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A new key neurohormone controlling reproduction, gonadotropin-inhibitory hormone (GnIH): Biosynthesis, mode of action and functional significance

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ABSTRACT

Identification of novel neurohormones that play important roles in the regulation of pituitary function is essential for the progress of neurobiology. The decapeptide gonadotropin-releasing hormone (GnRH) is the primary factor responsible for the hypothalamic control of gonadotropin secretion. Gonadal sex steroids and inhibin inhibit gonadotropin secretion via feedback from the gonads, but a neuropeptide inhibitor of gonadotropin secretion was, until recently, unknown in vertebrates. In 2000, a novel hypothalamic dodecapeptide that inhibits gonadotropin release was identified in quail and termed gonadotropin-inhibitory hormone (GnIH). This was the first demonstration of a hypothalamic neuropeptide inhibiting gonadotropin release in any vertebrate. GnIH acts on the pituitary and GnRH neurons in the hypothalamus via a novel G protein-coupled receptor for GnIH to inhibit gonadal development and maintenance by decreasing gonadotropin release and synthesis. GnIH neurons express the melatonin receptor and melatonin stimulates the expression of GnIH. Because GnIH exists and functions in several avian species, GnIH is considered to be a new key neurohormone controlling avian reproduction. From a broader perspective, subsequently the presence of GnIH homologous peptides has been demonstrated in other vertebrates. Mammalian GnIH homologous peptides also act to inhibit reproduction by decreasing gonadotropin release in several mammalian species. Thus, the discovery of GnIH has opened the door to a new research field in reproductive neurobiology. This review summarizes the advances made in our understanding of the biosynthesis, mode of action and functional significance of GnIH, a newly discovered key neurohormone, and its homologous peptides.

Contents

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Abbreviations: GnIH, gonadotropin-inhibitory hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; GTH, gonadotropin; PRL, prolactin; GH, growth hormone; GABA, γ-aminobutyric acid; RFamide, Arg-Phe-NH_2; RFRP, RFamide-related peptide; fGRP, frog growth hormone-releasing peptide; R-RFa, *Rana* RFamide peptide; fNRP, frog nociception-related peptide; gfLPXRFa, goldfish LPXRFamide peptide; PrRP, prolactin-releasing peptide; C-RFa, *Carracius* RFamide peptide; NPFF, neuropeptide FF; NPAF, neuropeptide AF; NPSF, neuropeptide SF; QRFP, pyroglutamylated RFamide peptide; 26RFa, 26-residue RFamide peptide; GPCR, G protein-coupled receptor; TMs, transmembrane domains; PVN, paraventricular nucleus; POA, preoptic area; ME, median eminence; SON, supraoptic nucleus; NTS, nucleus of solitary tract; DMN, dorsomedial nucleus; VMN, ventromedial nucleus; 3′/5′ RACE, 3′ and 5′ rapid amplification of cDNA ends; Px, pinealectomy; Ex, orbital enucleation; SD, short day photoperiods.

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1. Introduction

The reproductive axis integrates information from a wide range of systems via direct and indirect neurochemical inputs. Many of the neuropeptide pathways involved in the transduction of environmental stimuli into neuroendocrine signals have been well studied. A classic example of this is the gonadotropin-releasing hormone (GnRH) system. GnRH regulates secretion of both of the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and acts as a key neurohormone for vertebrate reproduction. Since the discovery of GnRH, a hypothalamic decapeptide, in the brain of mammals at the beginning of the 1970s (Matsuo et al., 1971; Burgus et al., 1972), several other GnRHs have been identified in the brain of non-mammals (King and Millar, 1982; Miyamoto et al., 1982, 1984; Sherwood et al., 1983, 1986). It has also been generally accepted that GnRH is the only hypothalamic regulator of the release of pituitary gonadotropins, and that no other neuropeptide has a direct influence on the reproductive axis. Some neurochemicals and peripheral hormones [e.g., γ-aminobutyric acid (GABA), opiates, gonadal sex steroids, inhibin] can modulate gonadotropin release to a degree, but GnRH was considered to be unusual among hypothalamic neuropeptides in that it appeared to have no hypothalamic antagonist. However, this dogma was challenged by the discovery in 2000 of a vertebrate hypothalamic neuropeptide that inhibits pituitary gonadotropin release (Tsutsui et al., 2000).

