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Review

GnRH, anosmia and hypogonadotropic hypogonadism – Where are we?

Paolo E. Forni [a,*], Susan Wray [b,*]

[a] Department of Biological Sciences and the Center for Neuroscience Research, University at Albany, State University of New York, Albany, NY 12222, United States
[b] Cellular and Developmental Neurobiology Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD 20892, United States

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ABSTRACT

Gonadotropin releasing hormone (GnRH) neurons originate the nasal placode and migrate into the brain during prenatal development. Once within the brain, these cells become integral components of the hypothalamic–pituitary–gonadal axis, essential for reproductive function. Disruption of this system causes hypogonadotropic hypogonadism (HH). HH associated with anosmia is clinically defined as Kallman syndrome (KS). Recent work examining the developing nasal region has shed new light on cellular composition, cell interactions and molecular cues responsible for the development of this system in different species. This review discusses some developmental aspects, animal models and current advancements in our understanding of pathologies affecting GnRH. In addition we discuss how development of neural crest derivatives such as the glia of the olfactory system and craniofacial structures control GnRH development and reproductive function.

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1. The GnRH neurons – regulators of fertility

The hypothalamic–pituitary–gonadal (HPG) axis is considered to be an evolutionary innovation specific to vertebrates (Sower et al., 2009; Campbell et al., 2004). The neuroendocrine gonadotropin releasing hormone (GnRH) neurons are integral components of this axis, regulating sexual development and reproductive function (see Fig. 1). In mammals, the primary terminal field of the neurosecretory GnRH neurons is the median eminence. Here, the cleaved and amidated GnRH decapeptide is released into portal vessels where it is transported to the anterior pituitary gland. GnRH activates receptors on pituitary gonadotropes, triggering synthesis and release of the gonadotropins luteinizing hormone (LH) and follicle stimulating (FSH). LH and FSH are necessary for gonadal function. In the ovary, LH acts upon theca cells that produce the androgen substrate required for ovarian estrogen biosynthesis. In the testis, LH induces Leydig cells to produce testosterone. In both males and females, FSH stimulates maturation of germ cells. Thus, if GnRH release is compromised it translates into impaired reproductive maturation and function – e.g. hypogonadotropic hypogonadism (HH). HH can result from defects in GnRH neuronal development (Schwanzel-Fukuda et al., 1989; Quinton et al., 1997; Wray, 2002), GnRH synthesis (Cattanach et al., 1977), release (Kirilov et al., 2013; Seminara et al., 2003; de Roux et al., 2003; Giacobini et al., 2014) or ligand/receptor (GnRH/GnRHR) pairing (Quinton et al., 1997; Tello et al., 2012; Chevrier et al., 2011; Pralong et al., 1999).

Recent work has given us a better understanding of the cellular composition of the developing olfactory area, development of the GnRH cells and perturbations leading to HH. However, we still do not fully understand the cell types involved in GnRH neuronal development. This review discusses some of the similarities and differences of the GnRH system among animal models. In addition, we highlight some recent animal studies on GnRH neuronal embryonic lineage, craniofacial development and olfactory ensheathing cells that may explain the diversity of phenotypes observed in HH patients that resulted from a developmental perturbation.

2. GnRH peptides

During early evolution, three paralogous GnRH genes (*gnrh1*, *gnrh2 and gnrh3*) arose from two rounds of genome duplication

Abbreviations: GnRH-1, gonadotropin releasing hormone; HPG, hypothalamic–pituitary–gonadal; LH, luteinizing hormone; FSH, follicle stimulating hormone; GnRHR, gonadotropin releasing hormone receptor; HH, hypogonadotropic hypogonadism; TN, terminal nerve; OMP, olfactory marker protein; KS, Kallmann syndrome; OB, olfactory bulb; OECs, olfactory ensheathing cells; OP, olfactory pit; E, embryonic day; FGF8, fibroblast growth factor 8; BMP, bone morphogenic protein; BLBP, brain lipid-binding protein.

