

Physiology of gonadotropin-releasing hormone (GnRH): beyond the control of reproductive functions

Abstract

GnRH is the hypothalamic main regulator of the hypothalamic-pituitary-gonadal reproductive axis, but it was found to exert additional functions due to the wide distribution of its receptors both in central nervous system (from cortex to spinal cord) and in peripheral organs and tissues. The possible activity of GnRH/GnRHR system at the level of the hippocampus has raised the interest on the effects of the decapeptide and its analogues on neurogenesis and neuronal functions. Recently, it has been observed that GnRH is decreased in mouse hypothalamic ageing and that restoring normal GnRH levels may attenuate brain and systemic aging processes.

Other studies have also pointed out on neurogenic and neuro protective actions of GnRH in several models of neurodegeneration, as in Alzheimer's disease and in spinal cord injury models. A direct effect of GnRH on cholesterol and estrogen synthesis in human neuronal-like cells has been also proposed as a mechanism involved in neuro protective activity. Since GnRH analogues are known to be safe and effective, a new possible lines of therapeutic intervention to control some of the defects present in aging and neurodegenerative diseases may be delineated. In conclusion, brain GnRH/GnRHR system is a novel and extremely interesting target, since it mediates several actions possibly integrated in a complex control of reproductive functions with neurogenesis, neuroprotection, sex behavior and cognition.

Keywords: gonadotropin releasing hormone, physiology, neuroprotection, neurogenesis, analogues

Volume 2 Issue 5 - 2016

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Received: May 07, 2016 | **Published:** July 05, 2016

Abbreviations: cAMP, cyclic adenosine monophosphate; DAG, diacylglycerol; IP3, inositol 1,4,5-triphosphate; HPG, hypothalamic-pituitary-gonadal; APP, amyloid precursor protein; MAPK, mitogen-activated protein kinase; ERK1/2, extracellular signal-regulated kinase; PI3K, phosphatidylinositol-3-kinase; EGR1, early growth response 1; PP, phosphotyrosine phosphatase; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated b cells; DHCR24, 3-betahydroxysterol delta-24-reductase; St AR, steroidogenic acute regulatory protein; IKK- β , inhibitor of nuclear factor kappa-b kinase subunit beta; A β , amyloid beta peptide

Introduction

Gonadotropin releasing hormone (GnRH) is 35year-old neuropeptide recognized as the central regulator of reproductive functions.¹ It was actually one of the earliest hypothalamic-releasing hormones sequenced and characterized and led its discoverer Andrew Schally to be awarded by the Nobel prize in 1977.² The peptide is a sequence of ten aminoacids (Figure 1A) with a cyclized proline at the N-terminal and a glycine-amide residue at C-terminal, which confer some resistance to terminal peptidases.

In mammals, GnRH is mainly produced by a limited number of hypothalamic neurons, which do not form a defined nucleus but show a dispersed organization in the mediobasal hypothalamus. Making axonal contacts with the hypothalamo-hypophyseal portal vessels, GnRH neurons release the decapeptide in the bloodstream directed to the adenohypophysis in a pulsatile manner.³ At the pituitary level,

the decapeptide interact with specific G protein-coupled receptors (GnRHR) present on gonadotrope cells inducing the release of the two gonadotropins (LH, luteinizing hormone and FSH, follicle stimulating hormones) which in turn coordinate male and female gonadal functions promoting the folliculogenesis and the ovulation in female, the spermatogenesis in male, and the production of sex steroid hormones (estrogen, progesterone and testosterone) (Figure 1B).^{4,5}

GnRHR may be coupled either to G α q/11 or G α s subunits which activate different intracellular responses including cAMP and DAG/IP3 pathways, as well as the mitogen-activated protein kinase (MAPK) cascades.⁶ The separate activation of G α q/11 or G α s subunits, by changes in the frequency of decapeptide pulsatile release, is the basis for the differential control of gonadotropin release.⁷ The actions of GnRH on reproductive functions cover the whole lifespan and characterize the maturation, the pubertal activation and the adult functions of the hormonal hypothalamo-pituitary-gonadal axis. Because of its importance on reproductive functions, a series of synthetic analogues, with agonist or antagonist activities have been developed soon after GnRH identification (Table 1).^{8,9}

The pharmacological approach with GnRH analogues has been so far limited to the induction of puberty or, more in general, for recovery of fertility through a pulsatile administration; on the contrary, a continuous administration of GnRH agonists or antagonist is used to block the gonadotropin release and the reproductive axis (chemical castration).¹