In a search for novel neuropeptides regulating the release of pituitary hormones, Tsutsui et al. identified a novel hypothalamic dodecapeptide (SIKPSAYLPLRFamide) that directly acts on the pituitary to inhibit gonadotropin release in quail and termed it gonadotropin-inhibitory hormone (GnIH; Tsutsui et al., 2000; Fig. 1). This was the first demonstration of a hypothalamic neuropeptide inhibiting gonadotropin release in any vertebrate. From the past 8 years of research, we now know that GnIH exists in several avian species, such as quail, chickens and sparrows, and acts as a new key neurohormone for the regulation of avian reproduction by decreasing gonadotropin release and synthesis (Tsutsui et al., 2000, 2005, 2006, 2007a,b; Satake et al., 2001; Bentley et al., 2003, 2006; Ubuka et al., 2003, 2005, 2006a, 2008; Ukena et al., 2003a; Ciccone et al., 2004; Osugi et al., 2004; Yin et al., 2005).

Because a gonadotropin-inhibitory system is an intriguing new concept, Tsutsui et al. have further identified GnIH homologous peptides in other vertebrates including mammals. Interestingly, mammalian GnIH homologous peptides as well as GnIH identified in birds act to inhibit gonadotropin release in several mammalian species, such as rats, hamsters, and sheep (Kriegsfeld et al., 2006; Ubuka et al., 2006b; Johnson et al., 2007; Clarke et al., 2008; Gibson et al., 2008; Murakami et al., 2008). Thus, GnIH, a newly discovered hypothalamic neuropeptide, and its homologous peptides appear to act as a new key neurohormone controlling vertebrate reproduction. The discovery of GnIH has changed our understanding about regulation of the reproductive axis drastically in the last 8 years, but we are only at the beginning of an exciting new era of research on reproductive neurobiology.

2. Discovery of gonadotropin-inhibitory hormone (GnIH)

2.1. Brief history

GnIH possesses the RFamide (Arg-Phe-NH_2) motif at its C-terminus (i.e., RFamide peptide). The first isolation of RFamide peptide occurred in an invertebrate species almost 30 years ago (Price and Greenberg, 1977) and 6 years later the first RFamide peptide in vertebrates was discovered in chickens (Dockray et al., 1983). In vertebrates, the study of RFamide neurobiology has gathered vast momentum in recent years.

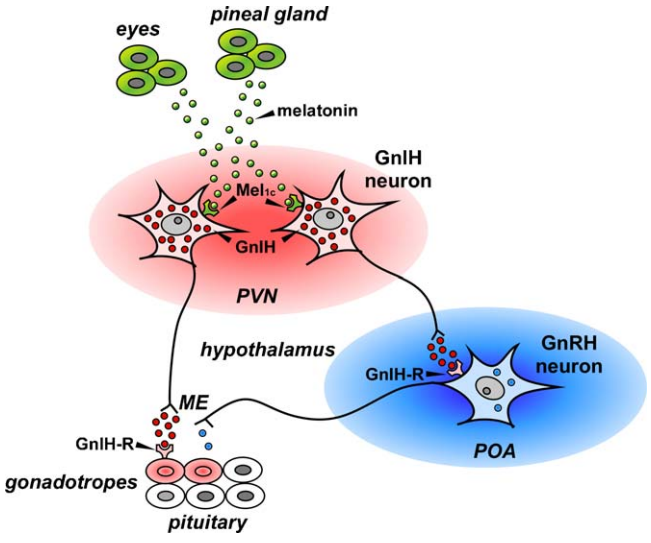

Fig. 1. The proposed mechanisms of action of GnIH on gonadotropin synthesis and release and the action of melatonin on GnIH expression. GnIH is a newly discovered hypothalamic neuropeptide that inhibits gonadotropin release in the quail brain (Tsutsui et al., 2000). Cell bodies of GnIH neurons are localized in the paraventricular nucleus (PVN). Terminals of GnIH neurons are localized in the median eminence (ME) and GnRH neurons in the preoptic area (POA). GnIH receptor (GnIH-R) is expressed in gonadotropes in the pituitary and GnRH neurons in the POA. Thus, GnIH acts directly on gonadotropes in the pituitary via GnIH receptor to inhibit gonadotropin release and synthesis. GnIH may also act on GnRH neurons in the POA to inhibit GnRH release. Melatonin originating from the pineal gland and eyes induces GnIH expression in GnIH neurons. Melatonin receptor (Mel_{1c}) is expressed in GnIH neurons. Thus, melatonin acts directly on GnIH neurons via melatonin receptor (Mel_{1c}) to induce GnIH expression.