Physiology of the Hypothalamic-Pituitary-Testicular Complex: A View by Stages in the Light of Recent Advances

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Abstract: The male gonadotropic axis consists of the hypothalamus, pituitary gland and testes. Testosterone is produced by the Leydig cells in the presence of pituitary luteinizing hormone (LH). LH and FSH (follicle stimulating hormone) are themselves regulated by gonadotropin-releasing hormone or GnRH, released in pulses by the anterior hypothalamic neurons.

The embryonic migration of GnRH neurons, which is a critical step in this process, is now better understood thanks to the identification of new genes that are involved. The regulation of the gonadotropic function has itself been illuminated by the identification of new peptide regulatory factors which include kisspeptins.

This review traces the physiology of male gonadotrope axis based on new knowledge relating to its establishment, its operation and its regulation, allowing a better understanding of the congenital hypogonadotropic hypogonadism.

Keywords: Male gonadotrope axis, regulation of the gonadotropic axis, migration of GnRH, kisspeptines, congenital hypogonadotropic hypogonadism.

INTRODUCTION

The function of the male gonadotropic axis can be divided into three stages: the hypothalamic explants which provide pulsatile secretion of GnRH (Gonadotropin Releasing Hormone), the release of FSH (follicle stimulating hormone) and LH (luteinising hormone or lutropin) which act on the testes and trigger the production of spermatogenesis and testosterone.

The various structures of the gonadotropic axis communicate *via* rhythmic and pulsatile signals which are its unique feature; and any disruption in production or function of one of the hormones involved is responsible for endocrine disruption leading to the various clinical pictures of gonadotropin deficiency.

This review aims to shed light on the physiology of the Hypothalamic-Pituitary-Testicular Complex and its admittedly poorly understood regulatory processes, which have recently been clarified by new research including the description of the role of kisspeptin and its receptor GPR54 in the regulation of GnRH secretion from the hypothalamus.

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HYPOTHALAMIC STAGE

GnRH Neurons

In humans, GnRH neurons are located mainly in the arcuate nucleus of the medio-basal hypothalamus and the preoptic area of the anterior hypothalamus.

In fact, their origin is not in the brain. These neurons migrate during embryonic development from the olfactory epithelium and reach their normal position by the 9th week of gestation.

This migration of GnRH neurons, together with the olfactory neurons, is a unique model for neurons. It seems that it is controlled by both chemical and mechanical actions.

An abnormal migration of these neurons results in Kallman's syndrome, a genetic disease associated with hypogonadotropic hypogonadism with anosmia or hyposmia. Hypogonadism is related to a deficiency of GnRH, and the lack of a sense of smell to an aplasia or hypoplasia of the olfactory bulbs and tracts [1].

Anosmin is a glycoprotein involved in the migration of GnRH neurons and is found in the olfactory bulbs, which implies it is also involved in the early stages of morphogenesis and the migration route taken into the brain [2].

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Many genes involved in the migration have been identified. Their mutation results in different phenotypical variations of Kallmann's syndrome: the Kal1 gene coding for anosmin [3], the Kal2 gene coding for FGFR1 (fibroblast growth factor receptor 1), a membrane receptor that is involved in signalling anosmin [4] the KAL3 and KAL4 genes, identified in 2006, coding respectively for Prokineticin Receptor-2 (PROKR2) and Prokineticine 2 (PROK2) that play a part in the function of anosmine-1 and FGFR1 [5].

More recently, the NELF gene (Nasal embryonic LHRH factor) [6] the FGF8 gene, which is a ligand of FGFR1, [7] and the WDR11 gene [8] have all been identified.

The cell bodies are located in the hypothalamic nuclei, whereas their axons terminate in contact with the capillary network behind the anterior pituitary gland, at the level of the pituitary stem, where GnRH is released [9].

Characteristics of GnRH

GnRH (gonadotropin-releasing hormone) or Gonadotropin is a decapeptide synthesised and released within the hypothalamus [1]. Its precursor, prepro-GnRH is composed of 92 amino acids (aa) and contains:

- 23 aa at the N-terminal
- 10 aa from the GnRH decapeptide
- A Glycine–Lysine–Arginine sequence
- A final DE56 aa sequence, the GnRH associated peptide (GAP) is cosecreted with GnRH

Proteolytic cleavage of the precursor gives rise to the GnRH peptide and GAP, a process which is poorly understood.

