).

Moreover, studies have found GnRH and its receptors in unexpected locations, such as the placenta and various areas of the brain beyond the pituitary gland, where its primary activity occurs (Marques *et al.* 2000). This review aims to explore the impact of GnRH beyond its typical endocrine and reproductive functions, focusing on its influence on the entire nervous system.

STUDIES OF GNRH

Current research is exploring new avenues for GnRH treatment, as represented in Figure 2. These include its potential in male fertility (Johnson & Finlayson, 2016) and endocrine disorders such as acromegaly (Chieffo *et al.* 2013) and Cushing's syndrome (El Ghorayeb *et al.* 2015). In addition, investigations are underway for its efficacy in treating prostate cancer (Margel *et al.* 2019) and breast cancer (Leonard *et al.* 2017). For example, research investigated the protective role of GnRH analogues against angiogenesis induced by various stressors, such as excitotoxicity, oxidative stress, and inflammation. GnRH analogues were found effective in reducing cell proliferation in endometrial tissue (Tesone *et al.* 2008).

Moreover, researchers are examining GnRH's role in appetite regulation, body weight control, and its potential in combating obesity and eating disorders (London & Volkoff, 2019). The hormone's functions extend to neuroprotection (Marbouti *et al.* 2020) and neuroregeneration (Montoya-García *et al.* 2023), which are crucial for understanding sexual maturation and the regulation of the reproductive cycle in humans (Tzoupis *et al.* 2020). This highlights the extensive possibilities for investigating GnRH's multifaceted effects on diverse systems.

GnRH has significant potential as a therapeutic approach (García-Guerra *et al.* 2020; Lee *et al.* 2023; Zheng *et al.* 2014) and can be administered through various means, such as injections (Kutlu & Dinç, 2021), subcutaneous implants (Uddin *et al.* 2023), and nasal sprays (Toms-Whittle *et al.* 2011). However, before incorporating this hormone into any pharmaceutical form, it is essential to establish the correct dosage concentrations and understand its side effects. Previous studies have reported potential side effects such as hot flashes, headaches, nausea, and mood fluctuations (Rodríguez Hierro, 2006).

Furthermore, GnRH treatment could increase the risk of cancer and cardiovascular diseases in some cases (Clarke & Pompolo, 2005). Therefore, a comprehensive analysis should be conducted when considering GnRH as an alternative treatment, considering the potential side effects globally.