* Address: Dept. of Biological Sciences and the Center for Neuroscience Research, University at Albany, SUNY 1400 Washington Avenue, Albany, NY 12222, United States (P.E. Forni). Address: NINDS, NIH, Building 35, Rm. 3A-1012, Bethesda, MD 20892-3703, United States (S. Wray).

E-mail addresses: pforni@albany.edu (P.E. Forni), wrays@ninds.nih.gov (S. Wray).

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(Okubo and Nagahama, 2008). Various isoforms of GnRH decapeptides have been found in all vertebrates: ranging from agnathans to mammals (Kelsall et al., 1990; Montaner et al., 1998; Uchida et al., 2010). Characterization of non-mammalian vertebrates species including fishes, amphibians and reptiles identified up to 15 different GnRH variants (Kavanaugh et al., 2008; Lethimonier et al., 2004) that were classified into three main phylogenetic groups, (Uchida et al., 2010; Powell et al., 1986; Calvin et al., 1993; Meglio et al., 1991; Sherwood et al., 1986; King and Millar, 1985; Hayes et al., 1994), prior to gene identification, and historically named after the first class or species in which they were characterized (King and Millar, 1985, 1982; Schally et al., 1971; Gordon and Reichlin, 1974; Miyamoto et al., 1982; Sherwood et al., 1983). However, identification of the *gnrh* genes revealed a genetic twist – the *gnrh* genes expressed in vertebrates varies within teleosts as well as within mammals (Fig. 2). All 3 GnRH genes are found in ancient teleosts including *medaka* (Oka, 2009; Kawabata et al., 2012; Karigo et al., 2014). However, genetic studies have shown that though multiple GnRH paralogs originated during evolution, the GnRH-3 family was lost in the tetrapod lineage (Tostivint, 2011). In most teleosts, GnRH-3 is expressed by neurons of the terminal nerve/olfactory region and believed to function as a neuromodulator and to be indirectly linked to the reproductive neuroendocrine axis (Oka, 2009). Observations made in sea bass indicate that GnRH-3 neuronal projections can innervate the retina and modulate retinal function (Servili et al., 2012). *Gnrh2* (Human chromosome 20) is the most ancient form of GnRH. GnRH-2 peptide is often referred to as mesencephalic GnRH based on the anatomical location of the cells expressing the peptide. Studies in fish suggest that GnRH-2 might be a neuromodulator in the auditory system (Oka, 2009; Kanda et al., 2010; Maruska and Tricas, 2011) or a melatonin-releasing factor in the pineal gland, participating in sleep/wake cycles (Servili et al., 2010). However, during evolution, the preproGnRH-2 gene as well as the GnRH-2 receptor has been deleted or inactivated from the genome of many mammals (Stewart et al., 2009). Thus, a physiological role for GnRH-2 in mammals remains controversial. *Gnrh1* is present in most vertebrates (Human chromosome 8) but notably absent in modern teleosts including zebrafish (Abraham et al., 2009; Zohar et al., 2010; Yanicostas et al., 2009; Palevitch et al., 2010). In modern teleosts, GnRH-3 adopted the role of GnRH-1 in reproduction (Palevitch et al., 2007). GnRH-1 is the only form of the GnRH gene that exists in the rodent genome (Fernald and White, 1999) (summarized in Fig. 2). In mammals, GnRH-1 cells are located in the forebrain, distributed bilaterally on either side of midline. The actual location of GnRH-1 cells can vary rostrally to caudally depending on the species (Hoffman et al., 1992). The pivotal function of the GnRH-1 peptide in controlling the HPG axis was proven in mice carrying a loss of function mutation in GnRH-1 gene, hpg mice (Mason et al., 1986a). These mice exhibit deficient pituitary gonadotropin secretion and failure of gonadal postnatal development (either testes or ovary). In addition, GnRH-1 function in controlling the HPG axis was elegantly demonstrated by one of the very first examples of gene therapy/rescue experiment in animals. In 1986, A.J. Mason and coworkers showed that transgenic expression of GnRH-1 was sufficient to re-established reproductive competence in both hpg male and female mice (Mason et al., 1986a, 1986b). Proof of the same role for the GnRH-1 system in humans came from the identification of homozygous loss of function mutations in the GnRH1 gene in a family carrying normosmic HH (Bouligand et al., 2009).