GnRH is transported along axons then released into the hypothalamic-pituitary portal system at the median eminence.

It is secreted in a pulsatile manner, which is necessary for its action on the gonadotropic cells of the anterior pituitary. This has been clearly demonstrated experimentally in both animals [10] and humans [11].

The origin of this pulsatility, which has been controversial for a long time, seems to have been discovered, after a study of GT1 cells. These are the cells that secrete GnRH in a pulsatile manner, confirming the intrinsic ability of this isolated secretion [12].

The pulsatility can be determined by measuring plasma GnRH levels. Its half-life is very short. It can be accurately determined by studying the pulsatility of LH or the α subunit.

The appearance of GnRH pulsatile secretion after foetal and perinatal activation follows a period of dormancy and marks the beginning of puberty [13].

The mechanism triggering the pulsatility remains unclear. It could be the result of a cessation of the negative feedback control on the GnRH neurons or because of a change in the gonadostat function with respect to the negative feedback of gonadal steroids [13, 14].

This pulsatile release is primarily nocturnal. In the male it results in the synthesis of LH becoming greater than that of FSH. Any anomaly in this reactivation shows the clinical picture of non-syndromic congenital hypogonadotropic hypogonadism which may be evident both at birth, with the appearance of a micropenis or cryptorchidism, or later, as delayed puberty or infertility, when the deficiency is not so severe [15].

PITUITARY STAGE

The GnRH Receptor

In the pituitary gonadotrope, GnRH binds specifically to a membrane receptor and belongs to the seven-transmembrane, G-protein (Gq/G11) coupled receptor family.

This receptor is a protein with 327 aa, seven transmembrane domains, one extracellular domain and three intracellular loops.

The binding of GnRH to its receptor takes place in the extracellular domain. It is accompanied by dissociation of the G protein and an activation of phospholipase C.

Phospholipase C hydrolyzes phosphatidylinositol 4.5 bisphosphate to form inositol triphosphate (IP3) and diacylglycerol (DAG). This is followed by the activation of intracellular calcium, which in turn activates protein kinase C [16].

This action requires microaggregation of the GnRH receptor, required to stimulate the synthesis of the FSH and LH α and β subunits.

Pulsatile secretion of GnRH also has the effect of increasing its receptor mRNA, whereas continuous stimulation reduces both the volume and sensitivity [9].

Many mutations of the GnRH receptor have been described in humans since 1997. These mutations lead to a more or less complete lack of the gonadotropic function, which can lead to the clinical picture of fertile eunuchs in cases of partial deficiency [17, 18].

Advances in genetics have helped to highlight the involvement of new genes in normosmic congenital hypogonadotropic hypogonadism, including the inactivating mutation of the GPR54 gene [15].

The family-based gene mapping method has led to the localisation of a candidate region on chromosome 19 (19p3.3). Where the GPR54 gene is localised the loss of function of the GPR54 gene is associated with gonadotropic deficiency [19].

GPR54 is a G protein-coupled receptor. Analysis by PCR or in situ hybridisation shows that this receptor is expressed in many tissues of the body including the hypothalamus [20] and the pituitary gland gonadotropic cells [21].

The Kiss1 gene was identified in 1996. The protein expressed by this gene is a metastasis suppressor in tumour cells [22]. A peptide with 54 aa called Kisspeptin 54 (Kp54) capable of activating GPR54 has been detected.

It has been shown that activation of GPR54 by kisspeptins was a modulator of the gonadotropic axis without interfering with the other axes during the life of the foetus, or even at puberty and adulthood, and that the inactivating mutation of GPR54 was associated with isolated gonadotropin deficiency [23, 24].

The Structure of Gonadotropins

Gonadotrophins, LH (luteinizing) and FSH (folliculotropic), as well as TSH and HCG, belong to the family of glycoprotein hormones.

FSH and LH are heterodimers formed by the noncovalent association of α and β subunits:

- The α subunit is common to the four hormones in this species and is made up of 92 aa in humans.
- The β subunit differs from one hormone to another. It is this subunit which confers biological specificity. It consists of 111 aa for FSH and 117 aa for LH.