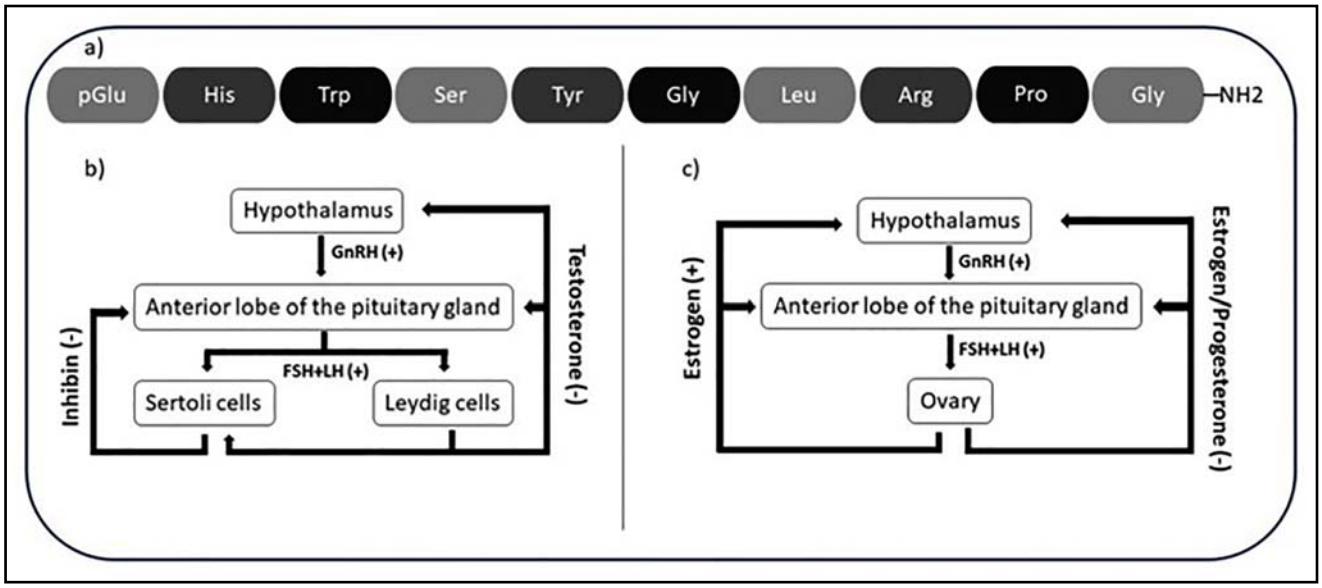

Fig. 1. a) Components of Gonadotropin-Releasing Hormone (GnRH) - Amino acid structure. b) Feedback mechanism of GnRH in the male reproductive system: In this system, inhibin and testosterone act as regulators of the hormone in a negative manner. c) Feedback mechanism of GnRH in the female reproductive system: Progesterone plays a negative feedback role in this system, while estrogens exhibit a dual role, acting both as stimulants and inhibitors within the system.

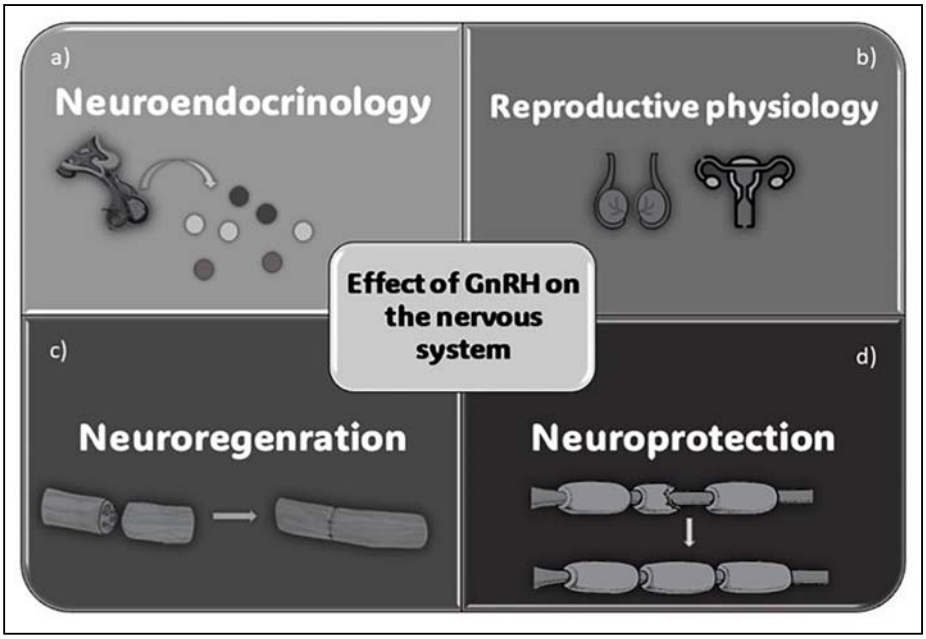

Fig. 2. a) Impact of Gonadotropin-Releasing Hormone on the nervous system: influence on the growth and development of secondary sexual characteristics. **b**) Direct effects on reproduction: correlation with different infertility pathologies. **c**) Effects on neuroregeneration after trauma: proven impact on both the spinal cord and peripheral nerves. **d**) Neuroprotective and neuroenhancing effects: restoration of myelin sheath integrity, coupled with neuroplastic effects for enhanced neural function.

GNRH RECEPTOR ON THE NERVOUS SYSTEM

The gonadotropin-releasing hormone receptor (GnRH-R) is part of the metabotropic receptor family. These receptors consist of a single chain of amino acids, with specific structures like an extracellular amino-terminal domain and seven transmembrane domains forming α-helices that connect with both extracellular and intracellular loops (Ramakrishnappa *et al.* 2005).

In mammals, there are different forms of GnRH-R. For example, humans and chimpanzees have the functional receptor form Type I, while Type II is silenced genetically in these species (Morgan & Millar, 2004).

The physiological action of the GnRH receptor is mainly observed in gonadotropin cells and in breast, ovary, and prostate tissues. GnRH receptors have also been identified in various brain regions, including the hypothalamus (Ciechanowska *et al.* 2010), cerebral cortex (Wilson *et al.* 2006), hippocampus (Schang *et al.* 2011) and more recently, the spinal cord (Díaz-Galindo *et al.* 2021).

Regarding the spinal cord, studies have reported that the activation of GnRH receptors in nerve cells affects cell survival, differentiation, and growth, suggesting the significant role of the receptors in fostering neuroplasticity (Manfredi-Lozano *et al.* 2022) and nerve regeneration (Díaz-Galindo *et al.* 2020).