3. Embryonic development of GnRH neurons

Deficits in the sense of smell and hypogonadism were first reported in 1856 by A. Maestre de San Juan and later, in 1944, by Kallmann et al. (1944). Kallmann noticed a co-segregation of anosmia and hypogonadism in individuals from three families and suggested a hereditary nature of this syndrome, now commonly know as Kallmann syndrome (KS). The anatomical link between anosmia and hypogonadism would remain unknown for four decades.

Although genetic changes have added unexpected twists to understanding the hypophysiotropic GnRH system (for other reviews see Wray, 2002, 2010; Okubo and Nagahama, 2008; Karigo and Oka, 2013) a striking similarity has been conserved throughout evolution in the development of the GnRH neurons responsible for controlling the HPG axis. In the late 1980s, developmental studies in mice, by two independent groups (Schwanzel-Fukuda and Pfaff, 1989; Wray et al., 1989a, 1989b), revealed that GnRH-1 neurons migrate from the nose to the brain in association with developing sensory axons of the olfactory/vomeronasal/terminal nerve system (see Fig. 3). These studies found the crucial developmental link between the two main components affected in syndromic forms of HH (e.g. KS) (Schwanzel-Fukuda et al., 1989). Further characterization in mice indicated that the GnRH-1 cells migrated along a pathway (Wray et al., 1994) that is a subset of putative vomeronasal/terminal nerve fibers (Wray et al., 1994; Yoshida et al., 1995). GnRH-1 neurons have been subsequently described to originate in the developing nose and migrate along subsets of fibers to the brain in birds, amphibians, reptiles, medaka and mammals.

3.1. The olfactory placode

Although GnRH-1 gene expression has been reported at morula and blastocyst stages, and transient expression is observed in both neuronal and non-neuronal cell types (Wray, 2002), birth dating studies in mice have shown that GnRH expressing neurons

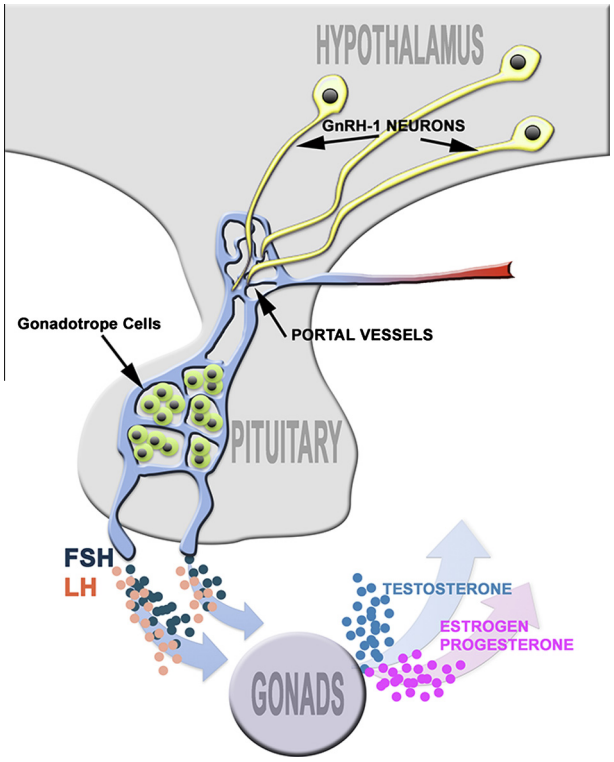

Fig. 1. Hypothalamic–pituitary–gonadal (HPG) axis. GnRH-1 cells extend their axons to the median eminence where they release GnRH-1 into the portal capillary system. Gonadotrope cells of the anterior pituitary, synthesize and release gonadotropins, LH and FSH. Pituitary release of FSH and LH, control sex steroid synthesis in the gonads.