Each subunit is glycosylated on asparagine residues, and has a large number of disulfure bridges, which maintains the structure of the molecule.

These subunits are not active in the free state. They need to combine to carry out their biological activity, which is due to chains of oligosaccharides [25].

The heterogeneity of the gonadotropins is related to changes in the peptide and oligosaccharide structures. In the case of the α subunit, the heterogeneity is related to a deletion of one to four residues in the N-terminal, while for the β subunit, it is in the N and Carboxyl-C terminals [26].

Isoforms of FSH and LH differ in their isoelectric properties, their bioactivity and plasma half-life, which also makes them very difficult to study.

The Synthesis and Secretion of Gonadotropins

LH and FSH are synthesised by gonadotroph cells which make up 15-20% of all anterior pituitary cells.

The gene for the α-subunit (chromosome 6q21q23) and β subunit (chromosome 11p11) are transcribed into mRNA with a predominance of the α subunit over the β subunit.

Gonadotropins are stored in dimeric form or as free α subunits in secretory granules.

They are released as a result of pulsatile GnRH-stimulated exocytosis. The half-life of LH is about 30 minutes and that of FSH between 100 and 200 minutes.

Mutations in genes coded for LH present the clinical picture of congenital hypogonadism that seems less common in men than in women and are associated with more or less severe alterations in spermato-genesis [27]. A reported case of the mutation of β-LH associated with preserved spermatogenesis could be explained by the existence of a low residual activity of LH, responsible for a local testosterone production compatible with normal spermatogenesis [28].

Mutation of the β-FSH in humans is associated with varying degrees of impaired spermatogenesis possibly with no loss of fertility [29].

TESTICULAR STAGE

Gonadotropin Receptors

In humans, the LH receptor is located in the Leydig cells and the FSH receptor in the Sertoli cells.

These receptors belong to the family of 7-transmembrane receptors coupled to G proteins. They are characterised by a large extracellular domain involved in hormone recognition and binding.

Transmembrane and intracellular domains are primarily involved in the transmission of the hormonal signal [30].

Inactivating mutations of the FSH receptor is associated with oligoasthenospermia [31].

Testicular Function

The testicle has two functions: spermatogenesis and testosterone production, which are interrelated and controlled by the pituitary gonadotropins.

LH binds to its receptor in the Leydig cell that controls the synthesis of testosterone from cholesterol. FSH acts directly on the seminiferous epithelium in the Sertoli cell, which produces inhibin and activin.

Both FSH and intratesticular testosterone, linked to ABP (Androgen Binding Protein), is required for normal spermatogenesis.

Sertoli cells are the site of synthesis of many growth factors involved in different stages of spermatogenesis.

REGULATION OF THE GONADOTROPIC AXIS

Regulation of the male gonadal axis is very complex. Beyond the classic relationship between negative feedback of testosterone and gonadotropins, and gonadal peptides (activin and inhibin), the role of other peptide and environmental regulatory factors, such as kisspeptin, has been studied recently [32].

The production of GnRH in the hypothalamus is controlled by negative feedback of the sex steroids that slows down the frequency of pulses.

Feedback is also provided by both testosterone and dihydrotestosterone (DHT), either by direct action on the steroid receptors in the hypothalamus or *via* a neural system.

Several factors are involved in the secretion of gonadotropins:

GnRH

The frequency of GnRH pulses is a key factor which determines whether FSH or LH is synthesised. A rapid frequency of pulses favours the synthesis of mRNA from the LH α and β subunits. A slow frequency favours the synthesis of mRNA from the FSH β-subunit.

The Sex Steroids

Testosterone is the primary regulator of the hypothalamus-pituitary-adrenal axis in humans.

By acting directly on sex steroid receptors in the gonadotropic cells, testosterone inhibits the synthesis of mRNA in the LH α and β subunits.

In the pituitary, its inhibitory effect comes about mainly through estradiol derived from the aromatisation of testosterone. Testosterone also decreases the pituitary response to GnRH by reducing the number of receptors.