EFFECT OF GNRH ON THE NERVOUS SYSTEM

Summary of research on GnRH and its contribution to investigating its effects on the nervous system

The text discusses the significance of numerous studies exploring GnRH's role in the nervous system. It notes the diverse methods and models used in these studies. To help readers comprehend and navigate this vast information, condensing it into a table is vital. Table 1 serves as a visual summary, organizing key findings for easy reference to various approaches and results.

Neuroendocrinology and reproductive physiology

In the field of neuroendocrinology and reproductive physiology, research on the impact of GnRH has taken various approaches, including investigating infertility. Studies have extensively explored the mechanisms of GnRH secretion and its potential involvement in metabolic disorders and infertility, for example following the marker VAX1 in mice (Hoffmann *et al.* 2016). This includes examining infertility associated with the loss of GnRH neurons using the gen DMXL2 in mice (Tata *et al.* 2014) and the competitive effects of GnRH agonists in an endometriosis model in women (Kolanska *et al.* 2017).

Other research focuses on the neuroendocrinology of aging, where GnRH plays a regulatory role in the aging process. Studies have used GnRH as a treatment in age-related hypogonadotropic hypogonadism mice to investigate changes in the neuroendocrine system (Luo *et al.* 2018). Similarly, studies have explored GnRH's effect on hypothalamic programming of systemic aging and its role in the reproductive cycle of adult mice (Su *et al.* 2013; Zhang *et al.* 2013).

Concurrently, investigations are ongoing regarding the regulation of puberty, with GnRH being a key player in activating the hypothalamic-pituitary-gonadal axis during this developmental stage. Studies on GnRH aim to understand the negative effects resulting from anomalies in this axis, which are commonly affected by hormone secretion during sexual development in a mice model with suppression treatment (Anacker

Tab. 1. Summary of the works related to the effect of gonadotropin-releasing hormone on the nervous system

Effect	Development stage	Study model	Analysis method	Contribution	Reference
Neroendocrinology	Preclinical	Mice	Measuring the reproductive cycle and IGF-1 levels.	IGF receptor signaling in the GnRH neuron is crucial for the onset of puberty.	Divall, *et al.* 2010
	Preclinical	Mice	Hypothalamic expression of IKK-b and NF-kB.	GnRH mediates aging and induces neurogenesis in adults.	Zhang, *et al.* 2013
	Preclinical	Mice	Measurement of sex hormones and sexual behaviors in old mice.	NGF regulates the release of GnRH, thus improving sexual function and sperm quality.	Luo, *et al.* 2018
	Preclinical	Mice	Behavior is evaluated as well as brain activity in the hippocampus.	Chronic treatment with a GnRH analogue has profound effects on female behaviors as well as neuronal activity in the hippocampus.	Anacker, *et al.* 2021
	Clinical	Human	Measuring Anti-Müllerian hormone levels.	There are changes in AMH levels after administration of a GnRH analogue.	Su, *et al.* 2013
Reproductive	Preclinical	Mice	Identifying the DMXL2 mutation and the subsequent expression of its protein in the brain and pituitary.	The DMXL2 mutation has a direct effect on GnRH neurons and in turn on the correct development of puberty.	Tata, *et al.* 2014
	Preclinical	Mice	Measuring GnRH expression and observing sexual changes in anatomy and physiology.	Deletion of Vax1 from GnRH neurons suppresses GnRH expression and causes infertility.	Hoffman, *et al.* 2016
	Clinical	Human	Analysis of a database with cycles of GnRH-agonist protocol and GnRH-antagonist protocol of 218 women with endometriosis.	GnRH agonists give higher pregnancy rates while GnRH antagonists negatively affect endometrial receptivity.	Kolanska, *et al.* 2017
Neuroregeneration	In-vitro	Rat embryo	Chemical and morphological analysis of Neurofilaments.	GnRH affects the outgrowth number and length of neurites in cultured cerebral cortical neurons. 1 nM of GnRH is sufficient to induce neurite outgrowth.	Quintanar & Salinas, 2008
	Preclinical	Rat	Clinical signs, axonal morphometry and neurofilament analysis.	GnRH reduces the severity of experimental autoimmune encephalomyelitis.	Quintanar *et al.* 2011
	Preclinical	Rat	Motor behavioral tests, micturition capacity and che```mical analysis of neurofilaments.	GnRH treatment improves locomotor activity, urinary function, and neurofilament protein expression after CNS injury.	Calderón-Vallejo & Quintanar, 2012
	Preclinical	Rat	Kinematic analysis of gait, orthometric analysis of the spinal cord and spinophilin expression.	GnRH treatment improves recovery from march and reduces histopathological damage in injured nervous tissue.	Calderón-Vallejo *et al.* 2015
	Preclinical	Rat	Locomotor behavior and kinematic gait evaluation. Micturition reflex. Histology of white and gray matter and microglial cells.	LA partially improves lotomotor activity, gait, micturition reflex, spinal cord morphology and decreases microglial area in a rat model of SCI.	Díaz Galindo *et al.* 2015
	Preclinical	Rat	Expression of spinophilin, β-actin and neurofilaments. Morphometric analysis and neurite length outgrowth.	GnRH has neurotrophic effects on neurite outgrowth in cultured neurons of rat spinal cord embryos.	Quintanar *et al.* 2016