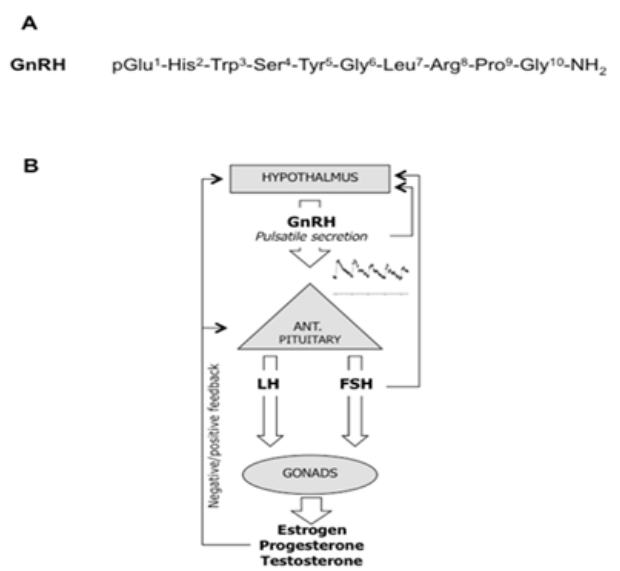


Figure 1 Amino acid sequence of GnRH (A) and the hypothalamo-pituitary-gonadal axis organization (B).

Table 1 Sequences of some GnRH analogues

| | |
|-------------|---|
| GnRH | pGlu ¹ -His ² -Trp ³ -Ser ⁴ -Tyr ⁵ -Gly ⁶ -Leu ⁷ -Arg ⁸ -Pro ⁹ -Gly ¹⁰ -NH ₂ |
| Agonists | |
| Buserelin | pGlu ¹ -His ² -Trp ³ -Ser ⁴ -Tyr ⁵ -D-Ser(tBu) ⁶ -Leu ⁷ -Arg ⁸ -Pro ⁹ -NH ₂ |
| Leuprolide | pGlu ¹ -His ² -Trp ³ -Ser ⁴ -Tyr ⁵ -D-Leu ⁶ -Leu ⁷ -Arg ⁸ -Pro ⁹ -NH ₂ |
| Antagonists | |
| Cetrorelix | Ac-D-Nal ¹ -D-Cpa ² -D-Pal ³ -Ser ⁴ -Tyr ⁵ -D-Cit ⁶ -Leu ⁷ -Arg ⁸ -Pro ⁹ -D-Ala ¹⁰ -NH ₂ |

tBu, tert-butyl; Et, ethyl; Cpa, chlorophenylalanine; Pal, 3-pyridylalanine; Cit, citrulline; Nal, 2-naphthylamine

Discussion

Since 1979 it has become increasingly clear that, in mammals, GnRH could also exert extrapituitary functions.¹⁰ In fact, GnRH/GnRHR systems were also found to be expressed in peripheral organs, in particular in the female reproductive tract,¹¹ and in several tumors,¹² where their activation is associated with a strong antiproliferative/antimetastatic activity.^{13,14} These findings gave a further impulse to the development of new GnRH analogs for the therapy of gynecological diseases and endocrine tumors.¹⁴ More recently, GnRHR were found also in human lung epithelial cells and their activation by GnRH improves the chloride transport defect present in cystic fibrosis, suggesting a new therapeutic use of GnRHR analogs.¹⁵ Extrapituitary GnRHRs share the same mRNA sequence and protein molecular size with the pituitary receptor^{16,17} although some of them, particularly those present in peripheral organs, may show a different pharmacological profile, leaving the assessment of their identity a still open question.¹⁸⁻²¹ It has been also reported that pituitary and peripheral GnRHR differ in terms of activated intracellular signaling pathway;²² GnRHR present in peripheral and tumoral tissues are generally coupled with the Gai subunit, and their activation leads to a decrease of intracellular cAMP levels. Different intracellular signaling cascades, such as MAPK (p38, ERK1/2, and JNK), PI3K and PP are linked to this pathway activation and involved to mediate the growth/survival effects of GnRH analogues.²³

Recent findings have focused the attention also on the possible role of GnRH in neuronal functions. GnRHR show a well documented wide distribution in the central nervous system, in particular at the level of the limbic system (hippocampus, amygdala), a region involved in cognitive and sexual behavior, as well as in entorhinal and frontal cortex, subiculum, septum and in spinal cord motor neurons. Although genetic identification of the GnRHR in the different brain areas indicates a similarity, their activation may elicit different intracellular responses, suggesting a possible differential effect on brain functions.²⁴ Acting as neuromodulator, GnRH might play therefore important additional functions on brain physiology other than the control of gonadotropin secretion, even if its exact role in different brain structures has not been completely defined.