Inhibin and Activin

These two glycoproteins are synthesised by the Sertoli cells and play a part in the feedback control of FSH. Inhibin reduces FSH synthesis, whereas activin stimulates it.

The kisspeptins, discussed above, are powerful stimulators of FSH and LH. This has been demonstrated in animal and human studies [33-35]. Their action is hypothalamic in humans [36].

The involvement of other peptides has also been suggested. Leptin is a peptide hormone secreted from adipocytes which acts, by means of a receptor belonging to the family of cytokines, on body fat by a hypothalamic anorectic effect.

A mutation which deactivates the leptin gene or its receptor is associated with severe obesity associated with CHH (congenital hypogonadotropic hypogonadism) hypogonadismes hypogonadotrophiques congénitaux [37]. The administration of leptin in animals with mutations of the leptin gene restores fertility [38, 39]. Moreover, the role of leptin in the regulation of the kisspeptin/GPR54 system is suggested by the decrease in KiSS1 production in the

arcuate nucleus of the obese, non-diabetic, leptin-deficient ob/ob mouse [40].

NeurokininB (NKB) is a substance expressed in hypothalamic neurons and which appears to play a key role in regulating the secretion of GnRH. TAC3 and TACR3 mutations, which respectively code neurokinin B (NKB) and its receptor (NKBR) have recently been reported in several rare cases of CHH [41].

CONCLUSION

Advances in molecular genetics have identified mutations in many genes involved in the function of the gonadotropic axis and which define CHH more accurately.

The characterisation of the role of the kisspeptin/GPR54 system in neuroendocrine regulation of the gonadotropic axis represents a major advance in reproduction research.

REFERENCES

[1] El Ansari N. Le syndrome de Kallmann-De Morsier, aspect génétique. Andrologie 2008; 18: 127-30. http://dx.doi.org/10.1007/BF03040390

[2] Dodé C, Hardelin JP. Syndrome de Kallmann-De Morsier, insuffisance de signalisation par les FGF. Med Sci 2004; 20: 8-9.

[3] Hardelin JP, Levilliers J, Blanchard S, *et al*. Heterogeneity in the mutations responsible for X chromosome-linked Kallmann syndrome. Hum Mol Genet 1993; 2: 373-7. http://dx.doi.org/10.1093/hmg/2.4.373

[4] Hébert JM, Lin M, Partanen J, Rossant J, McConnell SK. FGF signaling through FGFR1 is required for olfactory bulb morphogenesis. Development 2003; 130: 1101-11. http://dx.doi.org/10.1242/dev.00334

[5] Dodé C, Teixeira L, Levilliers J, *et al*. Kallmann syndrome: mutation in the genes encoding prokineticin-2 and prokineticin receptor-2. PloS Genet 2006; 10: 1648-52.

[6] Xu N, Bhagavath B, Kim HG, *et al*. NELF is a nuclear protein involved in hypothalamic GnRH neuronal migration. Mol Cell Endocrinol 2010; 19: 47-55. http://dx.doi.org/10.1016/j.mce.2009.11.016

[7] Falardeau J, Chung CJ, Beenken A, *et al*. Decreased FGF8 signaling causes deficiency of gonadotropin-releasing hormone in humans and mice. J Clin Invest 2008; 118: 2822-31. http://dx.doi.org/10.1172/JCI34538

[8] Kim HG, Ahn JW, Kurth I, *et al*. WDR11, a WD protein that interacts with transcription factor EMX1, is mutated in idiopathic hypogonadotropic hypogonadism and Kallmann syndrome. Am J Hum Genet 2010; 87: 465-79. http://dx.doi.org/10.1016/j.ajhg.2010.08.018

[9] Conn MP. The molecular basis of gonadotropin-releasing hormone action. Endocrine Rev 1986; 7: 3-10. http://dx.doi.org/10.1210/edrv-7-1-3

[10] Young J, Shaison G. Hypogonadisme hypogonadotrophique: données récentes. Rev Franç Endoc 1998; 39: 304-21.

[11] Goetghebeur E. Hypogonadisme hypogonadotrophique par mutation du gène du récepteur du GnRH; 2000 thèse 00T0431502 bibliothèque interuniversitaire de médecine, université de Paris Descartes.