Effect	Development stage	Study model	Analysis method	Contribution	Reference
Neuroregeneration	Preclinical	Rat embryo	Analysis of urodynamic parameters and expression of neurofilaments NF68 and NF200.	Application of LA can improve bladder dysfunction in castrated rats, and perhaps considered as a treatment for overactive bladder conditions secondary to menopause.	Medina-Aguiñaga *et al.* 2018
	Preclinical	Rat	Behavioral tests that evaluate memory and learning. Expression of structural nervous compounds.	GnRH improves learning in old gonadectomized rats, and it is possible that the mechanism involves an increased number of dendritic contacts.	Gonzáles-Torres, *et al.* 2019
	Preclinical	Rat	Electromyography of the external anal sphincter, anorectal manometry, and volume of the cecum.	Leuprolide acetate treatment improves the neurogenic colon in ovariectomized rats with spinal cord injury.	Altamira-Camacho *et al.* 2020
	Preclinical	Rat	Kinematic analysis, electromyography, measurement of myelin sheath thickness and MAP-2 expression.	LA treatment improves of gait, walking speed and NCV, number of myelinated axons and MAP-2 expression in rats with sciatic nerve complete transection.	Hernández-Jasso *et al.* 2020
	Preclinical	Zebrafish	Location of the preoptic area, expression of neurogenesis activating proteins.	GnRH had an effect on the differentiation of cultured hypothalamic cells from adult zebrafish and increased proliferation overall and in neuroendocrine cell types.	Ceriani & Whitlock, 2021
	Preclinical	Rat	Intraocular pressure test, histological evaluation of the structural integrity of the retina and electroretinography.	Leuprolide acetate partially improves the morphology and electrical activity of the retina, promotes the recovery of nerve fibers from the optic nerve, and significatively reduces the astrogliosis in a rat model of glaucoma.	Esparza-Leal *et al.* 2023
	Preclinical	Rat	Quantification of genetic and protein expression of markers related to neuroinflammation. Sensitive behavioral tests.	GnRH can downregulate the expression of cytokines and glial markers 3 weeks after injury and subsequently induce sensory recovery.	Martínez-Moreno, *et al.* 2023
	Clinical	Human	Hormonal assays in children with central precocious puberty and either neurofibromatosis and/or optic gliomas.	LHRH is an effective treatment for the central precocious puberty associated with neurofibromatosis and/or optic gliomas.	Laue *et al.* 1985
	Clinical	Human	Sensitivity, motor activity and independence test.	Leuprolide acetate has an impact on independence in patients with spinal cord injury.	Quintanar *et al.* 2018