The expression of brain GnRHR occurs after birth and is restricted to postmitotic neurons;²⁵ this excludes their involvement in neuronal embryonic development and suggests a possible role in postnatal development or in brain plasticity. Actually, activation of GnRHR alters the electrical properties of hippocampal neurons through a protein kinase C-dependent action¹⁰ and exerts a significant control of synaptic plasticity. In fact, the activation of GnRH receptors with the analog leuprolide was found to increase the intrinsic neuronal excitability of pyramidal neurons (of region CA1 and CA3)²⁶ and an enhancement of synaptic transmission mediated by ionotropic glutamate receptors.²⁷ GnRH was found to regulate the expression of pre- and post-synaptic markers spinophilin, synaptophysin and Egr1 in neurons obtained from hippocampus.^{25,28} Hippocampal GnRHR has been implicated in the regulation of aromatase activity,²⁸ suggesting that the observed neurotrophic effect of GnRH could be mediated by a possible intervention on local synthesis of estrogen, known to affect synaptogenesis and expression of both spinophilin and synaptophysin.²⁹ This observation also suggests that estrus cycle-dependent synaptogenesis, occurring in the rat female hippocampus, may be regulated by the cyclic release of hypothalamic GnRH. However, GnRH projections may be widespread in the brain¹⁰ and GnRH might reach the hippocampal region from cerebrospinal fluid or from neurons located in other brain regions; GnRH fibers have been found in the hippocampus and a population of septal GnRH neurons were found to project axons through a septo hippocampal tract.³⁰⁻³² From a physiological point of view, GnRH signaling was found to modify some specific behaviors (i.e., sexual behavior); moreover, it was reported that administration of the GnRH agonist leuprolide improves cognitive function in a mouse model of dementia.³³

Aging is an inexorable process through which both physiological and pathophysiological events occur and the hypothalamus may play a key role in aging development. In a very elegant study, Zhang et al.³⁴ described how infection-unrelated inflammatory changes in the mediobasal hypothalamus are implicated in programming systemic aging in mice. This appears due to an over activation of the immunity nuclear factor NF-κB. Further studies revealed that IKK-β and NF-κB might mediate an ageing-related hypothalamic decline by the inhibition of GnRH production. Accordingly, systemic GnRH treatment of mice displaying an over activation of NF-κB, associated to cognitive impairment and reduced neurogenesis, may abrogate this pro-aging phenotype promoting neurogenesis and delaying many effects of systemic ageing (skin atrophy, bone, muscle and cognitive decay, improving health and lifespan). In addition, the increase of β-sitosterol, a phytosterol with anti-inflammatory property, into the neuronal plasma membrane could also prevent the decrease of GnRH production induced by tumor necrosis factor-α (TNF-α)-NF-κB activated pathway.³⁵ Therefore, the hypothalamus has a role in ageing development by an immune-neuroendocrine integration, and anti-

inflammatory/GnRH associated therapies could have a potential role to counteract ageing-related health problems.³⁴

A relationship between GnRH and Alzheimer's Disease (AD) has also been reported. Alzheimer disease (AD), a complex, neurodegenerative disease characterized by synaptic dysfunction, memory loss, neuroinflammation and neuronal cell death, is one of the most common forms of dementia owing to the pathophysiological class of ageing-related disorders. Senile plaques and neurofibrillary tangles are the two main histological brain lesions making definitive the post-mortem diagnosis of an AD patient. A change in the production of gonadal steroids (e.g. at the end of reproductive life) may be associated with cognitive senescence and it has been proposed to be implicated in the neuropathology of AD. Actually, in brains of aged hypogonadal *hpg* mice (carrying an inactivating genetic mutation in the *GnRH* gene with consequent deficiency of gonadotropins and gonadal sex hormones) were found high levels of AD markers, like presenilin 1, APP C-terminal fragment, and Ab; these changes are limited to the hippocampal region and have been linked to the androgen depletion present in this animal model.³⁶

Although, as stated above, GnRH has been described to exert a control on synaptic plasticity in the hippocampus, a brain region strongly affected in AD, the relation GnRH-AD has been so far mainly described in term of its regulatory action on gonadal steroid hormone production, which may predispose to AD. However, the evidence that modifications of the brain and serum LH levels may change biochemical and cellular markers consistent with the neurodegenerative modifications observed in the AD brain^{37,38} call into question the hypothesis on gonadal steroid-dependent AD susceptibility. Moreover, the observation that GnRH treatment abrogated the aging phenotype observed in mice studied by Zhang et al.,³⁴ whereas sex steroids did not, support the notion that GnRH may be involved in AD independently of its hormonal activity. Actually, studies using GnRH leuprolide therapy, aimed at down regulating peripheral LH, show a decrease the toxic Ab load in the brain and a significant improvements in cognitive performance.^{33,37,39} Animal studies utilizing GnRH antagonists, (cetorelix), which also lowers serum levels of LH, also show cognitive improvements.⁴⁰