[12] Crowley WF, Crowley Jr, Spratt DI, Santoro NF. The physiology of Gonadotropin-releasing hormone secretion in men and women. Rec Prog Hormone Res 1985; 41: 473-537.

[13] Plant T, Witchel S. Puberty in Nonhuman primates and Humans. In: Plant T, ed. Physiology of Reproduction. Boston: Elsevier, 2006; pp. 2177-230.

[14] Veldhuis JD, Keenan DM, Pincus SM. Regulation of complex pulsatile and rhythmic neuroendocrine systems: the male gonadal axis as a prototype. Prog Brain Res 2010; 181: 79-110. http://dx.doi.org/10.1016/S0079-6123(08)81006-0

[15] El Ansari N. Les hypogonadismes hypogonadotrophiques congénitaux masculins, quelles données récentes? Andrologie 2011; 21: 68-74. http://dx.doi.org/10.1007/s12610-011-0127-2

[16] Pierce JG, Parson TF. Glycoprotein hormones: structure and function. Annu Rev Biochem 1981; 50: 465-95. http://dx.doi.org/10.1146/annurev.bi.50.070181.002341

[17] De Roux N, Young J, Misrahi M, *et al*. A family with hypogonadotropic hypogonadism and mutations in the gonadotropin releasing hormone receptor. N Engl J Med 1997; 337: 1597-602. http://dx.doi.org/10.1056/NEJM199711273372205

[18] Bhagavath B, Ozata M, Ozdemir IC, *et al*. The prevalence of gonadotropin-releasing hormone receptor mutations in a large cohort of patients with hypogonadotropic hypogonadism. Fertil Steril 2005; 84: 951-7. http://dx.doi.org/10.1016/j.fertnstert.2005.04.029

[19] De Roux N, Genin E, Carel JC, Matsuda F, Chaussain JL, Milgrom E. Hypogonadotropic hypogonadism due to loss of function of the KiSS1-derived peptide receptor GPR54. Proc Natl Acad Sci USA 2003; 100: 10972-6. http://dx.doi.org/10.1073/pnas.1834399100

[20] Muir AI, Chamberlain L, Elshourbagy NA, *et al*. AXOR12, a novel human G protein-coupled receptor, activated by the peptide KiSS-1. J Biol Chem 2001; 276: 28969-75. http://dx.doi.org/10.1074/jbc.M102743200

[21] Richard N, Galmiche G, Corvaisier S, Caraty A, Kottler ML. KiSS-1 and GPR54 genes are co-expressed in rat gonadotrophs and differentially regulated *in vivo* by oestradiol and GnRH. J Neuroendocrinol 2008; 20: 381-93. http://dx.doi.org/10.1111/j.1365-2826.2008.01653.x

[22] Lee JH, Miele ME, Hicks DJ, *et al*. KiSS-1, a novel human malignant melanoma metastasis-suppressor gene. J Natl Cancer Inst 1996; 88: 1731-7. http://dx.doi.org/10.1093/jnci/88.23.1731

[23] Rodet F, Huijbregts L, Villanueva C. Le couple kisspeptine/GPR54, un acteur majeur de la régulation neuroendocrine de la reproduction. Médecine de la reproduction, gynécologie et endocrinologie 2008; 10: 123-30.

[24] Tenenbaum-Rakover Y, Commenges-Ducos M, Iovane A, Aumas C, Admoni O, de Roux N. Neuroendocrine phenotype analysis in five patients with isolated hypogonadotropic hypogonadism due to a L102P inactivating mutation of GPR54. J Clin Endocrinol Metab 2007; 92: 1137-44. http://dx.doi.org/10.1210/jc.2006-2147

[25] Fan NC, Jeung EB, Peng C, *et al*. The human Gonadotropin-releasing hormone (GnRH) receptor gene: cloning, genomic organisation and chromosomal assignment. Mol Cell Endocrinol 1994; 103: 1-6. http://dx.doi.org/10.1016/0303-7207(94)90087-6

[26] Stojilkovic SS, Reinhart J, Catt KJ. Gonadotropin-releasing hormone receptors: structure and signal transduction pathways. Endocrine Rev 1994; 15: 462-87. http://dx.doi.org/10.1210/edrv-15-4-462