Effect	Development stage	Study model	Analysis method	Contribution	Reference
Neuroprotection	In-vitro	Rat	Protein expression of neurofilaments, MBP, β-actin and α-tubulin. Axonal morphometry and quantification.	Leuprolide acetate influences the recovery of locomotion, weight gain and increased NF expression in animals with EAE.	Guzmán-Soto *et al.* 2012
	Preclinical	Sheep	Spatial orientation test and qPCR analysis on the expression of genes associated with synaptic plasticity and endocrine signaling.	GnRHa treatment was associated with significant sex- and hemisphere-specific changes in mRNA expression of genes associated with synaptic plasticity and endocrine signaling.	Nuruddin *et al.* 2013
	Preclinical	Rat	GI transit time test and galactose absorption. Fecal weight and fat content analysis. Enteric neuronal subpopulations analysis and blood assays.	GnRH analogs may develop enteric neuropathy and dysmotility. A marked enteric neuronal loss with modest effects on GI function is found after buserelin treatment.	Sand *et al.* 2014
	Preclinical	Rat	NF-κB activation assay and assessment of proinflammatory cytokine levels.	LA causes a reduction in the severity of locomotor activity, as well as in the activation of NF-κB and the number of proinflammatory markers in rats with EAE.	Guzmán-Soto *et al.* 2016
	Preclinical	Rat	Expression of IL-1β, TNF-α, IFN-γ, CXCL-1 and motor activity and behavior test.	Treatment with LA partially reverses HIE-induced neuroinflammation and prevents anxiety-like behavior in neonatal rats.	Pedroza-García *et al.* 2023
	Clinical	Human	Computed tomography and hormonal assays.	Treatment with buserelin reduces the symptoms of sciatica due to compression of the pelvic cavity.	Takata & Takahashi, 1994
	Clinical	Human	Transrectal ultrasound and blood hormone assays.	GnRH antagonists may reduce the risk of apoplexy in pituitary adenoma patients.	Sasagawa *et al.* 2015

et al. 2021). These studies delve into the neurobiological mechanisms of kisspeptin activation from GnRH neurons during puberty in transgenic mice model (Clarkson *et al.* 2010), as well as how IGF-1R signaling that is necessary for the timely activation of the GnRH pulse at puberty, giving insight into the complex circuits that link somatic development with reproductive function (Divall *et al.* 2010). Overall, GnRH research predominantly focuses on regulating reproductive functions and the neuroendocrine system.

Neuroregeneration and Neuroprotection

GnRH has been a central focus of nerve regeneration research at the Quintanar Research Laboratory. In 2008, a study conducted by Quintanar and Salinas explored GnRH's effects on neurite growth, length, and cytoskeletal neurofilament expression in cortical neurons of rat embryos (Quintanar & Salinas, 2008). Interestingly, the presence of the hormone resulted in increased dendritic projection, sparking further investigation into its neuroregenerative potential. Subsequently, a study in 2011 by Quintanar *et al.* observed a reduction in symptoms of autoimmune encephalomyelitis following GnRH treatment in rats (Quintanar *et al.* 2011). A year later, Calderón-Vallejo and Quintanar reported improved locomotor activity, urination, and expression of nervous system structural proteins in rats with spinal cord injuries after GnRH treatment (Calderón-Vallejo & Quintanar, 2012). In 2015, Calderón-Vallejo *et al.* investigated GnRH's effects on spinal cord injury in rats, revealing significant improvements in gait dynamics, spinal cord morphology, and spinophilin expression (Calderón-Vallejo *et al.* 2015). Subsequently, a 2016 study by Quintanar *et al.* demonstrated GnRH's marked neurotrophic effect on neuronal cell cultures derived from the spinal cord of rat embryos, further supporting its role in nerve regeneration (Quintanar *et al.* 2016).

Additionally, various studies have explored GnRH's impact on memory, learning tasks, and spinophilin expression in the hippocampus of aging rats. The results pointed to GnRH treatment as a neurological enhancer amidst natural cognitive decline in aging (González-Torres *et al.* 2019). Furthermore, GnRH's involvement

in regulating neurogenesis has been investigated, with reports suggesting its potential to foster neurogenesis in brain areas like the hippocampus, implying a role in nervous tissue repair and regeneration (Ceriani & Whitlock, 2021).

More recently, in 2023, Martínez-Moreno *et al.* reported GnRH's influence on sensory recovery post-spinal cord injury in rats, demonstrating positive physiological modifications in the expression of regenerative, pro-inflammatory, and glial markers (Martínez-Moreno *et al.* 2023). As GnRH's neuroregenerative effects become increasingly evident in both in vitro and in vivo models, reports also suggest neuroenhancing and neuroprotective effects, underscoring its potential therapeutic value in neurological conditions. GnRH has demonstrated neuroprotective effects, as shown in animal studies where its administration has reduced cell death and improved cognitive function.

Exploration of GnRH's neuroprotective properties has focused on its role as a promoter of myelination, specifically facilitating myelination processes in peripheral nerve cells via Schwann cells in a model of experimental autoimmune encephalomyelitis in rats (Guzmán-Soto *et al.* 2012). Additionally, GnRH modulates synaptic plasticity through sexual neurosteroids in female brains, potentially improving cognitive abilities (Fester & Rune, 2015).

While previous studies have addressed neuroprotection from various angles, further investigation is necessary for a comprehensive understanding of the mechanisms driving the nerve response.