More recently, it has been reported a higher hippocampal level of GnRH and GnRHR mRNA in both male and female plaque-bearing AD transgenic mice (tgArcSwe), respect to age matched controls.⁴¹ The treatment of these animals with the GnRH leuprolide caused sex-related significant down-regulation of the expression of both the peptide and of its receptor, even though without significant changes in the plaque load; this may be suggestive of an insufficient effect of GnRHR activation in a more severe and advanced stage of the disease or an effect of GnRH weaker than the transgene phenotype of the animal model.⁴¹ Finally, clinical trials using leuprolide acetate has been shown to stabilize cognition in women with mild-to-moderate AD.⁴² These findings clearly support the role of GnRH as a potential regulator of AD pathogenesis and lead to view the hypothalamic GnRH-NF- κ B axis as an interesting mediator of aging-related neurodegenerative processes. Despite a series of reports suggesting the possible utilization of GnRH in AD, some negative effect of the analogs on cognitive functions have been reported⁴³ that will have to be accurately considered in further clinical investigations. Nevertheless, the premise exists that GnRH may be involved in AD and GnRH-based therapeutics could be considered among the potential future treatments for AD.

GnRH may exert additional effects on steroidogenesis; it has

been found that exposure of human neuronal-like cells (SH-SY5Y neuroblastoma cells) to nanomolar concentration of GnRH up-regulates the expression of enzymes involved in cholesterol (DHCR24) and sterol (StAR) synthesis, enhancing both cell cholesterol and estrogen levels.⁴⁴ Notably, DHCR24 is a crucial enzyme for cholesterol biosynthesis also called selenin-1 (for SElective Alzheimer's Disease INDicator-1) since has been found downregulated in brain areas affected by AD.⁴⁵ However, high levels of DHCR24 may also exert neuro protective functions in several models conferring resistance against oxidative stress, protecting neurons from apoptosis, by modulation of caspases and conferring resistance against Ab-mediated toxicity.^{22,45,46} These last observations suggest a possible mechanism of GnRH-induced neuroprotection through the induction of DHCR24 and are indicative of a possible relationship among GnRH action and the neuronal sterol environment.

Finally, a neurotropic effect of GnRH has been proposed. GnRH was shown to induce changes in neurite outgrowth and length in rat cortical neurons in vitro.⁴⁷ GnRHR, have been also described in the spinal cord motoneurons^{48,49} and their activation with GnRH increases the expression of neurofilaments and myelin basic protein with partial improvement of locomotor activity and bladder function in rats with spinal cord injury.⁵⁰ The treatment with the GnRH leuprolide has also been shown to decrease the severity of clinical signs on locomotion of rats with experimental autoimmune encephalomyelitis, suggesting its possible utilization for the therapy of multiple sclerosis.⁵¹ A promising approach to repair of spinal cord injury includes the administration of neurotropic factors together to immunomodulators and in this context leuprolide would be a potential treatment of spinal cord damages because of its safety and lack of significant side effects.⁵²

Conclusion

In conclusion, GnRH seems to play a physiological role in the hypothalamic control of ageing and in hippocampal neuronal homeostasis; the restoration of GnRH levels in these brain regions might represent a potential strategy for age-related health problems. GnRH peptide is an extremely interesting target since it exerts pleiotropic actions; actually, it is involved in the control of reproduction, by regulating gonadotropin secretion, and may affect both hypothalamic and hippocampal neurogenesis.

Since GnRH analogues are known to be safe, effective and able to cross the blood-brain barrier, a new possible line of therapeutic intervention to control some of the defects present in aging and neurodegenerative diseases may be delineated. For instance, an important aspect to take into consideration when reasoning on possible therapeutic strategies for AD is that both inhibition of neurodegeneration and regeneration of the brain are necessary. At this regard, GnRH system is an extremely interesting target since it might exert both actions.

These findings open new insights on the role of hypothalamic GnRH in the mechanisms of aging, in neuroprotection and in neurogenesis that go beyond its functions on HPG axis but that may be strongly coordinated by a complex integrated control of the reproductive success.

Acknowledgements

None.

Conflict of interest

Author declares that there is no conflict of interest.

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