[27] Lofrano-Porto A, Barra GB, Giacomini LA, *et al*. Luteinizing hormone beta mutation and hypogonadism in men and women. N Engl J Med 2007; 357: 897-904. http://dx.doi.org/10.1056/NEJMoa071999

[28] Achard C, Courtillot C, Lahuna O, *et al*. Normal spermatogenesis in a man with mutant luteinizing hormone. N Engl J Med 2009; 361: 1856-63. http://dx.doi.org/10.1056/NEJMoa0805792

[29] Layman LC, McDonough PG. Mutations of follicle stimulating hormone-beta and its receptor in human and mouse: genotype/phenotype. Mol Cell Endocrinol 2000; 161: 9-17. http://dx.doi.org/10.1016/S0303-7207(99)00217-8

[30] De Roux N, Morel Y et Hardelin JP. Anomalies génétiques de l'axe gonadotrope. La revue du praticien 1999; 49: 1277-82.

[31] Tapanainen JS, Aittomäki K, Min J, *et al*. Men homozygous for an inactivating mutation of the follicle-stimulating hormone (FSH) receptor gene present variable suppression of spermatogenesis and fertility. Nat Genet 1997; 15: 205-6. http://dx.doi.org/10.1038/ng0297-205

[32] Seminara SB, Messager S, Chatzidaki EE, *et al*. The GPR54 gene as a regulator of puberty. N Engl J Med 2003; 349: 1614-27. http://dx.doi.org/10.1056/NEJMoa035322

[33] Thompson EL, Patterson M, Murphy KG, *et al*. Central and peripheral administration of kisspeptin-10 stimulates the hypothalamic-pituitary-gonadal axis. J Neuroendocrinol 2004; 16: 850-8. http://dx.doi.org/10.1111/j.1365-2826.2004.01240.x

[34] Ramaswamy S, Seminara SB, Pohl CR, *et al*. Effect of continuous intravenous administration of human metastin 45-54 on the neuroendocrine activity of the hypothalamic-pituitary-testicular axis in the adult male rhesus monkey (Macaca mulatta). Endocrinology 2007; 148: 3364-70. http://dx.doi.org/10.1210/en.2007-0207

[35] Dhillo WS, Chaudhri OB, Patterson M, *et al*. Kisspeptin-54 stimulates the hypothalamic-pituitary gonadal axis in human males. J Clin Endocrinol Metab 2005; 90: 6609-15. http://dx.doi.org/10.1210/jc.2005-1468

[36] Rometo AM, Krajewski SJ, Voytko ML, Rance NE. Hypertrophy and increased kisspeptin gene expression in the hypothalamic infundibular nucleus of postmenopausal women and ovariectomised monkeys. J Clin Endocrinol Metab 2007; 92: 2744-50. http://dx.doi.org/10.1210/jc.2007-0553

[37] Strobel A, Issad T, Camoin L, Ozata M, Strosberg AD. A leptin missense mutation associated with hypogonadism and morbid obesity. Nat Genet 1998; 18: 213-5. http://dx.doi.org/10.1038/ng0398-213

[38] Chehab FF, Lim ME, Lu R. Correction of the sterility defect in homozygous obese female mice by treatment with the human recombinant leptin. Nat Genet 1996; 12: 318-20. http://dx.doi.org/10.1038/ng0396-318

[39] Farooqi IS, Wangensteen T, Collins S, *et al*. Clinical and molecular genetic spectrum of congenital deficiency of the leptin receptor. N Engl J Med 2007; 356: 237-47. http://dx.doi.org/10.1056/NEJMoa063988

[40] Smith JT, Acohido BV, Clifton DK, Steiner RA. KiSS-1 neurones are direct targets for leptin in the ob/ob mouse. J Neuroendocrinol 2006; 18: 298-303. http://dx.doi.org/10.1111/j.1365-2826.2006.01417.x

[41] Topaloglu AK, Reimann F, Guclu M, *et al*. TAC3 and TACR3 mutations in familial hypogonadotropic hypogonadism reveal a key role for Neurokinin B in the central control of reproduction. Nat Genet 2009; 41: 269-70. http://dx.doi.org/10.1038/ng.306

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