Synthetic analogue of GnRH, Leuprolide acetate, triptorelin, buserelin and goserelin

Leuprolide acetate (LA) is a synthetic form of GnRH, acting as an agonist by emulating the natural hormone function and transiently stimulating gonadotropin hormone excretion (Wilson *et al.* 2006). It differs from natural GnRH in its reduced susceptibility to degradation, granting it a longer-lasting effect. LA has been utilized for treating various nervous system conditions as pituitary apoplexy and spinal and bulbar atrophy, enhancing the perceived neuroregenerative and neuroprotective role of GnRH (Sasagawa *et al.* 2015; Suzuki *et al.* 2012).

Numerous studies have explored the neuroregenerative potential of leuprolide acetate. For example further investigations focused on spinal cord injury regeneration in rats, revealing structural and functional recovery through LA treatment as evidenced by gait analysis and spinal cord histology (Díaz-Galindo *et al.* 2015). Another study targeted spinal cord inflammation using an autoimmune encephalomyelitis model in rats, showing a significant reduction in NF-κB and pro-inflammatory cytokine markers IL-1β, IL-17A, and TNF-α (Guzmán-Soto *et al.* 2016). In 2018, a clinical trial administered 6 months of LA treatment to human patients with spinal cord injury, resulting in substantial improvements in sensory function, motor activity, and independence (Quintanar *et al.* 2018). Additionally, in the same year, LA treatment led to the recovery of urination in a rat model of spinal cord injury, reinforcing its efficacy in functional recovery (Medina-Aguiñaga *et al.* 2018). Furthermore, an article two years later demonstrated the positive effects of LA treatment on anal sphincter recovery in spinal cord injury in rats (Altamira-Camacho *et al.* 2020).

LA has also been used to treat significant disorders in the peripheral nervous system. In 2020, researchers investigated its effects on the peripheral nervous system using an animal model of complete sciatic nerve transection, confirming its ability to enhance nerve functionality and integrity post-injury (Hernández-Jasso *et al.* 2020). Moreover, improvements in electrical conductivity were reported in a glaucoma model in rats, with electroretinograms showing enhanced signals for the LA-treated groups (Esparza-Leal *et al.* 2023). In a recent study, LA administered to rats with neonatal hypoxic-ischemic injury resulted in a reduction of inflammatory markers and anxious behavior (Pedroza-García *et al.* 2023).

While LA is the most renowned GnRH analogue, other analogues are also under neuroscientific research. Triptorelin has been used to treat neurofibromatosis and/or optic glioma in case reports, demonstrating efficacy in suppressing gonadotropin and sex steroid levels and reducing neurofibromatosis manifestations (Kocova *et al.* 2015; Laue *et al.* 1985). Buserelin has shown potential as a treatment for cyclical sciatica in women and has been associated with adverse effects on enteric neuropathy (Sand *et al.* 2014; Takata & Takahashi, 1994). Goserelin has been explored in treating optic glioma and enhancing cognitive ability in a sheep model (Nuruddin *et al.* 2013).

CONCLUSION

The text delves into the multifaceted role of GnRH, a hormone known for its regulation of the hypothalamic-pituitary-gonadal axis, within the nervous system. It suggests that GnRH may also function as a neurotrophic factor, a molecule that promotes the growth, survival, and regeneration of nerve cells. While the exact mechanisms by which GnRH exerts these neurotrophic effects are still being investigated, research indicates that it triggers specific signaling pathways within nerve cells and stimulates the production of nerve growth factors.

Moreover, the presence of GnRH receptors in various tissues of the nervous system underscores its potential neuroprotective effects. Activation of these receptors has been associated with tissue recovery in response to injuries and neurological diseases, suggesting a role in promoting physiological healing processes. This finding has significant implications for patients with

neurological conditions, as enhancing tissue recovery can lead to improvements in overall quality of life.

In essence, understanding the intricate relationship between GnRH and the nervous system is vital for developing effective treatment strategies, particularly considering the increasing prevalence of neurological disorders. By elucidating the mechanisms underlying GnRH's neurotrophic and neuroprotective effects, researchers can pave the way for innovative therapeutic interventions aimed at improving neurological health and well-being.

ACKNOWLEDGMENTS

Special thanks to researchers Irma Hernández, Denisse Calderón, and Brenda Gutiérrez for their invaluable support. Thanks to CONAHCYT for fellowship 1091548 and grant CF-214971.

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